Agenda Item: 7.2
Prepared by: J Zych
Meeting Date: Arpil 2007

APN Petition for Exception to Rules 221.12 and 221.13(b)–Karen Corlett

Summary of Request: Consider the request from Karen Corlett for waiver of Rules 221.12 and 221.13(b) that state the advanced practice nurse's scope of practice is based upon educational preparation and that she must practice in the role and specialty appropriate to her educational preparation. Ms. Corlett is educated as a primary care pediatric nurse practitioner (PNP) who has been practicing in pediatric critical care based on informal education obtained on the job and national certification as an acute care pediatric nurse practitioner (ACPNP).

Historical Perspective: Ms. Corlett completed a primary care PNP program at Indiana University in 1997. Since completion of her primary care PNP program, she has worked in pediatric critical care areas. Section 301.152 of the Nursing Practice Act states that the board approves advanced practice nurses based on educational preparation (Attachment A). Therefore, the advanced practice nurse's scope of practice is based first and foremost upon his/her advanced practice nursing education. Additionally, Board rules require advanced practice nurses to work in the role and specialty appropriate to their educational preparation [see Attachment B-1 for current Rule 221.13(b)].

- The board has typically viewed the primary care prepared PNP's role in the acute care setting as more limited than that of the acute care pediatric nurse practitioner (ACPNP). It has never been considered equivalent to that of an ACPNP in the acute care setting. Primary care PNP educational preparation generally includes well-child care as well as prevention and management of commonly occurring pediatric acute illnesses and chronic conditions. Although there may be some overlap between the primary and acute care PNPs' scopes and there may be services that the primary care-prepared PNP may provide in an inpatient setting, this does not mean their scopes of practice are identical. Primary care PNP educational preparation does not generally include significant content related to medical diagnosis and management of critically ill children.

- Board rules have required advanced practice nurses to work in the role and specialty appropriate to their educational preparation for more than twenty-five years [see Attachment B-1 for current Rule 221.13(b) and B-2 for the Advanced Practice Rule 388.06.00.006(a) that was in effect in 1980]. This rule has been consistently enforced during that time. Medical diagnosis and management of patients in pediatric critical care settings has never been considered by the board to be appropriate for individuals prepared in primary care PNP programs. PNPs who were educated in a program that prepares them to provide primary care to pediatric patients have consistently been advised by board staff that practice in critical care settings is beyond their scope when they have contacted the board office. This is consistent with the responses given to adult and family nurse practitioners who inquire regarding practicing in adult critical care settings.

- Ms. Corlett was first employed as a PNP in a critical care unit in another jurisdiction. Her application for authorization to practice as an advanced practice nurse in Texas was received in the board office on October 16, 2003, and she was granted full authorization to practice as a PNP in Texas on November 7. 2003.

- Ms. Corlett obtained national certification as an ACPNP in 2005 without formal education in the ACPNP specialty through a waiver offered by the national certifying body. The national certifying body was advised by board staff in February 2005 that individuals who obtained certification as ACPNPs via the waiver process would not be eligible for recognition as ACPNPs in the state of Texas (Attachment C).

- Historically, Texas has recognized the ACPNP title for many years. The first individual recognized with the ACPNP title completed her program in April 1997 at the University of Texas Medical Branch. She was subsequently recognized in 1998 after completing 1000 hours of supervised practice post

graduation; therefore, educational preparation in an ACPNP program and recognition from the board were both available at the time Ms. Corlett completed her PNP program. It should be noted that the first individual recognized as an ACPNP in Texas was enrolled in and completed her ACPNP program at the same time the petitioner completed her PNP program.

- Texas has also recognized the Pediatric Critical Care Nurse Practitioner title for a number of years. The first Pediatric Critical Care Nurse Practitioner completed her pediatric critical care program in 1995 and was authorized to practice in Texas that same year. This individual was enrolled in her program before Ms. Corlett began her primary care PNP program.

- Individuals who were authorized to practice with the ACPNP title prior to the development and recognition of the ACPNP examination were required to complete supervised practice hours post graduation as provided for in Rule 221.7(c) (Attachment D); therefore, an acceptable alternative to national certification has been provided for graduates of ACPNP programs since the first graduate completed her program.

- Ms. Corlett did not provide any information indicating that her primary care PNP program included critical care content. Based on the information provided by the petitioner (Attachment G), it appears her only preparation related to critical care was obtained on the job rather than through formal education in an ACPNP program.

Based on this information, staff advised Ms. Corlett that it is beyond her scope of practice to provide advanced practice nursing care in pediatric critical care settings without the requisite education and authorization to do so from the Board of Nurse Examiners.

Board Actions related to Rules and Previous Requests for Waivers of a Similar Nature

The Board has received relatively few requests for waiver of educational preparation. Past actions related to rules and petitions are summarized as follows:

- **First Advanced Practice Rule:** Advanced Practice Rule 388.06.00.006(a) required advanced nurse practitioners (the term utilized prior to advanced practice nurse) to practice in an area appropriate to their educational preparation.

- **Petitioners Not Prepared in the Advanced Role and Specialty:** The Board considered and denied the following petitioners based on lack of formal educational preparation in the specific specialty:

    - **7/2001:** A clinical nurse specialist (CNS) educated in medical-surgical nursing requested authorization to practice as a CNS in oncology nursing. All clinical assignments and projects completed within the program focused on oncology. She had practiced as a CNS in oncology for twenty years in other jurisdictions and held national certification as an advanced oncology certified nurse. Although her educational preparation in the medical-surgical specialty area included oncology content, the Board determined that it was not equivalent to the depth of preparation in the oncology specialty area included in a dedicated oncology program.

    - **1/2004:** A graduate of a dual track program requested that the Board accept her clinical experiences in her oncology nurse practitioner courses as meeting part of the requirement for clinical experiences in the adult nurse practitioner (ANP) role and specialty. The Board determined that clinical hours completed in oncology do not demonstrate that the individual is prepared to practice in the second specialty.

    - **1/2004:** A 1979 graduate of a non-accredited ANP program requested authorization to practice as a gerontological nurse practitioner (GNP). She became certified as a GNP via a waiver from the certifying body and had been licensed as a GNP in other states. The Board reinforced that advanced practice nurses are not approved based on national certification.

- **7/2006:** A CNS initially requested that the Board waive required courses for prescriptive authority. He believed completion of other academic and continuing education courses and certifications demonstrated his underlying knowledge of the content areas. During the Board meeting, he modified his request–asking that the Board grant prescriptive authority while he completed the required courses. Both were denied.

- **Petitioner Requesting Approval to Practice While Meeting Educational Requirements:** In addition to the above referenced July 2006 petition, the Board considered and denied the following petitioner's request to practice while completing courses required for authorization to practice in Texas:

  - An applicant was required to complete an advanced assessment course. This applicant requested that she be permitted to practice as a nurse practitioner while completing the required course. The Board expressed concern that approval of such a request would set a precedent that must be followed with future applicants. This precedent could permit individuals to practice as nurses prior to meeting **all** curricular requirements outlined in Board rules.

Staff Summary and Analysis of the Petition:
Staff does not believe Ms. Corlett has sufficiently demonstrated that she has educational preparation appropriate for medical diagnosis and management of critically ill children. Staff offers the following rationale in support of this determination:

- Ms. Corlett states that there were no ACPNP educational programs available at the time she began her PNP program. Staff disagrees with this argument as there is currently an individual who holds authorization to practice as an ACPNP that completed her program at the same time Ms. Corlett was enrolled in a primary care PNP program. Both received master's degrees within a few weeks of each other. Therefore, it is incorrect to state that there were no ACPNP programs available at that time. There is another individual recognized as a Pediatric Critical Care Nurse Practitioner that completed her program and was recognized with that title in 1995, two years prior to Ms. Corlett's program completion date.

- The ACPNP title was first granted in 1998. Therefore, it is not a new title recognized by the Board. The Pediatric Critical Care Nurse Practitioner title was granted by the Board in 1995.

- Ms. Corlett claims she completed clinical experiences with a pediatric cardiologist and also completed projects and wrote papers dealing with acute and critical care issues in order to tailor experiences for a desired practice area. Writing papers and completing projects do not provide assurance that she is qualified to formulate appropriate differential diagnoses and management plans for critically ill children nor that she is prepared to diagnose and manage adverse reactions or complications that may arise. The program Ms. Corlett completed was a primary care PNP program and, as such, it is likely only her papers and projects addressed critical care issues. The petitioner has provided no information from her educational program to dispute this.

- Ms. Corlett attests that she met with a physician one to two times each week for approximately two to three months and read articles [included as part of Attachment G] for the purpose of advancing her knowledge in pediatric critical care. Two to three months of on the job training is not sufficient to replace formal educational preparation in the role and specialty and is significantly less than the Board's requirement for advanced practice nursing educational preparation. Rule 221.3(c)(3)(C) requires the program to be at least an academic year in length(Attachment E).

- Although Ms. Corlett holds national certification as an ACPNP, authorization to practice as an advanced practice nurse is not granted based on certification alone. The appropriate educational foundation for practice is required. This information was provided to the Pediatric Nursing Certification Board in early 2005, and staff clearly outlined concerns that granting waivers could encourage primary care PNPs to exceed their scopes of practice (Attachment C).

- Ms. Corlett indicates she contacted the board office and advised staff that she passed the ACPNP examination. If she advised board staff that she passed an examination that was not recognized by the Board at the time, it is unlikely that conversation would have included discussion of practice setting and educational preparation. However, there is no way to determine how questions were raised and responses provided for the specific conversation in question.

- Ms. Corlett puts forth that there were Board members who believed primary care PNPs could be grandparented and permitted to continue to practice in critical care settings. As in the above bullet point, it is not possible to know the exact questions raised and conversation held. Additionally, Board rules from as far back as 1980 prohibited primary care-educated PNPs from practicing in critical care as this is not an area appropriate to their educational preparation. This is not a new position of the Board; rather it is enforcement of a position the Board has held since passage of the first rules relating to advanced practice. Staff recently responded to a letter from Ms. Corlett's employer further clarifying that primary care-prepared PNPs have never been authorized to practice in critical care (Attachment F).

Petition Review Committee Recommendation: Four petition review committee members provided staff with their opinions. The fifth reviewer did not respond to staff's request for review. The four reviewers who provided an opinion unanimously recommended that the Board deny Ms. Corlett's request.

Summary of Rationale for this Recommendation: Reviewers offered the following comments in support of their opinion:

- Ms. Corlett provided no evidence that she has completed formal education in the acute care pediatric nurse practitioner specialty. Although there is some value in on-the-job training, it does not equate to formal education by any reasonable standard.

- Ms. Corlett has practiced entirely out of her scope since coming to Texas.

- Although there is overlap between the primary care pediatric and acute care pediatric nurse practitioner specialties, there are distinct differences between the two. The courses Ms. Corlett would be required to take at the University of Texas at Arlington (UTA) demonstrate the differences in the educational preparation. The courses that are required by UTA define the knowledge and skills needed for practice in critical care, and Ms. Corlett currently lacks those courses.

- Allowing Ms. Corlett to continue to practice in critical care based on national certification would set a precedent whereby others would have to be approved based on certification alone. Such a precedent that waives the rule requiring formal education specific to both the role and specialty would constitute a significant risk to public safety.

- Board rules are and have been very clear about the requirement for formal education in addition to national certification in an advanced role and specialty. The petitioner had the responsibility to be knowledgeable regarding Board rules.

Pros and Cons:
Pros: Granting permission for Ms. Corlett to continue to practice in critical care would meet the needs of a single individual and her employer. She has practiced in this area for some years without any known incidents and holds national certification in the specialty area.

Cons: Granting Ms. Corlett's request would be a deviation from Board Rules and previous Board actions. Granting this petition would allow this advanced practice nurse to exceed her scope without the formal education to do so. Exceeding one's scope of practice has been the basis for disciplinary action of advanced practice nurses in the past. Although Ms. Corlett and other primary care PNPs have been practicing in critical care settings, it has never been considered within their scope to do so.

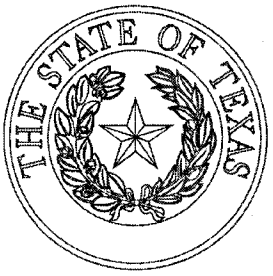
Granting Ms. Corlett's petition would potentially set a new precedent that would have to be followed in the future in that similar requests would likely be presented from individuals at or seeking all levels of licensure. It would put the Board in the position of having to independently review and approve informal educational programs and on the job training activities that will be considered sufficient to allow nurses to exceed the scopes of their licensure/authorization. There are no known criteria short of those required for formal educational programs that can assist the Board in such reviews nor is there any mechanism to assure the public that minimum competencies have been achieved for such programs.

Joint Recommendation of Staff and Petition Review Committee: Move to deny the request for authorization to continue practicing in pediatric critical care without authorization to do so from the board. Staff shall not grant such authorization until Ms. Corlett has completed an acute care pediatric nurse practitioner program and submits an application for authorization to practice in this role and specialty.

List of Attachments for Petition from Karen Corlett

A. *Texas Occupations Code*, § 301.152 (Nursing Practice Act)
B. Current 22 Tex. Admin. Code, § 221.13(b) and Rule 388.06.00.006(a) that was in effect in 1980
C. Letter from J. Zych to J. Wyatt, Executive Director of the Pediatric Nursing Certification Board dated February 22, 2005.
D. 22 Tex. Admin. Code, § 221.7(c).
E. 22 Tex. Admin. Code, § 221.3(c)
F. Letter from Ms. Corlett's employer to J Zych dated October 18, 2006 and Response from J. Zych dated November 29, 2006
G. Information provided by Ms. Corlett in support of the petition.

NURSING PRACTICE ACT, NURSING PEER REVIEW & NURSE LICENSURE COMPACT



TEXAS OCCUPATIONS CODE AND STATUTES REGULATING THE PRACTICE OF NURSING

As Amended September 2005

all personnel transactions are made without regard to race, color, disability, sex, religion, age, or national origin. The policy statement must include:

(1) personnel policies, including policies relating to recruitment, evaluation, selection, application, training, and promotion of personnel that are in compliance with the requirements of Chapter 21, Labor Code;
(2) a comprehensive analysis of the Board workforce that meets federal and state guidelines;
(3) procedures by which a determination can be made of significant under use in the board workforce of all persons for whom federal or state guidelines encourage a more equitable balance; and
(4) reasonable methods to appropriately address those areas of under use.

(b) A policy statement prepared under Subsection (a) must:
(1) cover an annual period;
(2) be updated annually;
(3) be reviewed by the Commission on Human Rights for compliance with Subsection (a)(1); and
(4) be filed with the Governor.

(c) The Governor shall deliver a biennial report to the Legislature based on the information received under Subsection (b). The report may be made separately or as part of other biennial reports to the legislature.

Subchapter D. General Powers and Duties of Board

Sec. 301.151. <u>General Rulemaking Authority.</u>

The Board may adopt and enforce rules consistent with this chapter and necessary to:

(1) perform its duties and conduct proceedings before the Board;

(2) regulate the practice of professional nursing and vocational nursing;

(3) establish standards of professional conduct for license holders under this chapter; and

(4) determine whether an act constitutes the practice of professional nursing or vocational nursing.

Sec. 301.152. <u>Rules Regarding Specialized Training.</u>

(a) In this section, "advanced practice nurse" means a registered nurse approved by the Board to practice as an advanced practice nurse on the basis of completion of an advanced educational program. The term includes a nurse practitioner, nurse midwife, nurse anesthetist, and clinical nurse specialist. The term is synonymous with "advanced nurse practitioner."

(b) The Board shall adopt rules to:
(1) establish:
(A) any specialized education or training, including pharmacology, that a registered nurse must have to carry out a prescription drug order under Section 157.052; and
(B) a system for assigning an identification number to a registered nurse who provides the Board with evidence of completing the specialized education and training requirement under Subdivision (1)(A);
(2) approve a registered nurse as an advanced practice nurse; and
(3) initially approve and biennially renew an advanced practice nurse's authority to carry out or sign a prescription drug order under Chapter 157.

(c) At a minimum, the rules adopted under Subsection (b)(3) must:
(1) require completion of pharmacology and related pathology education for initial approval;
(2) require continuing education in clinical pharmacology and related pathology in addition to any

continuing education otherwise required under Section 301.303; and
(3) provide for the issuance of a prescription authorization number to an advanced practice nurse approved under this section.

(d) The signature of an advanced practice nurse attesting to the provision of a legally authorized service by the advanced practice nurse satisfies any documentation requirement for that service established by a state agency.

Sec. 301.1525. Nurse First Assistants.

[Repealed by Acts 2005 (H.B. 1718), 79th Leg., eff. Sept. 1, 2005. Replaced by Sec. 301.353]

Sec. 301.1526. Certain Nurses Directly Assisting In Surgery.

[Repealed by Acts 2005 (H.B. 1718), 79th Leg., eff. Sept. 1, 2005. Replaced by Sec. 301.353]

Sec. 301.1527. Certain Nurses Directly Assisting In Surgery In Small Hospitals.

[Repealed by Acts 2005 (H.B. 1718), 79th Leg., eff. Sept. 1, 2005. Replaced by Sec. 301.353]

Sec. 301.153. Rules Regarding Advertising and Competitive Bidding.

(a) The Board may not adopt rules restricting advertising or competitive bidding by a person except to prohibit false, misleading, or deceptive practices by the person.

(b) The Board may not include in its rules to prohibit false, misleading, or deceptive practices by a person regulated by the board a rule that:
(1) restricts the person's use of any medium for advertising;
(2) restricts the person's personal appearance or use of the person's voice in an advertisement;
(3) relates to the size or duration of an advertisement by the person; or
(4) restricts the use of a trade name in advertising by the person.

Sec. 301.154. Rules Regarding Delegation of Certain Medical Acts.

(a) The Board may recommend to the Texas State Board of Medical Examiners the adoption of rules relating to the delegation by physicians of medical acts to registered nurses and vocational nurses licensed by the Board. In making a recommendation, the Board may distinguish between nurses on the basis of special training and education.

(b) A recommendation under Subsection (a) shall be treated in the same manner as a petition for the adoption of a rule by an interested party under Chapter 2001, Government Code.

(c) The Board in recommending a rule and the Texas State Board of Medical Examiners in acting on a recommended rule shall, to the extent allowable under state and federal statutes, rules, and regulations, act to enable the state to obtain its fair share of the federal funds available for the delivery of health care in this state.

Sec. 301.155. Fees.

(a) The Board by rule shall establish fees in amounts reasonable and necessary to cover the costs of administering this chapter. The Board may not set a fee that existed on September 1, 1993, in an amount less than the amount of that fee on that date.

(b) The Board may adopt a fee in an amount necessary for a periodic newsletter to produce and disseminate to license holders the information required under Section 301.158.

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BOARD OF NURSE EXAMINERS

FOR THE STATE OF TEXAS

RULES AND REGULATIONS

relating to

NURSE EDUCATION,

LICENSURE AND PRACTICE

Published: May 2006

333 Guadalupe, Suite 3-460, Austin, Texas 78701-3942

§221.13. Core Standards for Advanced Practice.

(a) The advanced practice nurse shall know and conform to the Texas Nursing Practice Act; current board rules, regulations, and standards of professional nursing; and all federal, state, and local laws, rules, and regulations affecting the advanced role and specialty area. When collaborating with other health care providers, the advanced practice nurse shall be accountable for knowledge of the statutes and rules relating to advanced practice nursing and function within the boundaries of the appropriate advanced practice category.

(b) The advanced practice nurse shall practice within the advanced specialty and role appropriate to his/her advanced educational preparation.

(c) The advanced practice nurse acts independently and/or in collaboration with the health team in the observation, assessment, diagnosis, intervention, evaluation, rehabilitation, care and counsel, and health teachings of persons who are ill, injured or infirm or experiencing changes in normal health processes; and in the promotion and maintenance of health or prevention of illness.

(d) When providing medical aspects of care, advanced practice nurses shall utilize mechanisms which provide authority for that care. These mechanisms may include, but are not limited to, Protocols or other written authorization. This shall not be construed as requiring authority for nursing aspects of care.

(1) Protocols or other written authorization shall promote the exercise of professional judgment by the advanced practice nurse commensurate with his/her education and experience. The degree of detail within protocols/policies/practice guidelines/clinical practice privileges may vary in relation to the complexity of the situations covered by such Protocols, the advanced specialty area of practice, the advanced educational preparation of the individual, and the experience level of the individual advanced practice nurse.

(2) Protocols or other written authorization:

(A) should be jointly developed by the advanced practice nurse and the appropriate physician(s),

(B) shall be signed by both the advanced practice nurse and the physician(s),

(C) shall be reviewed and re-signed at least annually,

(D) shall be maintained in the practice setting of the advanced practice nurse, and

(E) shall be made available as necessary to verify authority to provide medical aspects of care.

(e) The advanced practice nurse shall retain professional accountability for advanced practice nursing care.

The provisions of this §221.13 adopted to be effective February 25, 2001, 26 TexReg 1509.

§221.14. Nurse-Midwives Providing Controlled Substances.

(a) In this section "provide" means to supply, for a term not to exceed 48 hours, one or more unit doses of a controlled substance for the immediate needs of a patient;

(b) An advanced practice nurse recognized by the board as a nurse-midwife may provide one or more unit doses of a controlled substance during intra-partum or immediate post-partum care subject to the following conditions:

(1) Physician delegation of authority to provide controlled substances must be made through a physician's order, medical order, standing delegation order, or protocol that requires adequate and documented availability for access to medical care. Delegation may not include the use of a prescription sticker or the use or issuance of an official prescription form under §481.075, Health and Safety Code;

(2) The nurse-midwife's protocols or other orders must require the reporting of or monitoring of each patient's progress, including complications of pregnancy and delivery and the administration and provision of controlled substances to the patient;

(3) delegation is limited to three full-time equivalent nurse-midwives at the designated facility where the nurse-midwife practices; and

(4) the controlled substance must be supplied in a suitable container that is labeled in compliance with the applicable drug laws and must include:

(A) the patient's name and address;

(B) the drug to be provided;

(C) the name, address, and telephone number of the physician;

(D) the name, address, and telephone number of the nurse-midwife; and

RULES AND REGULATIONS

RELATING TO

PROFESSIONAL NURSE EDUCATION, LICENSURE AND PRACTICE

1988 REVISION

BOARD OF NURSE EXAMINERS

FOR

THE STATE OF TEXAS

Board of Nurse Examiners
For The State of Texas
510 South Congress, Suite 216
Austin, Texas 78704

BOARD OF NURSE EXAMINERS
FOR THE STATE OF TEXAS

RULES AND REGULATIONS

RELATING TO

PROFESSIONAL NURSE EDUCATION, LICENSURE AND PRACTICE

REVISED 1980

.003. Categories. Registered professional nurses holding themselves out to be advanced nurse practitioners may include but not be limited to the following:

(1) nurse anesthetist,

(2) nurse midwife,

(3) nurse practitioner,

(4) clinical nurse specialist,

(5) other titles as approved by the board.

.004. Credentialing.

(a) The registered nurse who practices as an advanced nurse practitioner shall submit to the board such evidence as is necessary to insure compliance with Rules .002 and .004.

(b) Evidence to be submitted to the board may include but is not limited to the following:

(1) current registration as a registered nurse in the State of Texas;

(2) transcript from post-basic program of study;

(3) evidence of certification in the area of practice by a national or state organization approved by the board; and

(4) name and address of consulting physician(s), if applicable.

(c) After review by the board, notification of acceptability of credentials shall be sent to the advanced nurse practitioner.

(d) Only those registered professional nurses whose credentials have been approved by the board may hold themselves out to be advanced nurse practitioners and/or use titles to imply that they are advanced nurse practitioners.

.005. Identification. The advanced nurse practitioner should wear a name tag which identifies her or him as a registered nurse and the appropriate area of practice (i.e., family nurse practitioner, nurse midwife, pediatric nurse clinician, etc.).

.006. Functions.

(a) Each advanced nurse practitioner shall practice in an area appropriate to her or his post-basic educational preparation.

(b) The advanced nurse practitioner may act independently or in

collaboration with the health team in the maintenance of mental and physical health; in the prevention of illness; in management, observation, and counsel of the ill and injured; or in supervision and teaching of nursing.

(c) Functions of the advanced nurse practitioner shall be clearly delineated by a written statement of policies which include standard and emergency procedures.

(1) Advanced nurse practitioners who manage the medical aspects of care must have written policies jointly developed by the nurse practitioner and consulting physician(s) and signed by both the nurse and the physician(s). These policies shall be reviewed at least annually.

(2) The scope and detail of said policies may vary in relation to the complexity of the situations covered and the area of practice and educational preparation of the individual advanced nurse practitioner.

(d) Within the limitations of her or his educational preparation and within written statements of policy, an advanced nurse practitioner may:

(1) assess the physical and/or mental health status of individuals through:

(A) eliciting and recording complete health and social histories and recording the results thereof,

(B) performing physical examination, and

(C) performing simple laboratory tests necessary to ascertain health status;

(2) interpret information collected in a health assessment;

(3) formulate and initiate a health care plan;

(4) recommend nonprescriptive measures for relief of symptoms;

(5) refer deviations from normal to the appropriate health care professional;

(6) provide health education;

(7) initiate and maintain health records;

(8) evaluate health care provided and modify as needed;

(9) work collegially with other health care professionals and agencies to provide and, where appropriate, coordinate services to individuals, families, and groups; and

(10) perform medical functions delegated by and done under the control and supervision of a physician licensed by the Texas State Board of Medical Examiners.

(e) Functions of the advanced nurse practitioner must be within the

Board of Nurse Examiners For the State of Texas

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Katherine A. Thomas, MN, RN
Executive Director

22 February 2005

Janet S. Wyatt, PhD, RN, CRNP
Executive Director
Pediatric Nurse Certification Board
800 South Frederick Avenue, Suite 104
Gaithersburg, MD 20877-4150

Dear Dr. Wyatt:

Staff of the Board of Nurse Examiners for the State of Texas (board) has received a copy of the Winter 2005 edition of the *PNCB News for Educators*. The purpose of this letter is to advise you of staff's concern regarding certain information contained in that newsletter and also to serve as a request for additional information.

In the first section of the newsletter that introduces the new acute care pediatric nurse practitioner exam, there is a statement indicating that all state boards of nursing recognize this examination. Board staff wishes to clarify that this examination has not been reviewed by the Board and, therefore, may not be considered a Board-recognized examination in the State of Texas. Board staff does not have authority to accept as meeting the certification requirement any certification examinations that have not been reviewed and recognized by the Board. Any newly developed examination must be reviewed based on the "Criteria for Evaluation of National Certification Examinations for Recognition from the Board of Nurse Examiners" that was adopted by the Board in October 2003. A copy of these criteria is enclosed for your review.

Although the Board accepts the PNCB's primary care pediatric nurse practitioner examination, previous acceptance of an examination/certification process does not "transfer" to newly developed examinations. The new examination is specifically targeted for pediatric nurse practitioners in the acute care setting. Therefore, this examination must be considered a new examination and must be reviewed using the criteria approved by the Board. The acute care pediatric nurse practitioner examination must be reviewed, and the Board must vote to recognize the examination during a regularly scheduled Board meeting before staff is authorized to accept this certification process as meeting the requirements for authorization to practice as an acute care pediatric nurse practitioner in the State of Texas.

If the PNCB wishes to have the acute care pediatric nurse practitioner examination reviewed for possible recognition by the Board, please provide the information outlined on the enclosed checklist so that the information may be reviewed using the criteria approved by the Board. Once staff's review is complete, the examination and results of the review will be provided to the Board for a determination of acceptability during a regularly scheduled Board meeting. A representative of PNCB may attend that meeting and address the Board at that time if the organization wishes to do so.

There is another statement in that same section of the newsletter that is also concerning to board staff because it is an inaccurate interpretation of the regulatory requirement in Texas. The final paragraph of that section of the newsletter states the following:

Members of the Board

Joyce Adams, PhD, RN, Houston; Thomas Barton, MSN, RN, Pampa; Deborah Bell, CLU, ChFC, Abilene; Virginia Campbell, BSN, RN, CNOR, Mesquite; Blanca Rosa Garcia, PhD, RN, Corpus Christi; Richard Gibbs, LVN, Mesquite; Rachel Gomez, LVN, Harlingen; Brenda Jackson, PhD, RN, San Antonio; Beverley Jean Nutall, LVN, Bryan; Anita Palmer, ME, MA, Olney; Phyllis Rawley, CPC, *Vice-President*; Linda Rounds, PhD, FNP, RN, *President*; Frank Sandoval, Jr., J.D., San Antonio

> *In response to growing specialization in advanced practice nursing, NCSBN encourages the linkage of certification requirements to the appropriate nurse practitioner role and scope of practice. Many states, including Texas, now ask all PNPs working in acute care settings to hold active certification for this role.*

Board staff wishes to advise you that the last sentence does not reflect the regulatory requirement as it appears in 22 Tex. Admin. Code, Sec. 221.4. The rule requires that advanced practice nurses hold national certification in the advanced practice role and specialty in which the board has authorized them to practice. Section 301.152 of the Nursing Practice Act (*Texas Occupations Code*) states that the board may approve advanced practice nurses on the basis of completion of an advanced educational program. Therefore, the board grants advanced practice nurses authorization to practice as and use titles that accurately reflect their advanced educational preparation, not their practice setting. Likewise, the rule requires that advanced practice nurses obtain national certification in the advanced role and specialty that is congruent with their advanced educational preparation rather than their practice settings. It is incorrect to state that Texas asks all pediatric nurse practitioners working in acute care settings to hold active certification for this role as the board has never issued such a statement nor does this appear as a requirement in board rule. Additionally, this statement is misleading in that pediatric nurse practitioners who have been educated and recognized by the board in primary care roles may infer that they may sit for this certification examination and hold themselves out as acute care pediatric nurse practitioners. Such individuals are not eligible for authorization to practice as or use the acute care pediatric nurse practitioner title in the State of Texas. Furthermore, advanced practice nurses have been disciplined by the board when their practice exceeded the scope of the role and specialty for which they were educated and held authorization to practice.

Thank you for your time and cooperation in this matter. Staff appreciates this opportunity to share concerns regarding information provided to advanced practice nurse educators in the Winter 2005 edition of the *PNCB News for Educators*. Staff wishes to work with the PNCB toward possible future recognition of the acute care pediatric nurse practitioner certification examination in the State of Texas. Should you have questions regarding the review process or the regulatory requirements for advanced practice nurses in the State of Texas, you may contact me by telephone at (512) 305-6845 or by e-mail at jolene.zych@bne.state.tx.us during regular business hours.

Sincerely,

Jolene Zych, MS, RNC, WHNP
Nursing Consultant–Advanced Practice

cc: Linda Rounds, PhD, RN, President, Board of Nurse Examiners for the State of Texas
Katherine Thomas, MN, RN, Executive Director, Board of Nurse Examiners for the State of Texas and co-chair, APRN Task Force, National Council of State Boards of Nursing
Nancy Chornick, PhD, RN, CAE, Director of Credentialing, National Council of State Boards of Nursing

BOARD OF NURSE EXAMINERS

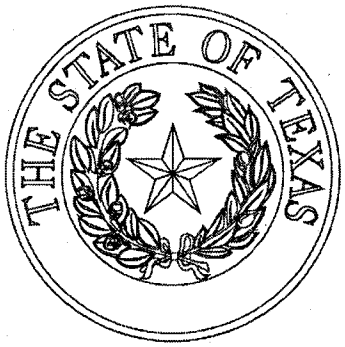
FOR THE STATE OF TEXAS

RULES AND REGULATIONS

relating to

NURSE EDUCATION,

LICENSURE AND PRACTICE



Published: May 2006

333 Guadalupe, Suite 3-460, Austin, Texas 78701-3942

§221.6. Interim Approval.

(a) Interim approval may be granted by the board pending completion of the application process for a period not to exceed 90 days. Extensions of the interim approval period shall not be granted.

(1) The registered nurse seeking interim approval as an advanced practice nurse must complete documentation provided by the board verifying that he/she meets all requirements of this chapter and has completed and mailed the appropriate documents to the educational program or organization for completion.

(2) A letter shall be issued by the board granting interim approval.

(3) An applicant is eligible for interim approval one time only per specialty and role.

(b) An applicant who submits a request for waiver from the requirements of the rules as set forth in §221.4 (relating to Full Authorization to Practice) and §221.5 (relating to Provisional Authorization) of this chapter shall not be eligible for interim approval.

(c) If an applicant is deemed ineligible for advanced practice authorization, the interim approval will be rescinded immediately, effective on the date the notice is sent by mail. The applicant must cease holding him/herself out as or using titles to imply that he/she is an advanced practice nurse.

The provisions of this §221.6 adopted to be effective February 25, 2001, 26 TexReg 1509.

§221.7. Petitions for Waiver and Exemptions.

(a) A registered nurse who submits a request for waiver from requirements of the rules must submit documentation as required by the board to support his or her petition and assure the board that he or she possesses the knowledge, skills and abilities appropriate for the role and specialty desired. Those petitioners who are under investigation or current board order are not eligible for waiver.

(b) Petitions for waiver from the program accreditation requirements of §221.3 of this chapter (relating to Education), may be granted by the board for individuals who completed their educational programs on or before December 31, 1996. Petitioners must meet the length of academic program requirements of §221.3 of this chapter and obtain national certification in the advanced role and specialty area.

(c) Petitions for waiver from the current certification requirements of §221.4 of this chapter (relating to Requirements for Full Authorization to Practice) and §221.8 of this chapter (relating to Maintaining Active Authorization as an Advanced Practice Nurse) may be granted by the board.

(1) Under this section, only those petitioners for which no national certification examination within the advanced role and specialty or a related advanced specialty exists will be considered for waiver by the board.

(2) The board may determine that an available national certification examination in a related specialty and/or role must be taken in lieu of an examination specific to the advanced specialty area.

(d) Waivers from the master's degree requirement will be granted to qualified certificate-prepared nurse-midwives and women's health care nurse practitioners who complete their programs on or after January 1, 2003 through December 31, 2006. Applicants must meet all other requirements as stated in §221.4 of this chapter.

(1) Those individuals approved on the basis of this waiver shall be limited to providing advanced practice nursing care within the geographical boundaries of the State of Texas. This shall not prevent the individual from utilizing Nurse Licensure Compact privileges to function as a registered nurse.

(2) The applicant must submit all required documentation necessary to demonstrate that the requirements (except for the master's degree) for authorization to practice have been met.

(3) The applicant must submit a written request for waiver of the master's degree requirement.

(4) Interim, provisional or full authorization may be granted to qualified certificate-prepared nurse-midwives and women's health care nurse practitioners.

(e) Exemptions granting authorization to utilize titles not authorized by §221.2 of this chapter may be granted to qualified applicants who complete their advanced educational programs prior to January 1, 2010. Applicants must meet all other requirements as stated in §221.4 of this chapter,

(1) The following specialty titles may be considered for exemption if the individual is not qualified for authorization to utilize a title authorized by §221.2 of this chapter:

(A) Acute Care Clinical Nurse Specialist,

Agenda Item: 7.2
Attachment E

BOARD OF NURSE EXAMINERS

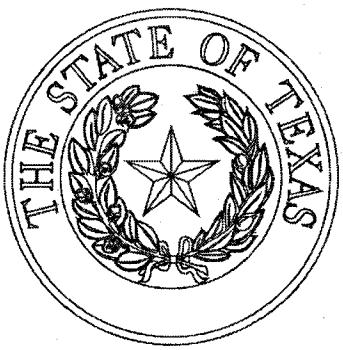
FOR THE STATE OF TEXAS

RULES AND REGULATIONS

relating to

NURSE EDUCATION,

LICENSURE AND PRACTICE



Published: May 2006

333 Guadalupe, Suite 3-460, Austin, Texas 78701-3942

§221.3. Education.

(a) In order to be eligible to apply for authorization as an advanced practice nurse, the registered nurse must have completed a post-basic advanced educational program of study appropriate for practice in an advanced nursing specialty and role recognized by the Board. RN to BSN programs shall not be considered post-basic programs for the purpose of this rule.

(b) Individuals prepared in more than one advanced practice role and/or specialty (including blended role or dual specialty programs) shall be considered to have completed separate advanced educational programs of study for each role and/or specialty area.

(c) Applicants for authorization to practice in an advanced role and specialty recognized by the Board must submit verification of completion of all requirements of an advanced educational program that meets the following criteria:

(1) Advanced educational programs in the State of Texas shall be approved by the Board or accredited by a national accrediting body recognized by the Board.

(2) Programs in states other than Texas shall be accredited by a national accrediting body recognized by the board or by the appropriate licensing body in that state. A state licensing body's accreditation process must meet or exceed the requirements of accrediting bodies specified in board policy.

(3) Programs of study shall be at least one academic year in length and shall include a formal preceptorship.

(4) Beginning January 1, 2003, the program of study shall be at the graduate degree level.

(5) Applicants prepared in more than one advanced practice role and/or specialty shall demonstrate that all curricular requirements set forth in this subsection have been met for each role and/or specialty.

(d) Applicants for authorization as clinical nurse specialists must submit verification of the following requirements in addition to those specified in subsection (c) of this section:

(1) completion of a master's degree in the discipline of nursing, and

(2) completion of a minimum of nine semester credit hours or the equivalent in a specific clinical major. Clinical major courses must include didactic content and offer clinical experiences in a specific clinical specialty/practice area.

(e) Those applicants who completed nurse practitioner or clinical nurse specialist programs on or after January 1, 1998 must demonstrate evidence of completion of the following curricular requirements:

(1) separate, dedicated courses in pharmacotherapeutics, advanced assessment and pathophysiology and/or psychopathology (psychopathology accepted for advanced practice nurses prepared in the psychiatric/ mental health specialty only). These must be graduate level academic courses;

(2) evidence of theoretical and clinical role preparation;

(3) evidence of clinical major courses in the specialty area; and

(4) evidence of a practicum/preceptorship/internship to integrate clinical experiences as reflected in essential content and the clinical major courses.

(5) In this subsection, the following terms have the following definitions:

(A) Advanced Assessment Course means a course that offers content supported by related clinical experience such that students gain the knowledge and skills needed to perform comprehensive assessments to acquire data, make diagnoses of health status and formulate effective clinical management plans.

(B) Pharmacotherapeutics means a course that offers content in pharmacokinetics and pharmacodynamics, pharmacology of current/commonly used medications, and the application of drug therapy to the treatment of disease and/or the promotion of health.

(C) Pathophysiology means a course that offers content that provides a comprehensive, system-focused pathology course that provides students with the knowledge and skills to analyze the relationship between normal physiology and pathological phenomena produced by altered states across the life span.

October 18, 2006

Jolene Zych, MS, RNC, WHNP
Board of Nurse Examiners for the State of Texas
Nursing Consultant - Advanced Practice
333 Guadalupe #3-460
Austin, Texas 78701
JOLENE.ZYCH@BNE.STATE.TX.US

Dear Ms. Zych,

I am the Director of Advanced Practice Services at Children's Medical Center Dallas. In my role, I oversee all of the Advanced Practice Nurses that practice in the various subspecialties here at Children's. One of those areas is the Pediatric Critical Care Service.

We currently employ 16 full time Advanced Practice Nurses in the Critical Care Service. These nurse practitioners practice in either the Cardiovascular ICU or in the Trauma/Neuro ICU. Of the 16 nurse practitioners here at Children's in critical care, 14 of them have either completed a Master's degree to prepare them as an acute care Pediatric Nurse Practitioner (ACPNP) or have completed a Pediatric Critical Care Nurse Practitioner Master's program.

As you may know, Children's is the principal pediatric teaching hospital for the University of Texas Southwestern Medical School. Subsequently the nurse practitioner's function here in a completely supervised medical education model where they examine patients, develop a plan of care, write a daily progress note and then present their patients during daily rounds to the Attending Physician. The Attending Physician then repeats the physical exam and either concurs or alters the plan of care developed by the nurse practitioner. The nurse practitioners do not bill for their services – all billing is via the UT Southwestern Attending Physician. This is a unit with only faculty physicians, fellows, and nurse practitioners. There are no pediatric residents.

The Attending Physician is physically present on the unit daily and then is immediately available via phone 24 hours per day, 7 days per week for any issues or questions. During times that the Attending Physician is not physically present, a pediatric intensivist Fellow is physically present on the unit to supervise the nurse practitioners 24 hours per day, 7 days per week.

The Critical Care Nurse Practitioners also have a Pediatric Intensivist, Dr. Maeve Sheehan, who serves as their Medical Director. She oversees their yearly skills day for validation of their proficiency with skills required to perform their role. She also provides a twice-monthly rounding session where she discusses interesting cases to supplement their knowledge of pediatric critical care medicine. The Pediatric Critical Care service also has weekly didactic lecture session providing educational information regarding the medical management of common pediatric critical care issues.

I am aware of the recent communications between 4 of our nurse practitioners with your staff at the Board of Nurse Examiners for the State of Texas (BNE). My first concern was the

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graduates of the University of Texas at Arlington School of Nursing's Acute Care PNP post Master's certificate program in August of 2003 and August of 2004. Those nurse practitioners included Allison Paige Clancy, Theresa Gray Rashdan, Kristin Milota, and Lisa Thompson. Thank you for your guidance in relation to outlining the steps required for getting them to the point of achieving recognition from the BNE as ACPNPs.

We have in the interim adjusted our staffing schedule so that only BNE recognized ACPNPs are covering the critical care service here at Children's, however this has created a strain on those ACPNP's recognized by the BNE, as well as limiting our critical care bed capacity with the winter cold, RSV, and Flu season approaching – historically a time of tremendous shortage of pediatric critical care beds in the Dallas area. In short, limiting the practice of these 3 nurse practitioners is having a negative impact on the care of pediatric patient's here at Children's Medical Center of Dallas.

My second concern is that 2 of our current nurse practitioners (employed for their expertise in pediatric ICUs) have not yet completed their Acute Care PNP post Master's certificate program. Both of these Nurse Practitioners are Primary Care educated and certified PNPs who have extensive experience functioning in the nurse practitioner role in critical care. However, we have currently suspended their practice in the critical care areas at Children's.

In fact, one of these individuals has:

- Nine years of experience as a Pediatric Nurse Practitioner in pediatric cardiovascular ICU nursing.
- In 2005 wrote a book chapter titled "Cardiovascular Disorders" in Richardson, V.E., *Practice Guidelines for Pediatric Nurse Practitioners*. Elsevier Publishing, 2005.
- Completed the PNCB's ACPNP examination in 2005 – scoring the highest of all who took the examination in 2005 and was recognized at the annual NAPNAP conference this year for her achievement.

She is beginning the Acute Care PNP post Master's certificate program at the University of Texas at Arlington in January 2007.

The other primary care PNP who has been practicing in critical care here at Children's is a current student of the Acute Care PNP post Master's certificate program at the University of Texas at Arlington with an expected graduation date of May 2007. She too has extensive pediatric critical care experience as both a registered nurse and as a pediatric nurse practitioner.

My request for these two individuals: Is there a process for them to request a waiver to have temporary recognition to continue their practice pending the successful completion of their Acute Care PNP post Master's certificate program?

Here at Children's we are committed to promoting the ACPNP role by financially supporting NPs who want to go back for the post-masters ACPNP education. Additionally we have worked diligently to restrict practice in critical care to only those individuals with prior experience or training as a pediatric nurse practitioner in critical care or acute care pediatrics. However, as you are aware, there is only one ACPNP education program in the State of Texas and the pool of available candidates is very small. Despite this limited pool of candidates, the number of

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children requiring critical care services is growing steadily. Here at Children's we have made a commitment to the community to provide care to children in need despite the ability to pay for these services, however our ability to provide this service hinges on our ability to safely staff critical care beds.

Other factor's influencing the growth of nurse practitioner roles in our institution is the limited number of subspecialty physicians and the Accreditation Council for Graduate Medical Education resident work hour restrictions. An area of particular need is that of the pediatric Cardiovascular ICU. There are very few subspecialty physicians available for a very specialized practice area such as this. The loss of a nurse practitioner with extensive knowledge and experience in this subspecialty as a nurse practitioner would be extremely detrimental to patient care.

My final area of concern is that of other areas of practice for nurse practitioner's here at Children's that may or may not be deemed acute care. We have 100 nurse practitioners in approximately 30 subspecialty areas here at Children's. As mentioned, we have been encouraging our nurse practitioner's to return to school for their Acute Care PNP post Master's certificate program (with financial assistance for tuition fees and time off for attending classroom activities). However, once again, the current pool of available candidates to meet the growing need for services is very small.

It has been common practice across the State of Texas to employe Primary Care educated and certified nurse practitioners in pediatric critical care areas. This is not an issue that is unique to Children's Medical Center of Dallas. My personal desire is to avoid another crisis such as the recent event where 5 of our Nurse Practitioner have been suddenly unable to practice in critical care. I am sure a similar crisis would occur in Houston, Fort Worth, Austin, and San Antonio if they became aware of the BNE's stance regarding NP practice in critical care by Primary Care educated and certified PNPs with years of critical care experience. Therefore this is an issue that the Texas BNE must quickly address.

Clear, unambiguous direction from the BNE would be very helpful and might include:

- A definition or set of criteria one could use to determine if the practice setting is considered acute care or primary care in scope.
- A deadline for when all nurse practitioners that practice in those areas defined by the above required criteria as acute care must have both the Acute Care PNP post Master's certificate program completed and successful completion of the PNCB's ACPNP examination.
- An interim plan for allowing primary care educated and certified PNPs to continue practicing in their current area of specialty before the imposed deadline mentioned above in the second bullet point (certainly aside from critical care areas).

A sudden requirement for Acute Care PNP education and certification in other clinical areas that are hospital based would certainly create a health care crisis for us here in Dallas – and likely also in pediatric institutions across the state.

I appreciate your thoughtful consideration of my requests and comments. Our utmost concern is providing safe care to our patients and their families while following the guidelines and rules imposed by the Texas BNE.

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I would also like to invite you to visit Children's for a day to tour our facility, spend time with our nurse practitioner's in their current roles, and to discuss our approach to all areas of practice here at Children's in terms of the need for Acute Care PNP vs. Primary Care PNP education and certification. As an alternative, Maeve Sheehan (the Critical Care Nurse Practitioner Medical Director) and I could visit your office provide additional information regarding nurse practitioner practice here at Children's Medical Center of Dallas.

Respectfully,

Joe Don Cavender, RN, CPNP-PC

Joe Don Cavender, MSN, RN, CPNP-PC
Director; Advanced Practice Services
Children's Medical Center Dallas
1935 Motor Street
Dallas, Texas 75235
214-456-2331
joe.cavender@childrens.com

CC:
Katherine Thomas, MN, RN – Executive Director of the Board of Nurse Examiners for the State of Texas.

Mary Stowe, MSN, RN – Interim Chief Nursing Officer, Children's Medical Center Dallas

Board of Nurse Examiners For the State of Texas

Location Address: William P. Hobby Building, Ste. 3-460, 333 Guadalupe Street, Austin, Texas 78701
Phone: (512) 305-7400 Fax: (512) 305-7401 Web: www.bne.state.tx.us

Katherine A. Thomas, MN, RN
Executive Director

29 November 2006

Joe Don Cavender, MSN, RN, CPNP–PC
Director, Advanced Practice Services
Children's Medical Center Dallas
1935 Motor Street
Dallas, TX 75235

Dear Mr. Cavender:

This letter is in response to your letter of October 18, 2006 regarding advanced practice nurses practicing in the pediatric critical care service at Children's Medical Center Dallas (Children's). You inquired regarding the differentiation of acute care and primary care pediatric nurse practitioner services and requested that the Board provide an "interim plan" for primary care educated and certified pediatric nurse practitioners (PNP) to continue to practice in their current areas of specialty.

The Advanced Practice Nursing Liaison Committee (liaison committee) is composed of three members of the Board of Nurse Examiners (BNE, Board). Your letter was provided to the liaison committee for review and this response is provided based upon their comments and opinions.

Section 301.152 of the Nursing Practice Act (*Texas Occupations Code*) states that advanced practice nurses in the state of Texas, including PNPs, are authorized to practice in a specific advanced role and specialty area based on completing an advanced practice nursing educational program that is acceptable to the Board. Therefore, their scope of practice is founded first and foremost upon their advanced practice nursing educational preparation, and they are required to practice in the role and specialty that is appropriate to their educational preparation [22 Tex. Admin. Code, Sec. 221.13(b)].

The requirement for advanced practice nurses to practice in the role and specialty appropriate to their advanced practice nursing educational preparation has been included in BNE Rule for more than twenty-five years and has been consistently enforced. Therefore, the liaison committee members and staff would respectfully disagree that this is a change in policy. PNPs who were educated in a program that prepares them to provide primary care to pediatric patients have consistently been advised by board staff that practice in critical care settings is beyond their scope when they have contacted the board office to inquire whether such services are within their scopes of practice to provide. This is consistent with the responses given to adult and family nurse practitioners who inquire regarding practicing in adult critical care settings.

Like the adult and family nurse practitioner roles, the PNP role has historically provided educational preparation targeted for care of patients in primary care settings. In general, the Board has viewed the primary care prepared PNP's role in the acute care setting as more limited than that of the acute care pediatric nurse practitioner (ACPNP). It is not considered to be equivalent to that of an ACPNP in the acute care setting. Primary care PNP educational preparation generally includes well-child care as well as prevention and management of commonly occurring pediatric acute illnesses and chronic conditions. Although there may be some overlap between the primary and acute care PNPs and there may be services that the primary care-prepared PNP may provide in an inpatient setting, this does not mean their scopes of practice are identical.

Members of the Board

Joyce Adams, PhD, RN, Houston; Deborah Bell, CLU, ChFC, Abilene; George Buchenau, Jr., BSN, RN, MBA, Amarillo; Virginia Campbell, BSN, RN, CNOR, Mesquite; Blanca Rosa Garcia, PhD, RN, Corpus Christi; Richard Gibbs, LVN, Mesquite; Rachel Gomez, LVN, Harlingen; Brenda Jackson, PhD, RN, San Antonio; Beverley Jean Nutall, LVN, Bryan; Anita Palmer, ME, MA, Olney; Phyllis Rawley, CPC, *Vice-President*; Linda Rounds, PhD, FNP, RN, *President*; Frank Sandoval, Jr., J.D., San Antonio

Primary care PNP educational preparation does not generally include significant content related to medical diagnosis and management of critically ill children.

The Guidelines for Determining APN Scope of Practice that were adopted by the Board in October 2005 further elaborate on the concept of expanding one's scope of practice.

> *. . . . there are finite limits to expansion of scope of practice without completing additional formal education. Advanced practice nurses cannot change their legally recognized titles or designations through experience or continuing education; these changes may only be achieved through additional formal educational preparation and meeting all legal requirements to use that title and practice in that specialty set forth by the BNE.*
>
> *The following questions may help to clarify whether a new activity/procedure can be incorporated into an individual's scope of practice:*
>
> *Is it consistent with one's professional scope of practice?*
> *Is it consistent with statutory or regulatory laws?*
> *Is it consistent with one's education in the role and specialty?*
> *Is it consistent with the scope of one's recognized title or does it evolve into another advanced practice title recognized by the board requiring additional formal education and legal recognition?*

Staff recognizes this is a difficult issue because of the way the advanced practice roles and specialties have evolved over time. However, the first individual who received recognition as an acute care PNP in the State of Texas completed her advanced practice educational program in this specialty in the spring of 1997 and received full authorization to practice as an acute care PNP in 1998. This title has been recognized ever since that time. Prior to the Board's recognition of the acute care PNP examination in July 2005, individuals who completed such programs completed 1000 hours of supervised practice post graduation to obtain their recognition in this role and specialty. The aforementioned acute care PNP would have been required to complete the supervised practice hours to obtain full authorization to practice.

The acute care PNP title was recognized by the Board long before its 2005 revisions to the rules relating to advanced practice titles. After more than a year of discussion on this issue, the Board limited the titles it recognizes to only those titles with the broadest educational foundation for practice and a corresponding certification examination. The acute care PNP role and specialty was considered one of the titles with a broad educational foundation and, therefore, continues to be recognized as an advanced practice title in Texas based on both formal educational preparation and national certification.

In regard to primary care PNPs continuing to work in critical care settings until they complete their acute care PNP educational programs, it is not consistent with the Nursing Practice Act and BNE rules to grant approval to practice prior to program completion. In the past, similar requests have been submitted as petitions to the Board and all were unsuccessful. The most recent request was considered by the Board in July 2006. A clinical nurse specialist in psychiatric/mental health nursing did not meet the curricular requirements for prescriptive authority in Texas, although he previously held prescriptive authority in another jurisdiction and had more than fifteen years of experience in his role and specialty. He requested that the Board grant him prescriptive authority, allowing him to prescribe medications during the time he was completing the required academic courses. The Board unanimously denied his request. The individuals you referenced in your letter may petition the Board if they wish to do so and may contact me for further information regarding the petition process.

As an interim measure while primary care PNPs complete the acute care PNP program, you may wish to consider the possibility of providing direct supervision of these PNPs under physicians or other acute care

PNPs or critical care PNPs. Rule 217.1(10) defines direct supervision as requiring another nurse (or, in this case, acute care PNP or physician) immediately available to coordinate, direct, and observe at firsthand another individual for whom the nurse is responsible. In the case of the primary care PNPs practicing in critical care settings the physician or appropriately authorized advanced practice nurse who agrees to provide direct supervision must:

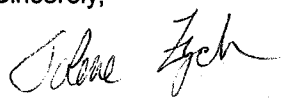
- Participate in the assessment, management, and follow-up of each patient and document such participation in the patient record,
- Remain physically present on the unit and immediately available to the primary care PNP **at all times**,
- Review and sign all patient records, and
- Authorize/Issue all patient care orders. Orders may not originate with the primary care PNP.

In regard to your request for a definitive list of criteria for determining whether a practice setting is considered within the acute care or primary care scope, staff cannot provide this to you as there are many situational factors that must be considered. For example, the average patient acuity on one unit in one pediatric facility may be very different on the same unit in a different pediatric facility. Likewise, patients themselves and their responses to treatments and procedures will vary. It is impossible to predict when and if a patient's actual response will vary from the intended response. One patient may well be within the scope of a primary care PNP one day, and beyond the primary care PNP's scope one day–or even one hour later. Yet a third factor is the variation in individual primary care PNP educational programs. It is important to consider that the 'clear, unambiguous direction" you believe might be helpful would prove to be even more restrictive to advanced practice nurses than the position the board has maintained for many years.

Staff recognizes that this is a difficult issue for both the facility and the PNPs that are affected. But it is important to keep in mind that authorization to practice as an advanced practice nurse in any role and specialty from the Board of Nurse Examiners provides the public with assurance that certain minimum criteria have been met and all individuals who are authorized to practice in a particular area have the same core educational preparation in the specialty in which they practice.

Thank you for your time and cooperation in this matter. Please be advised that this response to your inquiry is not a "position statement" or "advisory opinion" of the Board or the Advanced Practice Liaison Committee; rather, this is an opinion from board staff based solely on representations made in your letter dated October 18, 2006.

Sincerely,



Jolene Zych, MS, RNC, WHNP
Nurse Consultant–Advanced Practice

cc: Linda Rounds, PhD, RN, FNP, President, Board of Nurse Examiners
Katherine Thomas, MN, RN, Executive Director, Board of Nurse Examiners

The remaining documents are Attachment G. Ms. Corlett provided the documents in a 3-ring binder with colored tabs between each section. The tabs have been photocopied in order to clarify where one section ends and a new section begins. The original documents will be available at the Board meeting.

KAREN CORLETT RN, MSN, CPNP
4210 TOMBERRA WAY
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EMAIL:KAREN.CORLETT@CHILDRENS.COM
PHONE:214-353-9585 OR 817-602-2396

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November 16, 2006

RECEIVED
NOV 21 2006
By

Jolene Zych, MS, RNC, WHNP
Advanced Practice Consultant
Texas Board of Nurse Examiners
333 Guadalupe #3-460
Austin, TX 78701

Dear Jolene Zych and Members of the Board:

I am writing to request a waiver to the Board's rules 221.12, 221.13b and 221.3 as they pertain to scope of practice and educational preparation for advanced practice nurses.

I am a primary care educated pediatric nurse practitioner who has practiced in pediatric critical care since graduation from my master's PNP program in 1997. As you can see by the accompanying letters, I am respected for my professionalism, knowledge base, assessment skills and clinical decision making. I lecture in the pediatric acute care nurse practitioner program at the University of Texas at Arlington, and will be doing so for the program at Rush University in January. I have been a clinical preceptor for many pediatric acute care and critical care nurse practitioner students from programs across the country. As the first nurse practitioner in the cardiac intensive care unit at Children's Medical Center of Dallas, I have been a leader for the program, have worked actively to recruit and promote the service, and have oriented 7 novice acute and critical care PNP's to the role of the nurse practitioner in the cardiac ICU. I was an advocate for the development of the acute care pediatric nurse practitioner exam, and successfully took it in 2005, achieving the highest score in the country for that year. On review of my curriculum vitae, I think you will see that I have a wealth of pediatric experience as both an RN and APN, that I contribute to my field, and share my knowledge with my colleagues.

Recently, we have been informed that pediatric nurse practitioners practicing in critical care must have completed an acute care pediatric nurse practitioner program as well as having the acute care PNP certification. Some consider this quite clear on the website, but to me, what was clear was that I could not call myself an AC-PNP and I have been careful to not use that title. I identify myself as a pediatric nurse practitioner, I was educated as a PNP, and I practice as a PNP – in a critical care area. When I entered my PNP program in 1994, there were no acute care PNP programs in existence. As I now know, at that time there were 2 geographically distant critical care PNP programs in existence. All of the PNP's working in acute and critical care areas that I had as mentors were primary care educated, with clinical backgrounds in their current work areas. As you may know, PNP's entered specialty care areas early on in the PNP experience, most having graduated from primary care programs. When I began my PNP career in the pediatric ICU, there was a program of study developed by the pediatric intensivists and myself consisting of a curriculum of primarily journal articles and dedicated teaching sessions with one of the intensivists to discuss content 1-2 times per week.

While I do not disagree with the Board's efforts to optimize educational preparation for those entering into the pediatric acute care nurse practitioner arena, I do think there should be some option for those of us who have significant practice experience, and entered into practice when there were fewer educational programs. As

of November 2006, there are still only 12 programs nationwide that meet the requirements for individuals to sit for the Pediatric Nursing Certification Board's acute care pediatric nurse practitioner certification exam.

I am willing to advance my formal education, and have plans to enter an acute care pediatric nurse practitioner post master's certificate program in January of 2007. However, I would like the Board to grant permission for me to practice as an APN in the pediatric critical care arena under my current PNP license until my education is complete and I am able to be formally recognized as an acute care pediatric nurse practitioner by the Board of Nurse Examiners for the State of Texas.

Thank you for your time and attention to this request

Sincerely,

Karen Corlett

Karen Corlett RN, MSN, CPNP

Additional points I would like to have considered in my appeal to be allowed to practice as a pediatric nurse practitioner in a critical care area

-I have nearly 20,000 practice hours as a pediatric nurse practitioner in pediatric critical care.

-When I began my PNP program in 1994, there were no acute care pediatric nurse practitioner educational programs available.

-In my Pediatric Nurse Practitioner program, I spent clinical rotations with a pediatric cardiologist. Many of my papers and projects dealt with acute and critical care topics. During this era, it was up to PNP students to self tailor their educational experiences for their anticipated practice area, within the limits of the program.

-Upon starting my job in the PICU as a PNP, a curriculum was developed to ensure and advance my knowledge of pediatric critical care. I have attached the curriculum developed and provided you with copies of the articles we gathered for this endeavor. Dr Kim Boland, one of the pediatric intensivists, and I had meetings scheduled in her office 1-2 times per week throughout August, September, and early October of 1997 to accomplish this education.

-I achieved acute care pediatric nurse practitioner certification with the highest test score in the country in 2005, the year this certification exam became available. I called the Board in Spring 2005 to let them know I had passed the exam, the response I received was that the Board was not recognizing the exam so I could not use the CPNP-AC title. A letter was sent to the Board by the Pediatric Nursing Certification Board (PNCB) in early 2006 notifying them of my outstanding test score.

-When I relocated to Texas in 2003, the only option for licensure was as a pediatric nurse practitioner (PNP). I had no difficulty obtaining licensure as an RN and PNP in the state of Texas. I read the nurse practice act, and the advanced practice nurse information sent to me, and available on the website. I saw nothing that alluded to the fact that I should not be practicing in an intensive care unit.

-Ms Zych has relayed to me that the BNE has recognized the acute care pediatric nurse practitioner since before she arrived at the board in 1999. There was certainly no evidence of that option in any of the application documents I received in 2003. I do know that those PNP's who had come to Texas shortly before my arrival, and had graduated from acute or critical care programs outside of the state of Texas, were having difficulty with licensure in the state of Texas, and, were licensed as "other" and asked to take the primary care PNP certification exam.

-Even quite recently, there were Board members who were under the impression that those PNP's who were already working in critical care would be "grandfathered" in some fashion and had comforted some of the PNP's working in critical care that were primary

care trained. If there are board members who were confused as to the Board's stance, I understand why many APN's were unaware as well.

-I am an item writer for the Pediatric Nursing Certification Board's self assessment exercise for acute care pediatric nurse practitioners – their mechanism for certification maintenance for acute care certified PNP's.

-I have been a Clinical Instructor for the University of Texas at Arlington in their Acute Care Pediatric Nurse Practitioner Program since 2005.

-I will be lecturing in the Acute Care Pediatric Nurse Practitioner Program at Rush University in Chicago in January of 2007.

-I have oriented each nurse practitioner currently practicing in the cardiac intensive care unit at Children's Medical Center of Dallas.

-I have been a preceptor for several acute and critical care PNP students from programs across the country.

-I actively participate in the ongoing formal and informal education of the RN staff, respiratory therapists, medical students, residents and critical care and cardiology fellows.

-I further my knowledge base by attending weekly cardiac and critical care conferences at Children's Medical Center of Dallas.

-I further my knowledge by attending local, national and international conferences on pediatric critical care and cardiac critical care.

-My professional organization, the National Organization of Pediatric Nurse Practitioners (NAPNAP), and my certifying body, the Pediatric Nursing Certification Board (PNCB) both support my current practice as a PNP working in critical care.

-I am a clinically excellent, safe, educated, motivated, and professional PNP practicing in pediatric critical care.

Please see the accompanying files that document my training and success as a pediatric nurse practitioner working in pediatric critical care.

Thank you for your time and attention to these matters.

Sincerely,

Karen Corlett RN, MSN, CPNP

4210 TOMBERRA WAY • DALLAS, TEXAS 75220
PHONE 214-353-9585 • PAGER 972-356-0099 #18226 • E-MAIL
KAREN.CORLETT@CHILDRENS.COM

KAREN CORLETT RN, MSN, CPNP

OBJECTIVE

To care for acutely and critically ill pediatric patients in an inpatient setting

PROFESSIONAL EXPERIENCE

December 2003 to present Childrens Medical Center, Dallas Texas

Nurse practitioner – pediatric cardiac intensive care unit

Hired as the first nurse practitioner (with goal of seven) in the CICU to provide care to cardiac patients in a team comprised of attendings, fellows, and now NP's. Provide care to preoperative, postoperative and non-surgical cardiac patients in an 18 bed unit. Patient population from newborn to 21 yrs, program performs approximately 500 cardiac surgeries per year. Active ECMO program for cardiac support. Procedures include intubation, central and arterial access, chest tube placement, thoracentesis, line and wire removals. Interact daily with cardiac surgeons, cardiologists, consultant services and referring physicians.

Active in education, both formal and informal, to medical students, nursing staff, nurse practitioners, nurse practitioner students and fellows. Active in building the CICU nurse practitioner program via education, orientation, team building and mentoring. Attend and present at weekly conferences to promote quality, education and research within the divisions of critical care and cardiology.

July 1997 to December 2003 Kosair Children's Hospital, Louisville, KY

Nurse practitioner – pediatric critical care center

As part of the critical care team I assessed and managed patients in the 24 bed critical care center. Usually followed all patients in the unit but at times had a small, rotating patient load in addition to responsibilities to the whole unit. Initially hired as the 'high tech' nurse practitioner, role gravitated toward caring for the sickest of the ICU patients: complex congenital heart disease including post-op management, respiratory failure, sepsis, shock, ECMO support for both cardiac and respiratory failure, trauma. Performed a variety of invasive procedures.

Assisted in the development, training, and ongoing educational needs of the 'high tech' nursing team to provide advanced care to the most critically ill patients. Provided ongoing education to resident and nursing staff. Participated and presented at monthly journal club and critical care management conferences.

January 1994 to July 1997 Kosair Children's Hospital, Louisville, KY

Pediatric cardiovascular nurse clinician

Provided program development and patient coordination and services for the cardiology and cardiac surgery population of a pediatric tertiary care center. Collaborative responsibilities included patient and family teaching, patient assessments, cardiac transplant coordination, participation in daily multidisciplinary rounds, continuing nursing and inservice education for the staff, and representation to hospital committees.

Data collector, Pediatric Cardiac Care Consortium.

Developed critical pathways for post-operative pediatric cardiovascular patients.

Coordinated institution of a telemetry monitoring system.

June 1989 to January 1994 Cardiovascular and Pediatric Surgery Inc, PS, Seattle, Washington

Pediatric cardiac surgery nurse clinician

Actively involved in all phases of patient care and education of a cardiovascular surgery service whose schedule included approximately 400 cardiac operations a year. Participated daily as a member of the congenital cardiac surgery team.

Study Coordinator: Carbomedics small size heart valve study, Homograft valved conduit study.

June 1984 to December 1993 Children's Hospital and Medical Center, Seattle, Washington

Staff nurse

Staff nurse on 38 bed acute care floor for infants with a wide range of diagnoses including ventilator dependency. Evolution of responsibilities from team leader, to primary nursing care, to charge nurse with and without patient care responsibilities. Continued as per diem staff after accepting cardiac surgery clinician position.

EDUCATION

1995 to 1997 Indiana University Indianapolis, Indiana

Master's of Science in Nursing, Pediatric Nurse Practitioner Pathway

- Academic Achievement Award

1980 to 1984 University of Washington Seattle, Washington

Bachelor of Science in Nursing

KAREN CORLETT RN, MSN CPNP

LICENSES

Texas – Registered Nurse 701304, advanced practice authorization as a pediatric nurse practitioner. Prescriptive privileges granted

Kentucky – Registered Nurse 1075257

Washington – Registered Nurse 025801

CERTIFICATIONS

Certification as a Pediatric Nurse Practitioner - Primary Care (CPNP - PC) by the Pediatric Nursing Certification Board (PNCB)

Certification as a Pediatric Nurse Practitioner - Acute Care (CPNP-AC) by the Pediatric Nursing Certification Board (PNCB)

Basic Cardiac Life Support, Pediatric Advanced Life Support, Pediatric Advanced Life Support Instructor

PROFESSIONAL MEMBERSHIPS

National Association of Pediatric Nurse Practitioners (NAPNAP)

Society of Critical Care Medicine (SCCM)

Society of Pediatric Cardiology Nurses (SPCN)

Pediatric Cardiac Intensive Care Society (PCICS)

Board Member – Camp Bravehearts

SELECTED PRESENTATIONS

Blood Products: What to Give, When, and Why. 4th International Pediatric Cardiac Nursing Symposium. November 10, 2006.

Pediatric Pharmacology: Essential Skills for Nurses. Journal of Pediatric Nursing 22nd Annual Conference, September 2006.

Management of the Child Immediately After Cardiac Surgery; Pulmonary Artery Hypertension. Acute Care Pediatric Nurse Practitioner Program, University of Texas at Arlington. September 2006.

Pediatric 12 Lead EKG Interpretation. Acute Care Pediatric Nurse Practitioner Program, University of Texas at Arlington. September 2006.

Anatomy and Physiology of the Normal Heart, The Physiology of Congenital Heart Disease, and Near Infrared Spectrometry Monitoring in Pediatric Cardiac Patients. NP led lecture series. Children's Medical Center, Dallas. August 21 & 25, September 13 & 22, October 17, 2006.

Patent Ductus Arteriosus in the Preterm Infant. Neonatal Intensive Care Unit Staff Training lecture series. Children's Medical Center, Dallas. August 2006.

The Cardiovascular System. Acute Care Pediatrics for Nurse Practitioners Conference. Children's Medical Center, Dallas. July 2006

Pediatric Cardiac Intensive Care Update. Cardiovascular Nurse Practitioner Journal Club. Children's Medical Center, Dallas. December 2005.

Pulmonary Edema. Critical Care Physiology Conference. Childrens Medical Center, Dallas. October 2005.

Hypoplastic Left Heart Syndrome. Nurse Practitioner Led Cardiac Curriculum. Childrens Medical Center, Dallas. September and October 2005.

The Physiology of Congenital Heart Disease. Nurse Practitioner Led Cardiac Curriculum. Childrens Medical Center, Dallas. February 4, 2005.

The Normal Heart. Nurse Practitioner Led Cardiac Curriculum. Childrens Medical Center, Dallas. January 2005.

Cerebral Near Infrared Spectrometry Monitoring in patients with Congenital Heart Disease. CVICU monthly lecture series. January 11, 2005.

Anatomy and Physiology of the Normal Heart. Nurse Practitioner Led Cardiac Curriculum. Childrens Medical Center, Dallas. January 7, 2005.

Congenital and Acquired Heart Disease; Management of the Child Immediately After Cardiac Surgery; Pulmonary Artery Hypertension. Acute Care Pediatric Nurse Practitioner Program, University of Texas at Arlington. September 2004, October 2005

Pulmonary Artery Hypertension in Congenital Heart Disease. Monthly CICU nursing lecture series. September 2004.

12 Lead EKG Interpretation in Pediatrics. Acute Care Nurse Practitioner Program, University of Texas at Arlington. June and August 2004, September 2005, June 2006, September 2006.

Pulmonary Artery Hypertension. Critical Care Services NP lecture Series. July 2004.

Pulmonary Artery Hypertension in Congenital Heart Disease; Common Drugs in the Cardiac ICU; Cardiac Drugs – the ICU and Beyond. Cardiovascular Lecture Series. April 2004.

The Pediatric Respiratory System: Pathophysiology and Treatment Options. Critical Care Nursing Orientation. 1999-2003.

Cardiovascular Anatomy, Physiology, Pathophysiology and Treatment

Options. Critical Care Nursing Orientation. 1999-2003.

Temporary Cardiac Pacing; Principles of Cardiopulmonary Bypass. Monthly educational conference for pediatric medical residents. 1999-2003.

Oh, No, I Hear a Murmur: Cardiovascular Concerns for the Pediatric Nurse Practitioner. Pediatric Nurse Practitioner Program, Indiana University School of Nursing. Spring Quarter 2000-2003.

Advanced Ventilator Strategies. Formal presentation for ICU Nurses. 3-4 times yearly. 2001-2003.

General Post-operative Care of the Cardiac Patient; Principles of Cardiopulmonary Bypass; Hypoplastic Left Heart Syndrome; The Norwood Operation; The Bi-Directional Glenn Operation; Prostaglandin Dependent Lesions; Truncus Arteriosus; Heart Transplantation; Transposition of the Great Arteries; Temporary Cardiac Pacing: Cardiac Valve Surgery. The "High Tech Training Course" for ICU nurses. One to two times per year. 1997-2003

Diabetic Ketoacidosis; Post-operative Care of the Pediatric Cardiac Patient; Dysrhythmias: Pacemakers. "Beyond the Basics" for ICU nurses. April and June, 2002.

Pulmonary and Cardiovascular Systems Review; Diabetic Ketoacidosis. "Foundations of Critical Care". January and March, 1999.

SELECTED CONTINUING EDUCATION ACTIVITIES

4th International Pediatric Cardiac Nursing Symposium. November 9-11, 2006.

Acute Care Pediatrics for Nurse Practitioners. July 28-30, 2006.

Pediatric Cardiac Intensive Care Symposium 2005. (PCICS 2005). December 7-11, 2005.

The Fifth International Symposium on Pediatric Cardiac Intensive Care. December 1-4, 2004.

National Association of Pediatric Nurse Practitioners Annual Conference. 1998-1999, 2001-2006..

The 2nd International Conference on Pediatric Continuous Renal Replacement Therapy. June 2002.

Society of Critical Care Medicine International Conference. January 2002.

KAREN CORLETT RN, MSN CPNP

PUBLICATIONS

Corlett, K Cardiovascular Disorders. In: Richardson, V. *Practice Guidelines for Pediatric Nurse Practitioners.* Elsevier Health Sciences, 2005.

Austin EH 3rd, Edmonds HL Jr, Auden SM, Seremet V, Niznik G, Sehic A, Sowell MK, Cheppo CD, Corlett KM. Benefit of neurophysiologic monitoring for pediatric cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery.* 114(5):707-15, 1997 Nov.

HONORS/AWARDS

Winner, poster presentation session. Acute Care Special Interest Group, at the annual meeting of The National Association of Pediatric Nurse Practitioners. Washington, DC, March 2006.

Award for "Outstanding Performance on the National Exam for PNP's for 2005". For highest score on the Pediatric Nurse Practitioners –Acute Care Exam.

OTHER ACTIVITIES

Clinical Instructor. University of Texas at Arlington School of Nursing. Starting January 2005, current appointment through August 31, 2007.

Child Health Corporation of America, Prevention of Surgical Site Infection Collaborative Meeting. Kansas City, MO. August 2006.

Item Writer. Self Assessment Exercise for Certified Acute Care Pediatric Nurse Practitioners. Pediatric Nursing Certification Board. 2005-present.

Pediatric Speaker. American Nurses Credentialing Center Speakers Board. 2006, 2007.

Pediatric Left Ventricular Assist Device Training, The Thoratec VAD. Pittsburgh PA. June 21-23 2006.

Pediatric Left Ventricular Assist Device Training, The Berlin Heart. Children's Medical Center, Dallas, Spring 2006.

Pediatric Jet Ventilator Inservice. Children's Medical Center, Dallas. May 2006.

Heart Center Planning Committee. Children's Medical Center, Dallas, ongoing.

Surgical Site Infection Prevention Collaborative Team for cardiac surgical services. August 2005 to present.

Advanced Practice Advisory Group. Children's Medical Center, Dallas. Member, 2005 to present.

Advanced Practice Advisory Group. Children's Medical Center, Dallas. Chairperson, 2005 to present.

Planning Committee Co-chair: Acute Care Pediatrics for Nurse Practitioners 3 day conference. Children's Medical Center, Dallas. 2005 & 2006.

Active in interview process for faculty and fellow applicants for the Department of Pediatric Critical Care, University of Texas, Southwestern, Medical School.

Poster: Nurse Practitioners: The Brains and Heart of Critical Care Services, Children's Medical Center Dallas. Presented for:
-Acute Care Special Interest Group Poster Presentation. National Association of Pediatric Nurse Practitioners Annual Conference. Washington, DC. March 2006.
-Welcome Reception for Attendees of Journal of Pediatric Nursing 22nd Annual Conference. September 2006.

Oriented 6 novice NP's to the PNP role in the CVICU, February 2004 to present.

Precepted three acute care pediatric nurse practitioner students from University of Texas at Arlington, 2004 to present.

Precepted one acute care pediatric nurse practitioner student from University of California, San Francisco. Summer 2006.

Precepted one acute care pediatric nurse practitioner student from Rush University, Chicago. Spring 2006.

Precepted three pediatric critical care nurse practitioner students from the University of Pennsylvania, Spring and Summer 2004.

On the following pages, you will find the transcripts from my Master's program at Indiana University, and 2 proposed plans of study to complete a post-Master's certificate as an acute care pediatric nurse practitioner.

I have discussed programs of study with Dr Susan Grove, Dean of the School of Nursing at University of Texas at Arlington and Beth Bolick, program director for the acute care pediatric nurse practitioner program at Rush University in Chicago.

The following table, and the following transcript, illustrate the components of my basic pediatric nurse practitioner program that will be directly applied to my post-master's study program at UT Arlington, as approved by Dr Susan Grove

Semester	Required University of Texas at Arlington Class	Credited Class from Indiana University
Fall	NURS 5315 – Adv Patho	Nurs – Y 515 Pathophysiology
	NURS 5350 – Ad Pract Role	Nurs – C 556 Adv Nurs Mgmt of Pedi Client
Spring	NURS 5418 – Adv Assess	Nurs – C 550 Pediatric Health Assessment
	NURS 5334 – Adv Pharm	Nurs – Y 612 Pharm Primary Care
Summer	NURS 5314 – Invasive Skills	*required*
	NURS 5306 – Pediatric Mana	Nurs – C 551 Health Maint of Pediat Client
Fall	NURS 5441 – Acute Care Pedi	*required*
	NURS 5303 – Pshyc Mana	Nurs – C 661 Psy-Soc Assess Peds & Women
Spring	NURS 5444 – Complex Pedi	*required*
Summer	NURS 5631 – Adv Practicum	*Required clinical hours*

The following pages illustrate the Rush University program of study in the post master's certificate for acute care pediatric nurse practitioners. Ms Bolick and I have not met in person due to distance, but we have been in frequent phone and email contact to develop my plan of study. She is currently reviewing some additional evidence from my Indiana University PNP program to perhaps further decrease my required number of classes.

INDIANA UNIVERSITY
OFFICE OF THE REGISTRAR

Official Transcript

Name : Corlett,Karen M
Student ID : [redacted]
Address : 8512 Twin Springs Dr
Sellersburg, IN 471720000
United States

SSN : XXX-XX-[redacted]
Birthdate : 11-16-XXXX
Print Date : 10-19-2006
Request Nbr : 003022263

- - - - - Degrees Awarded - - - - -

Indiana University Degree
Indiana University Purdue University Indianapolis
Master of Science in Nursing
Major: Pediatrc Nur Practitnr
05-11-1997

- - - - - Beginning of Graduate Record - - - - -

Fall Semester 1994-1995 Indianapolis

Program : Nursing Grad Nondeg

Course		Title	Hrs	Grd
NURS-N	501	ISSUES IN NURSING	3.00	A
NURS-R	505	MEASUREMENT & DATA ANALYSIS	3.00	A

Semester:	IU GPA Hours:	6.00	GPA Points:	24.000
	Hours Earned:	6.00	GPA:	4.000
Cumulative:	IU GPA Hours:	6.00	GPA Points:	24.000
	Hours Earned:	6.00	GPA:	4.000

Spring Semester 1994-1995 Indianapolis

Program : Nursing Grad Nondeg

Course		Title	Hrs	Grd
NURS-R	500	NURSING RESEARCH	3.00	A

Semester:	IU GPA Hours:	3.00	GPA Points:	12.000
	Hours Earned:	3.00	GPA:	4.000
Cumulative:	IU GPA Hours:	9.00	GPA Points:	36.000
	Hours Earned:	9.00	GPA:	4.000

First Summer 1995 Indianapolis

Program : Nursing Graduate

Course		Title	Hrs	Grd
NURS-N	502	INTRO TO ANALYS NURS THEORIES	3.00	A

Semester:	IU GPA Hours:	3.00	GPA Points:	12.000
	Hours Earned:	3.00	GPA:	4.000
Cumulative:	IU GPA Hours:	12.00	GPA Points:	48.000
	Hours Earned:	12.00	GPA:	4.000

Fall Semester 1995-1996 Indianapolis

Program : Nursing Graduate

Course		Title	Hrs	Grd
NURS-C	661	PSY-SOC ASSES PEDS & WOMEN	3.00	A
NURS-G	513	PHYSIOLOGY OF MATERNAL-CHILD	1.00	A+
		Course Topic(s): PMC-1:GENETICS		
NURS-Y	612	PHARM PRIMARY CARE NURS PRAC	3.00	A

--- Record continued in next column ---

Semester:	IU GPA Hours:	7.00	GPA Points:	28.000
	Hours Earned:	7.00	GPA:	4.000
Cumulative:	IU GPA Hours:	19.00	GPA Points:	76.000
	Hours Earned:	19.00	GPA:	4.000

Spring Semester 1995-1996 Indianapolis

Program : Nursing Graduate

Course		Title	Hrs	Grd
NURS-R	590	NURSING STUDY	3.00	A
NURS-Y	515	PATHOPHYSIOLOGY	4.00	A+

Semester:	IU GPA Hours:	7.00	GPA Points:	28.000
	Hours Earned:	7.00	GPA:	4.000
Cumulative:	IU GPA Hours:	26.00	GPA Points:	104.000
	Hours Earned:	26.00	GPA:	4.000

First Summer 1996 Indianapolis

Program : Nursing Graduate

Course		Title	Hrs	Grd
NURS-C	550	PEDIATRIC HEALTH ASSESSMENT	3.00	A

Semester:	IU GPA Hours:	3.00	GPA Points:	12.000
	Hours Earned:	3.00	GPA:	4.000
Cumulative:	IU GPA Hours:	29.00	GPA Points:	116.000
	Hours Earned:	29.00	GPA:	4.000

Fall Semester 1996-1997 Indianapolis

Program : Nursing Graduate

Course		Title	Hrs	Grd
NURS-C	551	HEALTH MAINT OF PEDIAT CLIENT	5.00	A
NURS-J	692	INDEPENDENT STUDY IN NURSING	1.00	A
		Course Topic(s): ADV PRACTICE IN ONCOLOGY NS		

Semester:	IU GPA Hours:	6.00	GPA Points:	24.000
	Hours Earned:	6.00	GPA:	4.000
Cumulative:	IU GPA Hours:	35.00	GPA Points:	140.000
	Hours Earned:	35.00	GPA:	4.000

Spring Semester 1996-1997 Indianapolis

Program : Nursing Graduate

Course		Title	Hrs	Grd
NURS-C	556	ADV NURS MGMT OF PED CLIENT	2.00	A
NURS-J	692	INDEPENDENT STUDY IN NURSING	1.00	A
		Course Topic(s): IND.STDY:PEDIATRIC PRACTICE		
NURS-Y	555	COLLAB CL PRAC/HLTH CARE NURS	4.00	A

Semester:	IU GPA Hours:	7.00	GPA Points:	28.000
	Hours Earned:	7.00	GPA:	4.000
Cumulative:	IU GPA Hours:	42.00	GPA Points:	168.000
	Hours Earned:	42.00	GPA:	4.000

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THE WORDS "INDIANA UNIVERSITY" AND "VOID" APPEAR WHEN PHOTOCOPIED

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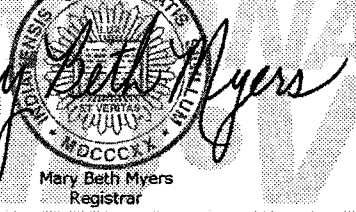
Send To:
Karen Corlett
4[illegible] Tomberra Way
Da[illegible], TX 75220
United States



Mary Beth Myers
Registrar

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PLEASE QUESTION AUTHENTICITY OF DOCUMENT IF SIGNATURE AND SEAL ARE MISSING OR DISTORTED

INDIANA UNIVERSITY
OFFICE OF THE REGISTRAR

Official Transcript

Name : Corlett,Karen M
[redacted]ent ID : [redacted]
[redacted]ess : 8512 Twin Springs Dr
Sellersburg, IN 471720000
United States

SSN : XXX-XX-[redacted]
Birthdate : 11-16-XXXX
Print Date : 10-19-2006
Request Nbr : 003022263

Student Graduate Program Summary

GPA Hours: 42.00 Transfer/Test Hours Passed: 0.00
Hours Earned: 42.00 Points: 168.000 GPA: 4.000

Indiana University Graduate Summary

IU GPA Hours: 42.00 Transfer/Test Hours Passed: 0.00
Hours Earned: 42.00 Points: 168.000 GPA: 4.000

Academic Objective as of Last Enrollment

Nursing Graduate
Pediatrc Nurs Practitioner MSN

--- End Of Record ---

Issued at: Indiana University/Purdue University Indianapolis
Mary Beth Myers, Registrar

THE WORDS "INDIANA UNIVERSITY" AND "VOID" APPEAR WHEN PHOTOCOPIED

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Send To:
Karen Corlett
4[illegible] Tomberra Way
D[illegible]s, TX 75220
United States

Mary Beth Myers
Mary Beth Myers
Registrar

In accordance with the Family Educational Rights and Privacy Act of 1974, information from this transcript may not be released to a third party without written consent of the student. **Transcript explanation on reverse side.**

PLEASE QUESTION AUTHENTICITY OF DOCUMENT IF SIGNATURE AND SEAL ARE MISSING OR DISTORTED

ACUTE CARE PEDIATRIC NURSE PRACTITIONER
POST-MASTERS CERTIFICATE

	Course # / Short Title / Class-Clinical	Fall Admission	Spring Admission	Summer Admission
FALL	NURS 5315 - ADV PATHO (3-0)	Nurs-Y 515 Pathophysiology 4hr		
	NURS 5350 - ADV PRACT ROLE (2-3)	Nurs-C 556 Adv. Nurs Mgmt of		
	Credit Hours = 6	Pedi client 2hrs A		3hr
SPRING	NURS 5418 - ADV ASSESS (2-6)	Nurs-C 550 Pediatric Health A		
	NURS 5334 - ADV PHARM (3-0)	Nurs-Y 612 Pharm Primary Care		
	Credit Hours = 7		Nurse Prac	3hrs A
SUMMER	NURS 5314 - INVASIVE SKILLS (2-3)	Sum 07		
	NURS 5306 – PEDIATRIC MANA (2-3)	Nurs-C 551 Health Maint of Pediat		
	Credit Hours = 6	Client 5hrs A		
FALL	NURS 5441 - ACUTE CARE PEDI (2-6) 90	Fall 07		
	NURS 5303 - PSYCH MANA (2-3)	Nurs-C 6161 Psy-Soc Assess Peds & Wom		
	Credit Hours = 7	3hrs A		
SPRING	NURS 5444 – COMPLEX PEDI (2-6) 90	Sp 07		
	Credit Hours = 4			
SUMMER	NURS 5631 - ADV PRACTICUM (0-24) (360 cl. Hrs.)	Sp 08		
	Credit Hours = 6			
	TOTAL SEMESTER HOURS = 36			

540 clinical

Name: Karen Corlett

Social Security Number: [redacted]

Address: 4210 Tomberra Way
Dallas TX 75220

Home Phone: 214 353 9585

Work Phone: 214 456 2033

Admission: Sp 07 Completion: Sp 08 Part-Time: ____ Full-Time: ____

PNP:

PNCB Certifications: Primary 1997
Acute Care 2005.

RUSH UNIVERSITY
CHICAGO, IL

Department of Women's and Children's Health Nursing

ACUTE/CHRONIC CARE PEDIATRIC NURSE PRACTITIONER (AC PNP)
RUSH is ranked 8th for Pediatric Nurse Practitioner programs in U.S. News & World Report!

- **Post Master's Certificate**

THE ROLE
The AC PNP program, formally known as the Pediatric Critical Care Nurse Practitioner Program (PCCNP), is designed to prepare experienced pediatric nurses for roles as advanced practice nurses in the subspecialty care of infants and children with complex acute/chronic conditions.

THE PROGRAM
The AC PNP specialty curriculum starts with a core knowledge set of pediatric concepts ranging from normal growth and development through health screening and maintenance. It then advances to provide in-depth education into specialty practice for nurse practitioners working with infants, children, and their families with complex health care needs. Specialty courses are provided in a combination of live and compressed formats. Graduates are prepared to meet the *Acute Care Nurse Practitioner Competencies* as defined by the National Organization of Nurse Practitioner Faculties. Students must have at least two years of recent pediatric experience and current Pediatric Advanced Life Support training before advancing to the specialty curriculum. Post-Master's Certificate study is individualized for each student based on previous graduate education and advanced practice nursing experience.

THE FACULTY
Rush College of Nursing faculty are highly experienced practitioner-teachers with doctoral and master's degrees and certification in their specialties. The Practitioner-Teacher model at Rush University allows faculty to maintain and enhance their clinical expertise and apply it to research and academic programs. Faculty are nationally known in their various areas of expertise and are actively involved in professional organizations. Faculty are also well published and frequently speak at regional, national, and international professional meetings.

CLINICAL SITES
Students complete clinical rotations in areas such as the PICU, NICU, ED, pain service, infectious disease, radiology, child life, nephrology, oncology, palliative care, and cardiovascular surgery, Clinical sites are available at Rush University Medical Center and throughout the Chicago metropolitan area. Distance clinical sites must be negotiated on an individual basis.

CAREER OPPORTUNITIES
Graduates of the AC PNP program work with patients and families to meet the demands of their disease, illness, or injury in a variety of settings that include, but are not limited to: intensive care, emergency care, specialty service, inpatient unit, and transport team.

CERTIFICATION AND ACCREDITATION

Completion of the program provides eligibility for certification as an Acute Care Pediatric Nurse Practitioner by the Pediatric Nursing Certification Board and for state licensure/certification where available.

To apply or for further information contact

College Admission Services
600 S. Paulina – Suite 440
Chicago, IL 60612
Telephone: 312-942-7100; Fax: 312-942-2219
e-mail: Rush_Admissions@rush.edu
web address: www.rushu.rush.edu/nursing
To apply on-line go to
www.rushu.rush.edu/nursing/admission.html

Faculty contact for the Acute/Chronic Care Pediatric NP program

Beth Bolick, RN, MS, APRN-BC, CPNP-AC, CCRN
312-942-3646
Beth_N_Bolick@rush.edu

The following are prerequisite graduate level coursework which must be completed prior to beginning the Post Masters AC PNP Specialty Content. These courses may be from a masters program from another institution or completed at Rush. An individualized program of study will be determined after transcript review.

GRADUATE NURSING CORE COURSES		QTR
NUR 502A	Professional Issues in Role Development	2
NUR 502B	Implementation of the APN Role	2
NUR 503	Physical Diagnosis: Assessment & Evaluation Across the Lifespan	4

ADVANCED PRACTICE NURSING CORE COURSES		
PHY 551	Advanced Physiology I	4
PPH 512	Advanced Pathophysiology II	4
NUR 529	Pharmacology	3
NUR 530H	Pharmacotherapeutics in Pediatrics	3
BHV 522	Child and Family Development Throughout the Lifespan	3
BHV 505	Interdisciplinary Palliative Care	2
NUR 505	Diagnostics for the Advanced Practice Nurse	3

SPECIALTY CURRICULUM CONTENT (Non-PNP applicants)		
NUR 533A	Advanced Practice in Maternal-Child Nursing	3
NUR 533F	Primary Care of the Child I	3
	(concurrent with 2 NUR 541 practicum hours)	2

The Post Masters AC PNP Specialty Content is 9-14 credits. It includes 2 Management courses and a *minimum of 500 hrs of clinical experience* divided between practicum and residency. *Additional clinical practicum hours may be required by area of concentration and/or individual student needs.* **A portion of the clinical hour requirement may be waived by NPs experienced in the AC PNP role. See Program Director for details.**

AC PNP SPECIALTY CONTENT

NUR 533R	*Pediatric Acute/Chronic Care I*	*3*
NUR 533S	*Pediatric Acute/Chronic Care II*	*3*
NUR 541	*Practicum*	*1-6*
*NUR 600***	*Nurse Practitioner Residency*	*2*

** NUR 600 Students register for 2 hours of credit for the purposes of tuition only *each quarter* until the total program clinical hour requirement of 500 clock hours is completed.

Karen Corlett Program of Study

Acute/Chronic Care Pediatric Nurse Practitioner (AC PNP)

Post Master's Certificate Option

- CF = compressed format, e.g. class in Chicago for one week of quarter W = on line

Year : Quarter 1 Fall	Quarter 2 Winter	Quarter 3 Spring	Quarter 4 Summer
	NUR 533R/CF *NUR 541*	*NUR 533S/CF* *NUR 600* *BHV 505* *PHY 551*	

The Pediatric Nursing Certification Board, Inc.
800 S. Frederick Avenue, Suite 104

Gaithersburg, MD 20877-4151
TOLL FREE (888-641-2767) FAX (301-330-1504)

PATHWAY II, III
Acute Care PNP
Skills
Verification Form

PATHWAY II, III—ACUTE CARE PNP SKILLS VERIFICATION FORM

To the applicant: Please print or type your name in the space provided below and forward this form to a physician supervisor or pediatric nurse practitioner who has knowledge of your acute care clinical practice skills and can verify your current practice competency as a acute care PNP.

Karen Corlett
PNP Name

[redacted]
SSN

Certification number (PNCB) 97248 ANCC _____
(include copy of certificate if through ANCC)

Percent of practice spent with: Inpatients 100% Outpatients _____
Number of acute care practice hours per week: 40

Please have a peer (Acute Care PNP or Physician) complete the following about your practice:

I, Erica Molitor-Kirsch the undersigned, have observed, Karen Corlett perform in the role of an acute care pediatric nurse practitioner. I attest that the above-named individual performs pediatric examinations and develops and carries out appropriate care according to standards generally accepted in pediatric acute care practice. I have served with this candidate in clinical practice for 14 (months/years). I attest that the above-named individual performs the following at a proficient level.

Yes	No		
X		1.	Performs a complete assessment of the complex, acute, critical and chronically ill child with a focus on identifying emergent, physiologic instability.
X		2.	Orders, performs and interprets diagnostic tests. Orders and utilizes technologic devices to sustain life.
X		3.	Constructs a differential diagnosis with priority according to urgent and emergent health needs.
X		4.	Designs a developmentally appropriate plan of care and incorporates developmental concepts and theory in the provision of therapeutic interventions.
X		5.	Intervenes to address and respond to children with rapidly changing clinical conditions, emerging health crises, organ dysfunction and failure.
X		6.	Provides therapeutic interventions in collaboration with other members of the health care team, including physicians, nurses, social workers, respiratory therapy and other designated care providers.
X		7.	Determines physiologic and psychological risks for children with complex, acute critical and chronic illness including nutritional, disease process and therapy related complications.
X		8.	Integrates education, research, ethical and legal principles, safety and diversity into assessment, plan and interventions for children.
X		9.	Incorporates aspects of family, diversity, cultural and spiritual competence in caring for children with acute, complex or chronic health care needs.
X		10.	Appropriately and accurately communicates health assessments and immediate plan of care to members of the health care team. Consults with subspecialty and community based providers to assure smooth transition and continuity of care across health care settings.

Signature Erica Molitor-Kirsch, M.D. Date 2/14/05

Print Name ERICA MOLITOR-KIRSCH, M.D. Position/Title ATTENDING PHYSICIAN PEDIATRIC CARDIAC ICU

Address 1935 MOTOR ST

DALLAS, TX 75235
City State Zip Code

Telephone 214-456-6435 Email erica.molitor-kirsch@childrens.com

PNCB

PEDIATRIC NURSING
CERTIFICATION BOARD

Promoting Excellence for Pediatric Nurse Practitioners and Nurses

January 17, 2006

Karen M. Corlett
4210 Tomberra Way
Dallas, TX 75220

Dear Karen:

We are happy to tell you that you received an outstanding score on the Pediatric Nurse Practitioners -- Acute Care Exam during the 2005 exam administration. In recognition of this accomplishment a plaque will be awarded to you for "Outstanding Performance on the National Exam for PNPs for 2005". The award for Outstanding Performance was established more than 20 years ago by the Executive Committee of the PNCB. We are extremely pleased to welcome you to this special group of CPNP™s.

Each year the recipient of the award for "Outstanding Performance" is recognized at the Awards Breakfast of the NAPNAP Annual Conference. The upcoming 27th Annual NAPNAP Conference is being held at the Wardman Park Marriott Hotel, Washington, DC, March 30-April 2, 2006. Please let us know if you are able to attend the conference. If so, the award will be presented to you personally at the Awards Breakfast on Friday, March 31, 8:00 AM.

Recognition of this special accomplishment will appear in the Journal of Pediatric Health Care. In order to recognize your achievement at the Awards Breakfast and to prepare this announcement for the journal, please send us some short biographical information about you, your education and experience, and current interests. Also, we would be honored to announce this accomplishment to several of your colleagues via a personal letter to them. Call or fax our office with the names or addresses so we may inform your colleagues of your special achievement as soon as possible.

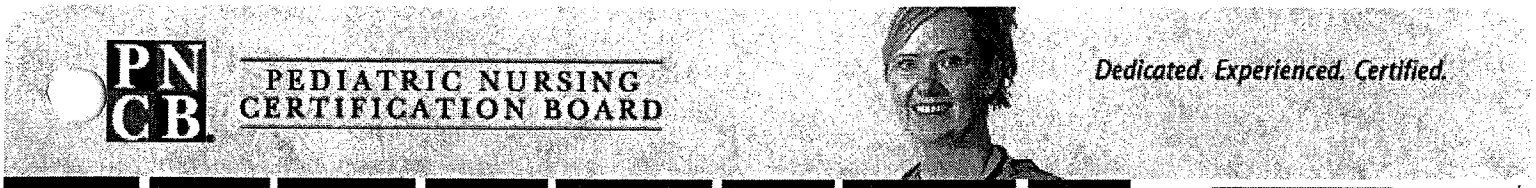
Congratulations again on this special achievement.

Sincerely,

Janet S. Wyatt

Janet S. Wyatt, PhD, RN, CRNP
Executive Director

800 SOUTH FREDERICK AVENUE, SUITE 204 GAITHERSBURG, MARYLAND 20877
(301)330-2921 FAX: (301)330-1504 (888)641-2767 WWW.PNCB.ORG



PNCB Recognized Acute Care PNP Programs

The program review process recognizes Acute Care PNP programs that have met the quality guidelines for Acute Care PNP education established by the Association of Faculties of PNP programs (AFPNP). The PNCB conducts program review throughout the year. New Acute Care PNP programs may apply for recognition through participation in the PNCB's PNP Program Review process.

To be added to the list of recognized Acute Care PNP programs please submit an Acute Care PNP Program Review application.

Acute Care PNP Recognized Programs

Code	Program	State
1191	The University of AL, Birmingham - AP of Nursing - Acute Care and Continuing Care Pediatrics	AL
856	California State University - Los Angeles - Masters and Post Masters Pediatric Acute Care	CA
1802	Emory University - Nell Hodgson Woodruff - School of Nursing - PNP Acute Care Program	GA
1198	Rush University - School of Nursing - Acute/Chronic PNP Program	IL
1838	University of Maryland - Acute Care PNP Program	MD
1822	Duke University - School of Nursing - Pediatric Acute/Chronic Care NP Program	NC
1126	Seton Hall University - College of Nursing - Acute Care PNP Program	NJ
1192	University of PA - School of Nursing - Pediatric Critical Care NP Program	PA
1193	University of PA - School of Nursing - Pediatric Acute/Chronic NP Program	PA
1194	University of PA - School of Nursing - Pediatric Oncology NP Program	PA
1855	Vanderbilt University - School of Nursing - PNP Program - Acute Care Track	TN
1196	The University of TX at Arlington - School of Nursing - Acute Care PNP Program	TX

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children's
MEDICAL CENTER

November 14, 2006

Jolene Zych, MS, RNC, WHNP
Board of Nurse Examiners for the State of Texas
Nursing Consultant - Advanced Practice
333 Guadalupe #3-460
Austin, Texas 78701
JOLENE.ZYCH@BNE.STATE.TX.US

Dear Ms. Zych,

I am the Director of Advanced Practice Services at Children's Medical Center Dallas. In my role, I oversee all of the Advanced Practice Nurses that practice in the various subspecialties here at Children's. One of those areas is the Pediatric Critical Care Service.

The intent of this letter is to provide endorsement for the Board of Nurse Examiners for the State of Texas (BNE) to grant a waiver to Karen Corlett, RN, MSN, CPNP-PC for her to continue her practice here in the Pediatric Cardiovascular Intensive Care Unit until:

- Completion of her post master's Acute Care Pediatric Nurse Practitioner program
- Full recognition by the Texas BNE as an ACPNP

Karen came to work for us here at Children's in December of 2003. She had worked for over 6 years as a Pediatric Nurse Practitioner in a Pediatric Intensive Care Unit at Kosair Children's Hospital in Louisville, Kentucky. At the time of her hire we were aware that Karen had attended a primary care PNP program. However, we made the decision to hire her based upon her extensive experience as a Pediatric Nurse Practitioner in the PICU and her glowing letters of recommendation from her collaborating physicians at Kosair Children's Hospital.

Karen quickly became the best pediatric nurse practitioner employed here at Children's Medical Center Dallas. She has had multiple performance reviews and all physician comments regarding her practice have been glowing. I have not had any concerns with her clinical practice communicated to me since the start of her employment with us here at Children's. She is the Chair of our Advanced Practice Advisory Group, a leadership role among all of our nurse practitioner's here at Children's. She is one of the primary preceptors and lecturers for the Acute Care PNP program at the University of Texas at Arlington, and in fact is rated highly as an educator by the students she precepts. Karen also took the CPNP-AC certification exam offered by the Pediatric Nursing Certification Board in the Spring of 2005 and scored the highest score among all who took that exam in the United States.

As background regarding Karen's practice here: Children's is the principal pediatric teaching hospital for the University of Texas Southwestern Medical School. Subsequently the nurse practitioner's here in Critical Care Services function in a completely supervised medical education model where they examine patients, develop a plan of care, write a daily progress note and then present their patients during daily rounds to the Attending Physician. The Attending Physician then repeats the physical exam and either concurs or alters the plan of care developed by the nurse practitioner. The nurse practitioners do not bill for their services – all billing is via the UT Southwestern Attending Physician. This is a unit with only faculty physicians, fellows, and nurse practitioners. There are no pediatric residents.

The Attending Physician is physically present on the unit daily and then is immediately available via phone 24 hours per day, 7 days per week for any issues or questions. During times that the Attending Physician is not physically present; a pediatric intensivist Fellow is available in the hospital for consultation and assistance 24 hours per day, 7 days per week.

The Critical Care Nurse Practitioners also have a Pediatric Intensivist, Dr. Maeve Sheehan, who serves as their Medical Director. She oversees their yearly skills day for validation of their proficiency with skills required to perform their role. She also provides a twice-monthly rounding session where she discusses interesting cases to supplement their knowledge of pediatric critical care medicine. The Pediatric Critical Care service also has weekly didactic lecture session providing educational information regarding the medical management of common pediatric critical care issues.

Here at Children's we are committed to promoting the ACPNP role by financially supporting NPs who want to go back for the post-masters ACPNP education. Additionally we have worked diligently to restrict practice in critical care to only those individuals with prior experience or training as a pediatric nurse practitioner in critical care or acute care pediatrics. However, as you are aware, there is only one ACPNP education program in the State of Texas and the pool of available candidates is very small. Despite this limited pool of candidates, the number of children requiring critical care services is growing steadily. Here at Children's we have made a commitment to the community to provide care to children in need despite the ability to pay for these services, however our ability to provide this service hinges on our ability to safely staff critical care beds.

I appreciate your thoughtful consideration of my requests and comments. Our utmost concern is providing safe care to our patients and their families while following the guidelines and rules imposed by the Texas BNE.

Respectfully,

Joe Don Cavender, RN, CPNP-PC

Joe Don Cavender, MSN, RN, CPNP-PC
Director; Advanced Practice Services
Children's Medical Center Dallas
1935 Motor Street
Dallas, Texas 75235
214-456-2331
joe.cavender@childrens.com

Lisa M. Milonovich
4138 Beechwood Lane
Dallas, Texas 75220
214-352-9983
lmilono@aol.com

November 11, 2006

Jolene Zych
Advanced Practice Advisory Committee
Texas Board of Nurse Examiners
333 Guadalupe #3-460
Austin, TX 78701

Dear Ms Zych,

I am writing this letter with regard to my colleague, Karen Corlett, who has requested a waiver from the BNE to practice as a pediatric nurse practitioner (PNP) in critical care. While I understand that the Board is making an effort to have all nurse practitioners obtain the education and certification that correlates to their area of practice, I feel that there should be some time period within which people who are currently practicing in subspecialty areas have to meet this requirement. This would be similar to the Master's degree requirement for nurse practitioners in the past. Until very recently, there have been only a few programs nationwide that prepared PNPs to practice in the acute/critical care setting. In addition, a certification exam for the pediatric acute care nurse practitioners has only been available for approximately 18months. The Pediatric Nursing Certification Board (PNCB) who administers this exam chose a two year period, which expires in March 2007, to allow PNPs who are primary care trained but practicing in acute care to sit for the exam. This seems like a reasonable "grandfathering" period for this group of individuals. It also indicates to me that this is a common practice across the country. Karen met this criteria established by the PNCB and took the exam in 2005 scoring the highest in the nation for that year. I believe that this accomplishment is an indication of Karen's knowledge base despite her lack of formal acute care education.

In addition to the above, Karen is an excellent clinician. She has many years of nursing and advanced practice experience and is a wealth of knowledge in many areas of pediatric critical care and advanced practice. Karen is extremely professional in her interactions with others and is respected by staff, peers and physician colleagues. She developed the role of the PNP in the cardiac intensive care unit at Children's Medical Center Dallas and has mentored many critical and acute care trained novice advance practice nurses and students to this unit and role. Karen has also presented at local and national meetings on a variety of topics related to pediatric critical care.

In summary, while I am supportive of the Board's intention to standardize education, certification and practice, I feel that a "grandfathering" period is necessary to allow excellent practitioners, like Karen, to continue to practice while working to achieve this requirement. I have worked with Karen for three years both in clinical and other advance practice roles and I feel that she is one of the best PNPs I have a ever encountered in my more than 20years of nursing. Thank you in advance for you consideration of Karen's request.

Lisa M. Milonovich RN, PCCNP

Lisa M. Milonovich RN, MSN, PCCNP
Pediatric Critical Care Nurse Practitioner

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS
Pediatric Cardiology University Consultants

Sarah D. Blumenschein, M.D.
Reenu S. Eapen, M.D.
David E. Fixler, M.D.
Vidu Garg, M.D.
Matthew S. Lemler, M.D.
Lynn Mahony, M.D.
Edgar Newfeld, M. D.

Claudio Ramaciotti, M.D.
Kathleen M. Rotondo,M.D.
William A. Scott, M.D.
Deepak Srivastava, M.D.
Daniel Stromberg, M.D.
Thomas M. Zellers, M.D.

November 14, 2006

To Whom It May Concern,

I have known Karen Corlett, RN, CPNP, for the past 3 years as a nurse practitioner in the Cardiac ICU at Children's Medical Center of Dallas. It is my strong feeling that she should be allowed to continue to practice in her current capacity due to her tremendous clinical ability, her outstanding (and well documented) depth of knowledge in critical care, and her importance to staff development arising from her considerable teaching and mentoring expertise.

Karen began work in Dallas as the first cardiac NP in our CICU. She was therefore instrumental in developing the role, and establishing NPs as integral members of the care team. In my capacity as Director of the CICU, I have worked closely with her on many, many occasions. Karen is an outstanding bedside care provider who is both knowledgeable about her patient's conditions, and diligent in the timely performance of clinical duties. She has great technical skill in the performance of procedures, and she is appropriately calm in stressful situations. On rounds, Karen is articulate and presents information in a clear, complete, and organized fashion. However, she is not a mere "reporter." She skillfully interprets data and develops plans therefrom in conjunction with her colleagues. Her formidable medical knowledge base (attested to by the highest score in the country on the acute care pediatric NP certification exam!) often allows her to serve as a resource to her peers.

That Karen possesses these qualities is no surprise given her extensive experience as a pediatric NP. Karen has worked in pediatric critical care for greater than 9 years, many of which were heavily weighted toward cardiac critical care. Her aptitudes, which have been recognized nationally, have earned her the opportunity to lecture at numerous conferences and to teach other aspiring NPs at two major training programs (the University of Texas, Arlington, and Rush University, Chicago). Moreover, we have had Karen precept all 6 of our novice cardiac NPs over the short life of our program, 4 of whom came from the critical care NP program at the University of Pennsylvania. Karen has successfully guided their development into highly valued and trusted practitioners, while providing leadership for our CICU NP group and growing its ranks.

To conclude, Karen's long history of critical care experience and exemplary performance in our CICU makes the current limitation of her practice *prima facie* seem arbitrary and unnecessary. She is viewed nationally as an intellectual leader in her discipline, and she has mentored and trained many NPs of lesser qualification and distinction who are allowed to work without restriction. Therefore, Karen Corlett, RN, CPNP, should be permitted to resume her important clinical work at our institution immediately.

Sincerely,

Daniel Stromberg, MD

Daniel Stromberg, MD
Associate Professor, Pediatrics
UT Southwestern Medical Center
Director, Cardiac Intensive Care Unit
Children's Medical Center of Dallas

Offices at Children's Medical Center 1935 Motor Street/ Dallas, Texas 75235/ Telephone (214) 456-2333 or Toll free 1-800-947-2323
After 5 p.m. & Weekends (214) 456-7000 Telefax (214) 456-6154

UT SOUTHWESTERN
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Department of Pediatrics
Division of Pediatric Critical Care

James A. Thomas, M.D.
Division Director

Robert M. Alisharan, M.D.
Deborah Carlson, Ph.D.
Mandeep S. Chadha, M.D.
Cindy M. Darnell, M.D.
Leslie B. Garner, M.D.
Brett P. Giroir, M.D.
Steven G. Kernie, M.D.
Ruth Levitz, Ph.D.
Fiona H. Levy, M.D.
Peter M. Luckett, M.D.
Fran Morriss, M.D.
J. Julio Pérez Fontán, M.D.
Maeve Sheehan, M.D.
Paul W. Sheeran, M.D.
Paul M. Shore, M.D., MS
Marita Thompson, M.D.
Brigham C. Willis, M.D.

Cardiac Critical Care
Raju T. Meyappan, M.D.
Erica Molitor-Kirsch, M.D.
Daniel Stromberg, M.D.
Tia Tortoriello, M.D.

14 November 2006

Texas Board of Nurse Examiners
333 Guadalupe # 3-460
Austin, TX 78701

RE: Karen Corlett, RN, CPNP, waiver to practice Pediatric Critical Care

Members of the Board:

This letter is in support of Karen Corlett's application for a waiver to practice Pediatric Critical Care. I have been a Pediatric Critical Care physician for nine years and worked closely with Karen for the last three years, during which time I have served as an Attending Physician in the Pediatric Cardiac Critical Care Unit at Children's Medical Center of Dallas.

Karen is an **exemplary Pediatric Critical Care Nurse Practitioner** with extensive experience in the field. She excels in the clinical arena where she is able to manage multiple critically ill infants and children with a calm demeanor, timely well-derived plans, and good technical skills. She communicates well with physicians, nurses, and families. She is aware of her limitations, accepting of guidance and eager to learn. Her ethics are above reproach. In our unit, she is viewed not only as a nurse practitioner who allows us to care for children more efficiently, but as a respected colleague. Her opinion is actively sought by critical care physicians and surgeons. In addition to her clinical contributions, she participates in the education of critical care fellows by whom she is well-respected as a senior member of the ICU team. Her intellect and clinical skills are further augmented by her pleasant personality, approachability, and positive attitude.

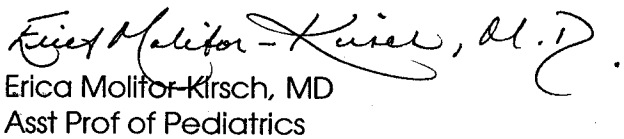
Karen is a **nationally recognized educator and leader in the field** of Pediatric Critical Care. She has lectured at critical care Nurse Practitioner programs across the country as well as at national meetings. She has oriented and precepted multiple critical care and acute care PNP students. At our institution, she initiated and

leads the PNP program in our Pediatric Cardiac Intensive Care Unit. She has more experience in pediatric critical care than the majority of critical care and acute care trained PNPs in the country. She achieved the **highest score on the acute care PNP certification exam in 2005** confirming her acute care expertise.

As you are aware, at the time of her training, acute and critical care PNP programs were not available, thus her formal training is not in critical care. However, her **extensive experience, national recognition, demonstrated proficiency and dedication in this field** should be considered in her application for a waiver to practice. I strongly urge you to grant her a waiver to practice Pediatric Critical Care without need for additional training. If after review of her record, you deem that further training is warranted, I urge that you grant her a waiver to practice critical care during the time it takes for her to complete such training.

Finally, given the shortage of well-trained Pediatric Critical Care providers, preventing competent individual from practicing, and thus depriving children of excellent critical care services due to a technicality is reprehensible. I urge to you to revise your recent stance regarding a matched education and practice to include a "grandfather" clause for competent individuals who trained before critical care programs were available or to provide a window of time in which these individuals can continue their practice while completing the "necessary" training.

Respectfully submitted,



Erica Molitor-Kirsch, MD
Asst Prof of Pediatrics
UT Southwestern
Cardiac Critical Care
Children's Medical Center of Dallas

Training Sessions for Critical Care Nurse Practioner

1) Intubation- Preparation, Process, Medication, Complications
   Sedation- Medications, their indications, pharmocodynamics, and adverse reactions
   Neuromuscular Blockers- Indications, pharmocodynamics and adverse reactions

2) Ventilatory Management
   - recognition of respiratory failure
   - ventilator modes
   - complications of positive pressure ventilation
   - scenarios of different pathophysiologic situations and the thought processes involved in choosing ventilator modes and settings

3) Respiratory Mechanics and Pulmonary function testing

4) Respiratory Pathology
   Asthma- pathophysiology, clinical manifestations, and management
   Upper Airway Obstruction- differential diagnosis, clinical manifestations, pathophysiology, management
   Acute Respiratory Distress Syndrome(ARDS)- clinical manifestations, pathophysiology, and management
   Bronchiolitis- clinical manifestations, pathophysiology, and management
   Respiratory failure based upon mechanical or respiratory pump failure- pathophysiology, management

5) Sepsis and Septic Shock
   - Definition (SIRS, Sepsis, Shock MOFS)
   - Pathophysiology
   - Etiology
   - Management including fluid resuscitation in shock, vasopressor and inotropic management, antibiotic therapy, oxygen delivery and oxygen consumption maximization, and usefulness of a Swann-Ganz catheter in these patients.
   - Discussion of areas of research involving new therapies which focus on immunomodulation.

6) Trauma
   - Blunt trauma of chest and abdomen
   - Burn resuscitation and management
   - Drowning and near-drowning
   - Head Injury

7) Neurological and Neurosurgical Intensive Care
   - Status epilepticus
   - Management of Increased intracranial pressure including pathophysiology, etiology, and therapy
     Hyperventilation
     Osmotic diuretics
     Fluid management
   - Brain death criteria

8) Endocrine Issues in the PICU
- Hyper and hypoosmolar states specifically SIADH, DI and CSW(cerebral salt wasting)
- Substrate utilization and insulin, cortisol and thyroid hormones effects on it.
- Magnesium and Calcium homoeostasis
- Diabetes mellitus and DKA

9) Inborn Errors of Metabolism
- review of when to suspect an IE and how to proceed with a general work up of these illnesses

10) Renal Issues in the PICU
- Diuretics including mechanisms of action, appropriate use, adverse effects and pharmacokinetics
- Acute renal failure
  >recognition
  >etiologies
  >management
- Dialysis, CAVH and CVVH

11) Hematology
- Definition of makeup of different blood products and when they are commonly used
- Coagulation abnormalities including etiology, definition, evaluation, and therapy
- Anemias including etiology, evaluation and therapy

12) Ingestions
- recognition
- evaluation
- management

NEUROMUSCULAR BLOCKING AGENTS

Maureen Hall, Pharm.D.

I. Succinylcholine
- A. Action: short acting depolarizing agent
- B. Dose: 1 - 1.5 mg/kg
- C. Onset of action: less than 2 minutes
- D. Duration of action: 15 minutes (prolonged in liver disease, infancy and pregnancy)
- E. Indications
  1. recommended only for emergent intubations in children
  2. not recommended for patients with increased ICP, increased intraocular pressure
  3. use with caution in patients at risk for developing hyperkalemia
- F. Adverse Effects:
  1. bradycardia
  2. increased intracranial, intraocular and intragastric pressures
  3. hyperkalemia
- G. Reversal with cholinesterase inhibitors is not indicated unless Phase II block is determined

II. Pancuronium
- A. Action: long acting nondepolarizing agent
- B. Dose: 0.1 mg/kg or 0.06-0.1 mg/kg/hr
- C. Onset of action: 3 - 4 minutes
- D. Duration of action: 1.5 hours
- E. Indications
  1. used prn to maintain paralysis in mechanical ventilated patients
  2. not recommended in patients with cardiovascular disease or severe renal impairment
- F. Adverse Effects:
  1. Hypertension, tachycardia, increased myocardial contractility and cardiac output due to weak sympathomimetic effects
  2. Decreased metabolism and prolonged effects in patients with renal or hepatic dysfunction
  3. Prolonged paralysis after long-term administration has been reported
  4. No histamine related adverse effects
- G. Effects can be reversed with cholinesterase inhibitors such as neostigmine, pyridostigmine or edrophonium

III. Vecuronium
- A. Action: intermediate acting nondepolarizing agent
- B. Dose: 0.1 mg/kg or 0.1 mg/kg/hr
- C. Onset of action: 3 minutes
- D. Duration of action: 30 - 45 minutes
- E. Indications
  1. intubation or prolonged paralysis in mechanically ventilated patients
  2. can be used in patients with cardiovascular disease or asthma
  3. use with caution in patients with severe renal dysfunction
- F. Adverse Effects:
  1. Prolonged effects in patients with severe renal impairment
  2. Prolonged paralysis after long-term administration has been reported
  3. No cardiovascular adverse effects or histamine related adverse effects
- G. Effects can be reversed with cholinesterase inhibitors

IV. Mivacurium
- A. Action: short acting nondepolarizing agent
- B. Dose: 0.2 mg/kg
- C. Onset of action: 2 - 3 minutes
- D. Duration of action: 20 - 30 minutes
- E. Indications
  1. intubation
  2. use with caution in patients with cardiovascular disease or asthma (<1% chance of severe histamine mediated reactions associated with rapid administration)
  3. use with caution in patients with severe renal dysfunction
- F. Adverse Effects:
  1. Prolonged effects in patients with severe renal or hepatic impairment
  2. Histamine mediated reaction associated with rapid administration. Reaction primarily manifested as flushing.
- G. Effects can be reversed by cholinesterase inhibitors

V. Atracurium

A. Action: intermediate acting nondepolarizing agent

B. Dose: 0.5 mg/kg or 0.4 - 1 mg/kg/hr

C. Onset of action: 3 minutes

D. Duration of action: 30 - 45 minutes

E. Indications

1. intubation or prolonged paralysis in mechanically ventilated patients
2. can be used safely in patients with severe renal or hepatic impairment without prolonged paralysis

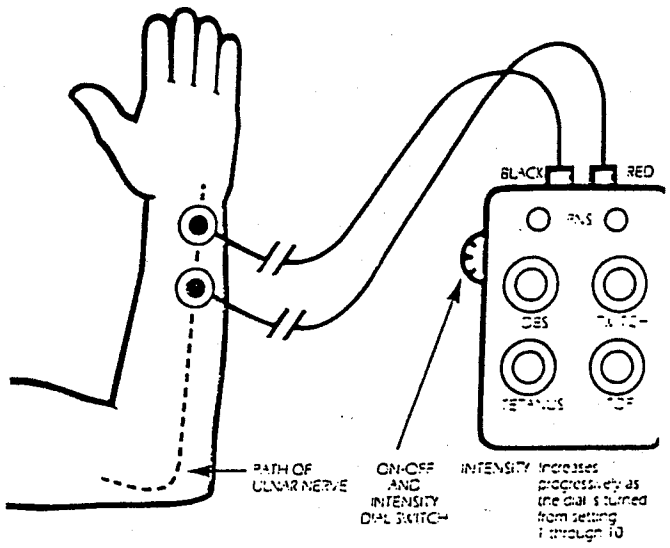
F. Adverse Effects:

1. histmine mediated reactions resulting in hypotension and tachycardia following rapid administration (recommended administration time: > 1 minute)
2. Atracurium's metabolite, laudanosine, does not cause blockade, but may be a convulsant. No documented cases of laudanosine-induced seizures to date
2. Prolonged paralysis is NOT evident in renal or hepatic failure

G. Effects can be reversed by cholinesterase inhibitors

TIPS ON THE PERIPHERAL NERVE STIMULATOR

1. Apply electrodes over ulnar nerve



2. Start at lowest output.

3. Press train of four (TOF) button.

4. Increase output until you obtain a response or you get no response on max output.

5. Response is thumb twitch only, not finger twitch.

6. 1 to 2 thumb twitches are appropriate.

7. Document number of twitches out of TOF (ex. 0/4, 1/4, 2/4, etc.)

8. 0/4 twitches = patient is over blocked - decrease or stop neuromuscular blockade.

9. 4/4 twitches = patient is under blocked - increase dose.

JC\lm

{Janet\Periph.tip}

DRUG THERAPY

ALASTAIR J.J. WOOD, M.D., *Editor*

NEW NEUROMUSCULAR BLOCKING DRUGS

JENNIFER M. HUNTER, M.B.

NEUROMUSCULAR blocking drugs are routinely used during the administration of anesthesia to allow surgical access to body cavities, in particular the abdomen and thorax, without hindrance from voluntary or reflex muscle movement. The introduction of these agents in 1942 marked a major advance in anesthesia and surgery, allowing the anesthesiologist to maintain respiratory function during prolonged and complex surgery. Neuromuscular blocking drugs are also used in the care of critically ill patients undergoing intensive therapy, to facilitate compliance with mechanical ventilation when sedation and analgesia alone have proved inadequate. In this review, I describe the pharmacology and uses of neuromuscular blocking drugs, as well as their side effects and disadvantages, with particular reference to conditions in which the drugs have an altered effect.

NEUROMUSCULAR TRANSMISSION AND BLOCKADE

The neuromuscular junction contains three types of nicotinic receptors: two on the muscle surface, one junctional and the other extrajunctional, and a presynaptic receptor on the parasympathetic-nerve ending.[1] On the arrival of a nerve impulse, a burst of molecules of the neurotransmitter acetylcholine is released from the presynaptic nerve ending. Acetylcholine crosses the junctional cleft and stimulates the postsynaptic junctional receptors, allowing ions to flow through them and depolarize the end plate. Acetylcholine is then rapidly broken down by the enzyme acetylcholinesterase, which is present in the junctional cleft. This neurotransmitter also stimulates the presynaptic receptors to mobilize more acetylcholine for subsequent release from the nerve ending. The extrajunctional receptors are not involved in normal neuromuscular transmission but may proliferate if the muscle is diseased or damaged, altering the effect of neuromuscular blocking drugs.

The postsynaptic receptors are concentrated on the junctional folds, immediately opposite the sites on the nerve ending where acetylcholine is released. They are proteins consisting of five subunits, designated α, β, δ, and ϵ, which are arranged concentrically; each receptor has two α subunits. One acetylcholine molecule binds to one α subunit. When two acetylcholine molecules bind simultaneously to the two α subunits of a receptor, a channel opens through the center of the receptor, allowing sodium and calcium ions to move into the muscle and potassium to move out. Each neuromuscular junction contains several million junctional receptors. After a burst of acetylcholine has been released from the nerve ending, at least 400,000 receptors open and allow sufficient current through them to depolarize the end plate and create the potential that triggers muscle contraction.

Depolarizing neuromuscular blocking drugs bind to the α subunit in the same way that acetylcholine does. If these drugs bind to a pair of α subunits, they stimulate an initial opening of the ion channel, producing a contraction known as a fasciculation. But since these drugs are not broken down by acetylcholinesterase, they bind for a much longer period than acetylcholine does, causing persistent depolarization of the end plate and a neuromuscular block.

Nondepolarizing neuromuscular blocking drugs compete with acetylcholine to bind to an α subunit. If they are attached to at least one α subunit, the ion channel through the center of the receptor will not open and no current will flow through it. The membrane will not depolarize, and the muscle will become flaccid. The physiology and pharmacology of neuromuscular transmission have been reviewed by Bowman.[2]

Depolarizing Neuromuscular Blocking Drugs

Succinylcholine (suxamethonium) is the only depolarizing neuromuscular blocking drug currently available. It has a structure similar to that of two molecules of acetylcholine (Fig. 1). The onset of the neuromuscular block is rapid (one minute), and its duration is short (seven to eight minutes).[3] Because of these characteristics, succinylcholine is used to facilitate rapid tracheal intubation during the induction of anesthesia, which is essential if aspiration of gastric contents is to be avoided. The drug is metabolized by plasma cholinesterase, which is synthesized in the liver. The side effects of succinylcholine, however, are formidable. Postoperative muscle pain is common, and hyperkalemia and increased intraocular and intragastric pressure may occur.[4] The drug may also trigger malignant hyperthermia, a rare but potentially fatal muscle disorder.[5]

Nondepolarizing Neuromuscular Blocking Drugs

The nondepolarizing neuromuscular blocking drugs — tubocurarine, gallamine, metocurine, alcuronium, pancuronium, atracurium, and vecuronium — were introduced between 1942 and 1982. These drugs are quaternary ammonium compounds that have at least one positively charged nitrogen atom to bind to the α subunit of the postsynaptic receptor (Fig. 1). They are either benzylisoquinolinium compounds (tubocurarine, metocurine, alcuronium, and atracurium), quaternary amines (gallamine), or aminosteroid compounds (pancuronium and vecuronium).

Although the nondepolarizing neuromuscular blocking drugs do not have the same adverse effects as suc-

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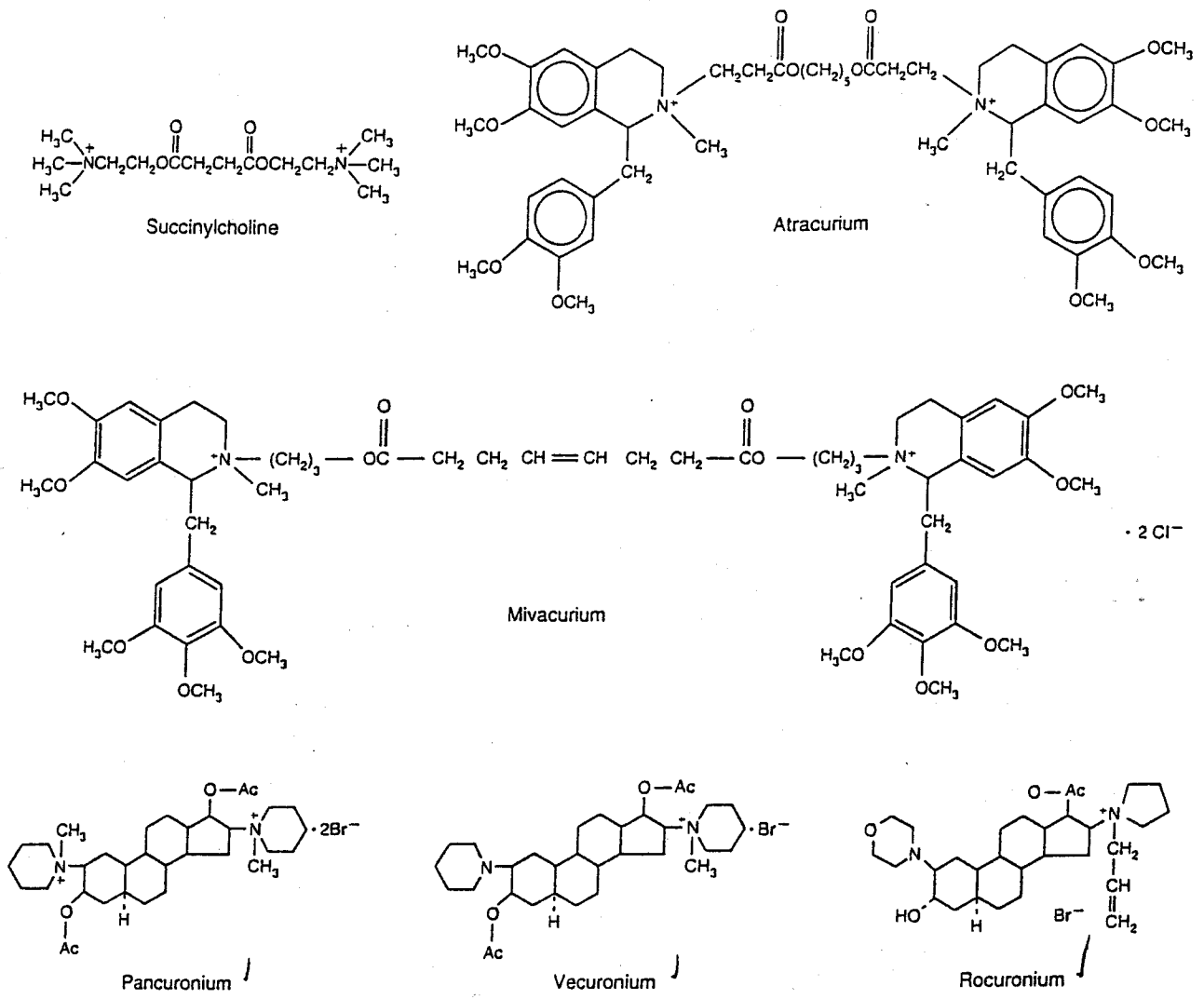

Figure 1. The Structure of Succinylcholine (Suxamethonium), the Benzylisoquinolinium Derivatives Atracurium and Mivacurium, and the Aminosteroid Compounds Pancuronium, Vecuronium, and Rocuronium.

Each drug contains at least one quaternary ammonium group [$N^+(CH_3)_3$], which binds to an α subunit of the nicotinic receptor. Succinylcholine is a depolarizing neuromuscular blocking drug; all the other agents are nondepolarizing drugs. The ester linkage on the carbon chains of the succinylcholine and mivacurium molecules is hydrolyzed by plasma cholinesterase.

cinylcholine, their onset of action is slower (Table 1). They also have a longer duration of action, making them more suitable for maintaining neuromuscular relaxation during major surgical procedures.

In the past three years, two new aminosteroid compounds, pipecuronium and rocuronium, and two new benzylisoquinolinium compounds, doxacurium and mivacurium, have become available. Other compounds, such as cisatracurium, the 1R *cis*–1′R *cis* isomer of atracurium, are being evaluated in clinical trials. These new compounds have been developed in an attempt to speed up the onset of action and diminish the side effects associated with the older drugs.

One drug will probably never satisfy all the requirements, however, because different uses call for different properties. Three types of drug have been proposed: a drug with a rapid onset of action (within 1 minute) but a short duration of action (5 to 10 minutes) that can be given by continuous infusion, a drug with a rapid onset of action and an intermediate duration of action (20 to 30 minutes), and for major surgery, a long-acting drug without cardiovascular effects.[20]

There is actually little need for a long-acting drug. Anesthesiologists require a nondepolarizing drug with a rapid onset of action (within 1 minute) and a short duration of action (about 10 to 12 minutes) that has no adverse cardiovascular effects. Such a drug could be given by continuous infusion during major surgery, thereby prolonging the duration of action.

Anticholinesterase Drugs

The effect of nondepolarizing neuromuscular blocking drugs can be reversed, once recovery from the blockade has commenced, by the administration of an anticholinesterase drug, such as neostigmine or edrophonium, that inhibits the action of acetylcholines-

Table 1. Onset and Duration of Action of Neuromuscular Blocking Drugs.

Drug	Dose	Time to Maximal Blockade*	Time to Recovery† 25%	75%
	mg/kg	minutes		
Quaternary amine				
Succinylcholine[6]	1.0	1.1	8	11 (90%)
Benzylisoquinolinium compounds				
Tubocurarine[7,8]	0.5	3.4	—	130
Metocurine[9]	0.4	4.1	107	—
Alcuronium[10]	0.2	7.1	47 (20%)	90 (70%)
Atracurium[11]	0.4	2.4	38	52
Doxacurium[12]	0.05	5.9	83	116
Mivacurium[13,14]	0.15	1.8	16	25
Cisatracurium[11]	0.1	7.7	46	63
Aminosteroid compounds				
Pancuronium[15,16]	0.08	2.9	86	—
Vecuronium[17]	0.1	2.4	44	56
Pipecuronium[18]	0.07	2.5	95	136
Rocuronium[19]	0.6	1.0	43	66

*The time to the maximal blockade of the train-of-four response after 2.0 to 2.5 times the ED_{95} (the dose required to produce a 95 percent reduction in twitch height).

†The times to 25 and 75 percent recovery of the T_1 response, except for succinylcholine and alcuronium, for which the percentage of recovery is given in parentheses.

terase at the neuromuscular junction. Acetylcholine thus accumulates, competing with the diminishing concentration of the neuromuscular blocking drug at the postsynaptic membrane and potentiating recovery from residual neuromuscular blockade.

Anticholinesterase drugs, especially neostigmine, also inhibit plasma cholinesterase activity and may therefore potentiate and lengthen the blockade produced by succinylcholine.[21] But neostigmine antagonizes the blockade produced by mivacurium, the new short-acting nondepolarizing agent that is also broken down by plasma cholinesterase.[22]

Pharmacodynamics

The clinical pharmacodynamics of neuromuscular blocking drugs are determined by measuring the speed of onset of the neuromuscular blockade and its duration. A peripheral muscle that is easily accessible during surgery, such as the adductor pollicis muscle in the hand, is monitored by electrical stimulation of its motor nerve (the ulnar nerve) to determine the duration of action. Such monitoring does not accurately reflect the behavior of certain other muscle groups, such as the respiratory or laryngeal muscles, because of variations in sensitivity and the duration of the response to neuromuscular blocking drugs.[23] The diaphragm is more resistant than the adductor pollicis and may remain paralyzed for a shorter period. The varying duration of the response to a neuromuscular blocking drug in different muscle groups is probably due to more rapid equilibration of the drug in muscles with greater blood flow.[24] Nevertheless, monitoring of the response to electrical stimulation provides more information than clinical evaluation and can detect a degree of residual blockade not otherwise apparent at the end of surgery.

During the monitoring procedure, supramaximal stimuli are applied to the nerve and the response is assessed by visual or tactile means. The mechanical response can be recorded by a strain-gauge transducer, or the evoked compound muscle action potential can be measured by electromyography. Various patterns of nerve stimulation are used to assess the degree of the blockade — for example, a tetanic burst (50 to 100 Hz) or single-twitch stimuli (up to 1 Hz). The train-of-four stimulus is popular; in this procedure four twitch stimuli (2 Hz) are applied at intervals of at least 10 seconds.[25] After the administration of a nondepolarizing drug, the height of the successive responses decreases, but no such decrease occurs when succinylcholine is given (Fig. 2). The ratios of the first response in the train to the control response (T_1:T_c) and of the fourth response to the first response (T_4:T_1) are used as measures of the blockade. Although the recovery of the T_1 response and that of the single-twitch response are similar, use of the T_4:T_1 ratio has the advantage of not requiring a base-line measurement. The return of full muscle power can be relied on only if the anticholinesterase is not given until the second twitch of the train-of-four response is detectable (20 to 25 percent recovery of T_1).

To compare neuromuscular blocking drugs, it is necessary to use comparably effective doses, since these

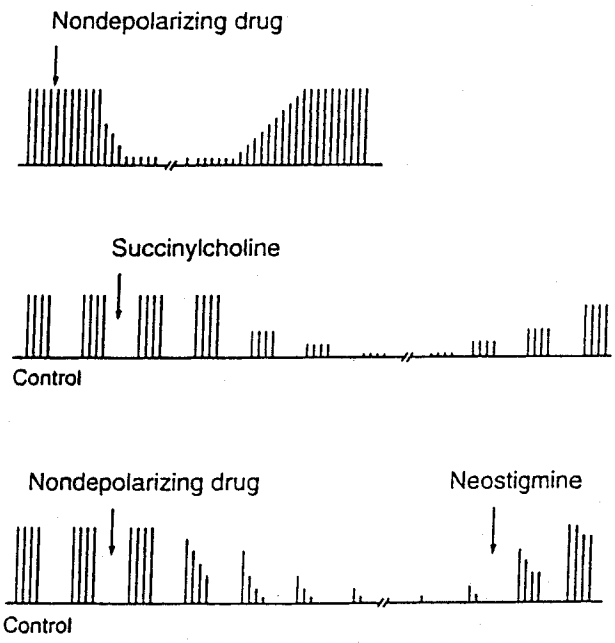

Figure 2. Effects of Neuromuscular Blocking Drugs on the Single-Twitch and Train-of-Four Responses.

The top panel shows the effect of a nondepolarizing neuromuscular blocking drug on the single-twitch response. A depolarizing drug would have the same effect. The middle panel shows the effect of succinylcholine on the train-of-four response after control values have been recorded. All four twitches are depressed equally; no fading of the train-of-four response occurs during the onset or duration of action. The bottom panel shows the contrasting effect of a nondepolarizing neuromuscular blocking drug, which causes a decrement in the train-of-four response. Recovery from the neuromuscular blockade is hastened by the administration of the anticholinesterase agent neostigmine.

drugs differ widely in potency. The dose required to produce a 95 percent reduction in twitch height (ED_{95}) is measured for this purpose. A doubling of this dose is usually suitable to facilitate tracheal intubation (Table 1). The depth and duration of neuromuscular blockade are potentiated by volatile anesthetic agents, particularly enflurane and isoflurane and, to a lesser extent, halothane,[26] and the effect is more marked with the longer-acting drugs. The duration of the blockade produced by nondepolarizing drugs is also increased by prior administration of succinylcholine.[27]

PHARMACOKINETICS

The plasma clearance, volume of distribution, and terminal half-life of neuromuscular blocking drugs have been determined in healthy subjects, patients with impaired renal or hepatic function, young and old subjects, and patients anesthetized with different volatile agents. The clearance and volume of distribution of neuromuscular blocking drugs in healthy subjects are shown in Table 2. (The values for the terminal half-life are not included because they are poorly correlated with the duration of action of a neuromuscular blocking drug administered in a bolus dose.) These drugs are highly ionized, water-soluble compounds; they have volumes of distribution not much greater than the extracellular-fluid volume (200 ml per kilogram of body weight).

Isomerism

Atracurium is a mixture of 10 geometric isomers with different clearance rates and terminal half-lives.[39] Mivacurium chloride is a mixture of three stereoisomers — one with a *cis–trans* configuration (57 percent), one with a *trans–trans* configuration (37 percent), and one with a *cis–cis* configuration (6 percent) — all of which are metabolized by plasma cholinesterase.[40]

Table 2. Pharmacokinetic Characteristics of Nondepolarizing Neuromuscular Blocking Drugs in Patients without Systemic Disorders.

Drug	Plasma Clearance	Volume of Distribution at Steady State
	$ml \cdot kg^{-1} \cdot min^{-1}$	$ml \cdot kg^{-1}$
Quaternary amine		
Gallamine[28]	1.3	207
Benzylisoquinolinium compounds		
Tubocurarine[29]	2.3	297
Metocurine[30]	1.2	472
Alcuronium[31]	1.3	321
Atracurium[32,33]	6.6	87
Doxacurium[34]	2.7	220
Mivacurium[35]		
Cis–cis	5.2	266
Cis–trans	95.0	210
Trans–trans	70.0	200
Cisatracurium*	5.1	153
Aminosteroid compounds		
Pancuronium[15]	1.8	241
Vecuronium[36]	5.3	199
Pipecuronium[37]	3.0	350
Rocuronium[38]	2.9	207

*Unpublished data.

Table 3. Urinary and Biliary Excretion of Neuromuscular Blocking Drugs.

Drug	Excretion (%)*	
	Urine	Bile
Quaternary amine		
Succinylcholine	<10	—
Gallamine[42]	95	<1
Benzylisoquinolinium compounds		
Tubocurarine[43]	45	12
Alcuronium[44]	80–85	15–20
Metocurine[30]	43	2
Atracurium[45]	10	—
Doxacurium[34]	25–30	—
Mivacurium[46]	<10	—
Aminosteroid compounds		
Pancuronium[47]	40	10
Vecuronium[48]	15	40
Pipecuronium[49]	38	2
Rocuronium[50]	9	54

*Percentage of a dose excreted in 24 hours.

The two more abundant isomers are 10 to 15 times more potent than *cis–cis* mivacurium, have very short half-lives,[41] and are responsible for the duration of action of a bolus dose. The *cis–cis* isomer is cleared at a rate closer to that of other nondepolarizing neuromuscular blocking drugs of intermediate duration (Table 2).

Elimination by Organs

Before the development of atracurium in 1982, all the available nondepolarizing neuromuscular blocking drugs were excreted by glomerular filtration (Table 3), and their action was prolonged in patients with renal dysfunction. Atracurium is degraded spontaneously in the plasma at body temperature and pH (Hofmann elimination) and by ester hydrolysis.[31] It is therefore the only nondepolarizing neuromuscular blocking drug with sufficient alternative pathways of disposition that the dose need not be reduced in patients with renal failure. Vecuronium, doxacurium, pipecuronium, and rocuronium are all excreted in the urine (Table 3). Since the aminosteroid drugs are deacetylated in the liver, their clearance and effect may be prolonged in patients with hepatic disease. These drugs are also excreted unchanged in the bile (Table 3); their clearance is decreased in the presence of extrahepatic biliary obstruction.

Active Metabolites

Deacetylation of some of the aminosteroid compounds produces metabolites with neuromuscular blocking activity. Such an effect has been demonstrated with 3-desacetylpancuronium[47] and 3-desacetylvecuronium. These water-soluble metabolites are half as potent as the parent compound and are excreted in the bile and urine. 3-Desacetylvecuronium may contribute to the cumulative effect of repeated doses of vecuronium.[52]

Laudanosine, the metabolite of Hofmann degradation of atracurium, does not have neuromuscular blocking properties but is epileptogenic at very high doses in animals.[53] It is excreted in part in the urine.[45] A plasma

laudanosine concentration of 17 μg per milliliter causes convulsions in dogs.[54] After a bolus dose of 0.5 mg of atracurium per kilogram in patients with renal failure, the peak plasma laudanosine concentration is 0.3 μg per milliliter[55]; after continuous infusions of atracurium (at least 0.6 mg per kilogram per hour) for 30 hours in patients with multiple organ failure who are undergoing intensive therapy, the plasma laudanosine concentration may reach 4.3 μg per milliliter.[56] In no instance, however, has any adverse effect been attributed to the accumulation of laudanosine.

Since cisatracurium is a more potent drug than atracurium[57] (ED_{95}, 0.05 and 0.23 mg per kilogram, respectively), a smaller mass of laudanosine should be produced when an equipotent dose is given, presumably with even less possibility of an effect within the central nervous system.

Specific Indications for Neuromuscular Blocking Drugs

Tracheal Intubation

Succinylcholine has a rapid onset of action, but its use to facilitate intubation is essential only in the presence of residual gastric contents. Otherwise, nondepolarizing drugs can be used, although their slower onset of action makes it necessary for the anesthesiologist to take gradual control of ventilation until the blockade is maximal (Table 1). The conditions for intubation will then be optimal, and there will be no need for succinylcholine. Rocuronium, one of the new nondepolarizing neuromuscular blocking drugs, has an onset of action that may be similar to that of succinylcholine, although the duration of its action is similar to that of vecuronium (Table 1).[19]

Short Surgical Procedures

Before atracurium and vecuronium became available, procedures of less than 30 minutes' duration that required muscle relaxation were difficult for the anesthesiologist to manage. The dose of a nondepolarizing drug such as tubocurarine had to be reduced; otherwise, the duration of action was too long. Administration of a lower dose had the disadvantage of delaying the onset of action and reducing the degree of neuromuscular blockade. The alternative was to administer bolus doses of succinylcholine repeatedly, which had the disadvantage of resulting in a widely variable degree of blockade and an increased risk of side effects. The shorter duration of action of atracurium and vecuronium makes them more suitable for brief procedures,[58] although if the operation lasts less than 15 minutes, even these agents are too long-acting (Table 1). The introduction of mivacurium has proved useful in this respect. The speed of its onset of action is similar to that of atracurium, but recovery is two to three times more rapid.[40]

Long Surgical Procedures

Longer-acting nondepolarizing drugs, such as tubocurarine, pancuronium, and now doxacurium and pipecuronium, may be more suitable for procedures lasting more than 90 minutes, although even with these drugs, repeated doses will be needed if the operation lasts many hours. Induced recovery from residual blockade after the administration of an anticholinesterase drug will take longer and may be less complete with long-acting drugs than with intermediate-acting drugs.[59]

A more satisfactory alternative may be the administration of shorter-acting drugs, such as atracurium, by continuous infusion.[60] An anticholinesterase drug is given after the infusion has been stopped, when recovery from the neuromuscular blockade has commenced. Neuromuscular function should be monitored throughout the procedure.

Intensive Therapy

Neuromuscular blocking drugs are occasionally used, in addition to analgesic and sedative drugs, to maintain adequate oxygenation in patients who are receiving mechanical ventilation in an intensive care unit. These drugs are particularly useful in patients with the adult respiratory distress syndrome, in whom the respiratory drive is substantial. Other indications are given in Table 4. For many years, the older agents, especially pancuronium, were given in repeated bolus doses. The cost of the drug itself was low, but in patients with organ dysfunction, the recovery from neuromuscular blockade could be slow, resulting in delayed weaning from the ventilator.[61] A similar effect can occur with vecuronium, in part because of the accumulation of 3-desacetylvecuronium, the active metabolite.[62]

Atracurium has proved useful in the care of critically ill patients. No evidence of delayed recovery from neuromuscular blockade was found when the drug was administered as a continuous infusion for many days.[63] Concern has been expressed, however, about the higher cost of this technique, as compared with the cost of bolus doses of pancuronium, in addition to the potential

Table 4. Indications for the Use of Neuromuscular Blocking Agents, in Addition to Sedative and Analgesic Drugs, in Patients Receiving Mechanical Ventilation in an Intensive Care Unit.

Endotracheal intubation and endoscopy
Decreased lung or chest-wall compliance (e.g., adult respiratory distress syndrome)
Struggling, coughing, or hiccuping, despite adequate sedation
Raised or potentially raised intracranial pressure
Inappropriate, unsuppressible respirations (e.g., central neurogenic hyperventilation, permissive hypercapnia to prevent barotrauma from the adult respiratory distress syndrome, asthma, or other conditions)
Tetanus
Status epilepticus
Status asthmaticus
Strychnine poisoning
Other indications
To reduce the metabolic demands of breathing
To prevent shivering (e.g., in patients with burns, during therapeutic cooling, or during the postoperative period)
For procedures during which movement may be hazardous (e.g., extracorporeal membrane oxygenation, line insertion, transportation, or radiologic procedures)

side effects of laudanosine. Early studies of cisatracurium in critically ill patients suggest that the speed of recovery is nearly identical to that of atracurium[64] but that plasma laudanosine concentrations are lower with cisatracurium (unpublished data).

Adverse Effects of Nondepolarizing Neuromuscular Blocking Drugs

Cardiovascular Side Effects

Neuromuscular blocking drugs have the potential to produce adverse effects at muscarinic receptors and nicotinic receptors other than those at the neuromuscular junction. These effects, which are common with the older drugs, include hypertension and tachycardia due to muscarinic blockade. Ganglionic blockade occurs with large doses of tubocurarine (Table 5). Atracurium and vecuronium have no direct cardiovascular effects.[38] The newer agents have been developed with the aim of avoiding these side effects, but rocuronium may have a slight vagolytic effect.[19] Although the absence of cardiovascular effects is considered advantageous, it may allow the effects of other anesthetic agents to become manifest (e.g., bradycardia with opioid analgesic drugs).

The release of histamine may lead to vasodilatation, hypotension, and compensatory tachycardia (Table 5). These effects are more pronounced with the older benzylisoquinolinium compounds, especially tubocurarine, than with atracurium and do not occur with the aminosteroid compounds.[65,66] Mivacurium stimulates the release of histamine to the same degree that atracurium does, but doxacurium and cisatracurium do not have such an effect.[57,65,67]

Critical-Illness Myopathy

A small fraction of patients with multiple-organ failure who receive mechanical ventilation for many days have severe muscle weakness on recovery. Some of these patients have received nondepolarizing neuromuscular blocking drugs.[68] Recovery from the myopathy may take several weeks. The condition is thought to be more common when an aminosteroid compound is used in conjunction with corticosteroid therapy,[69] but this impression may be influenced by the more frequent use of aminosteroid compounds than of atracurium in critically ill patients in North America. Two cases of persistent weakness after high doses of atracurium and a corticosteroid agent were recently reported.[70] Such myopathy is probably caused by several factors, such as immobility, metabolic disturbances, and multiple-drug therapy. It is unlikely that the effect is due solely to the use of neuromuscular blocking drugs.

Table 5. Adverse Cardiovascular Effects of Neuromuscular Blocking Drugs.

Ganglionic Blockade	Sympathetic Stimulation	Vagolytic Effect	Vagal Stimulation	Histamine Release
Tubocurarine* Metocurine Alcuronium	Gallamine* Pancuronium	Gallamine* Alcuronium Pancuronium ? Rocuronium	Succinylcholine	Tubocurarine* Gallamine Metocurine Succinylcholine Alcuronium Atracurium Mivacurium

*Denotes the drug producing the most marked effect.

Neuromuscular Blocking Drugs in Particular Groups of Patients

Neonates

Neonates may have a resistance to the action of depolarizing drugs,[71] but the results of electromyographic studies suggest that they do not differ from adults in their response to nondepolarizing neuromuscular blocking drugs.[72] A given plasma concentration of tubocurarine has a greater effect in neonates than in adults.[73] Because the volume of distribution of the drug is larger in neonates, however, an equivalent dose per unit of body weight will result in a lower plasma concentration. The two factors tend to balance one another, so that the required dose per unit of body weight does not differ greatly according to age.

Infants and Young Children

The physiologic factors influencing the distribution and effect of neuromuscular blocking drugs in infants and young children are intermediate between those in neonates and adults. For example, the plasma concentration of tubocurarine at which a 50 percent depression of the T_1 response occurs is higher in infants than in neonates, but not as high as in adults.[73] Cardiac output in relation to body weight is higher in infants and children than in adults, and the onset of the neuromuscular blockade may therefore be more rapid.

Elderly Patients

The action of neuromuscular blocking drugs may be prolonged in elderly patients, since renal function and hepatic function decline with advancing age. The plasma clearance of tubocurarine,[74] metocurine,[74] vecuronium,[75] and rocuronium[76] is reduced in elderly patients. The clearance of mivacurium is slightly decreased,[77] possibly reflecting a small reduction in plasma cholinesterase concentrations with increasing age. The plasma clearance of atracurium is not affected.[78] Cardiac output may be reduced in elderly patients, prolonging the delivery of the drug to the neuromuscular junction and slowing the onset of its action.

Patients with Renal Disease

Prolonged neuromuscular blockade was reported in 1963 in a patient with chronic renal failure who had received 120 mg of gallamine.[79] Despite repeated doses of anticholinesterase, recovery took five days. Prolonged blockade has subsequently been reported not only in other patients with renal failure who received gallamine, but also in similar patients who received pancuronium,[80] tubocurarine,[80] or vecuronium,[81] although in the latter patients the neuromuscular blockade did

not last as long. Decreased renal clearance, together with an increased volume of distribution in patients with edema, accounts for the delayed recovery.

Atracurium has improved the anesthetic care of patients with chronic renal failure, because its pharmacodynamics and pharmacokinetics are not altered in these patients.[82] There are multiple pathways for the elimination of atracurium, and only about 10 percent of a dose of the drug is excreted in the urine in 24 hours.[45] Therefore, the risk of residual neuromuscular blockade is low.

Pipecuronium and doxacurium should not be given to patients with renal failure, because the clearance of these drugs is markedly reduced.[34,83] Plasma cholinesterase activity may be reduced in patients with chronic renal failure, so that the duration of action of mivacurium is increased.[84] The plasma clearance of rocuronium is not affected by renal dysfunction, but patients with renal failure have a larger volume of distribution of the drug, and the terminal half-life is therefore longer.[38]

Patients with Hepatic Disease

Since patients with hepatic disease retain fluid, they may have a resistance to the effect of neuromuscular blocking drugs because of a larger volume of distribution.[85] When adequate neuromuscular blockade has been achieved, the action of the drugs metabolized or excreted by the liver will be prolonged.[86,87] The pharmacodynamics[88] and pharmacokinetics[32] of atracurium in patients with cirrhosis are similar to those in healthy subjects. Doxacurium may be given during prolonged procedures, such as liver transplantation (if renal function is normal),[34] but mivacurium may have a prolonged effect, since plasma cholinesterase activity is frequently reduced.[14] In patients with extrahepatic biliary obstruction, atracurium or doxacurium may be preferable. All the other nondepolarizing drugs except gallamine[42] are excreted in the bile (Table 3).

Patients with Cardiovascular Disease

Vecuronium is most suitable for patients with cardiovascular disease, because the drug has no cardiovascular effect. For major surgery, such as cardiac bypass procedures, doxacurium or pipecuronium can be used, especially if controlled ventilation is continued after surgery.

Patients with Neuromuscular Disorders

Succinylcholine should not be given to patients with any of the muscular dystrophies because of the risk of severe hyperkalemia or a malignant-hyperthermia–type syndrome.[89] Patients with myotonic dystrophy may have severe contractures after the administration of succinylcholine, preventing tracheal intubation. Reduced doses of nondepolarizing drugs with an intermediate or short duration of action should be given to such patients, and neuromuscular monitoring should be used.[89,90]

Patients with myasthenia gravis may have a resistance to succinylcholine, but their sensitivity to nondepolarizing drugs is increased.[91] Atracurium[92] and vecuronium[93] can be given in small doses, with recovery induced rapidly by an anticholinesterase drug.

Succinylcholine and possibly tubocurarine[94] and gallamine may trigger malignant hyperthermia. Pancuronium, atracurium, vecuronium, doxacurium,[95] mivacurium,[95] and rocuronium[96] are less likely to have such an effect.

Patients with Thermal Injury

Within 48 hours after a burn, extrajunctional nicotinic receptors develop on the membranes of damaged muscles. Administration of succinylcholine may then cause a massive efflux of potassium from the muscle cells. Plasma potassium concentrations as high as 13 mmol per liter have been reported, with cardiac arrhythmias and arrest.[97] Succinylcholine should therefore not be given to patients who have been burned. A marked resistance to nondepolarizing drugs has been reported in patients with severe burns, probably also as a result of the increased number of extrajunctional receptors.[98]

Patients with Reduced Cholinesterase Activity

An abnormally low plasma cholinesterase level can affect the rate at which succinylcholine or mivacurium is broken down. Several abnormal autosomal genotypes are recognized.[99] In patients who are heterozygous for the most common abnormality, the atypical gene, the duration of action of 1 mg of succinylcholine per kilogram is 30 minutes, as compared with 7 to 10 minutes in normal subjects. In patients who are homozygous for this defect, the blockade can last up to 3 hours, and 25 percent recovery of the T_1 response after a small dose of mivacurium (0.03 mg per kilogram) takes up to 80 minutes.[100] In heterozygotes, 25 percent recovery of the T_1 response after 0.2 mg of mivacurium per kilogram takes 32 minutes, as compared with 20 minutes in phenotypically normal patients.[100]

Plasma cholinesterase activity may also be reduced in pregnant women and patients with hepatic disease, renal disease, cancer, collagen disease, or hypothyroidism.[99]

Summary

The new nondepolarizing neuromuscular blocking drugs have specific advantages over succinylcholine. Rocuronium has an onset of action that is almost as rapid as that of succinylcholine and may be useful in patients with residual gastric contents. This drug may replace vecuronium, since the two agents are otherwise similar. The onset of action of mivacurium is similar to that of atracurium, but recovery from the blockade is more rapid (if the plasma cholinesterase level is normal), making mivacurium useful for short procedures. Although pipecuronium and doxacurium have minimal effects on the cardiovascular system, their long and variable onset and duration of action

limit their usefulness. The need for either drug is questionable. There is still a need, however, for a nondepolarizing drug that has an onset of action as rapid as that of succinylcholine but a duration of action similar to that of mivacurium, with no adverse cardiovascular effects and clearance from the body that is independent of organ function.

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REVIEW ARTICLES

CURRENT CONCEPTS

PULMONARY-FUNCTION TESTING

ROBERT O. CRAPO, M.D.

PULMONARY-FUNCTION tests provide objective, quantifiable measures of lung function. They are used to evaluate and monitor diseases that affect heart and lung function, to monitor the effects of environmental, occupational, and drug exposures, to assess risks of surgery, and to assist in evaluations performed before employment or for insurance purposes. The indications for pulmonary-function tests are summarized in Table 1. Spirometric examination, the most widely used such test, is the focus of this paper. Spirometry is the measurement of the movement of air into and out of the lungs during various breathing maneuvers. Such examinations should be readily available and routinely used in medical offices and hospitals where patients with heart and lung diseases are treated. Other common tests of lung function include the measurement of lung volumes, airway resistance, carbon monoxide diffusing capacity, and arterial-blood gases.

DIAGNOSTIC INDICATIONS

Pulmonary-function tests are useful in diagnosing and managing pulmonary diseases. The recommendations of the National Asthma Education Program indicate that such testing is essential in the diagnosis and management of asthma because of evidence that both patients and physicians have inaccurate perceptions of the severity of asthma that contribute to delays in treatment.[1] Indeed, underestimation of the extent of airflow (airway) obstruction is associated with increased mortality in asthma.[2]

Pulmonary-function tests can identify abnormalities of lung function that might otherwise be overlooked and can exclude the possibility of some respiratory disorders such as chronic obstructive pulmonary disease. Physicians cannot identify obstructive or restrictive patterns reliably from history taking and physical examination alone.[3-5] When physicians ordering lung-function tests were asked to predict the results, they correctly predicted an obstructive pattern 83 percent of the time.[4] However, predictions of normal or restrictive patterns were correct only about half the time.[4] Besides identifying abnormalities, lung-function tests allow the severity of an abnormality to be quantified and the presence of reversible airflow obstruction to be determined.

Pulmonary-function testing is sometimes indicated when there may be more than one explanation for a patient's symptoms. For example, a smoker who presents with dyspnea and obvious signs of congestive heart failure may also have obstructive lung disease. Failure to recognize and treat both disorders may limit the therapeutic response.

SCREENING AND MONITORING

Lung-function tests are included in many evaluations of fitness and some routine physical examinations. Such testing may provide interesting information, but in the absence of symptoms, physical findings, or risk factors its clinical usefulness is questionable. There is little evidence to support a policy of screening the general population with spirometry.[6] Some subgroups (e.g., cigarette smokers and people exposed to known agents of lung injury, such as asbestos or diisocyanates) are at higher risk of lung disease; screening and monitoring are appropriate for them.[6,7] It has been suggested that about 15 percent of cigarette smokers have an accelerated decline in the maximal volume of air exhaled, after a maximal inhalation, in the first second of a forced exhalation (i.e., the forced expiratory volume in one second, or FEV_1); ultimately, this condition leads to airflow obstruction and the possibility of early disability and death from chronic obstructive pulmonary disease.[8] Although the rates of loss of FEV_1 in smokers and nonsmokers overlap, nonsmokers tend to lose FEV_1 at a rate of 20 to 30 ml per year, whereas "sensitive" smokers (those with an accelerated decline in FEV_1) lose FEV_1 at a rate of more than 60 ml per year. In people under 35 years of age, cessation of smoking is associated with improved lung function; for those older than 35, the accelerated decline in lung function slows to the normal rate associated with aging.[8-10] Smokers with one normal spirogram cannot rest easy; they may still have an accelerated loss of lung function that is detectable only by serial measurements. Smokers may be more likely to stop smoking if they are informed of such functional abnormalities.

Serial measurement of lung function (monitoring) may be useful in tracking pulmonary expressions of diseases, quantifying responses to therapy, and making early diagnoses of lung injury after occupational exposures and drug or radiation therapy. Many diseases, including heart failure, rheumatoid arthritis, inflammatory bowel disease, and vasculitis, affect the lungs either directly or as a result of the adverse effects of treatment.[11] Monitoring lung function allows the physician to identify and quantify pulmonary involvement in such diseases. For example, serial measurement of vital capacity (VC) may help a physician

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are most likely to benefit from preoperative screening with spirometry and blood gas analysis.[21] Lower abdominal and head-and-neck surgery are associated with lower surgical risks. Spirometric testing and blood gas analysis are likely to help only patients without prior lung-function tests whose preoperative evaluation suggests the presence of pulmonary disease.[21]

Risk and Prognosis in Patients with Known Lung Dysfunction

Low levels of lung function, even in patients who have never smoked cigarettes, are associated with a poor prognosis in patients with heart and lung disease. Studies consistently find that reduced lung function (usually FEV_1) is associated with an increased risk of death from chronic obstructive pulmonary disease, non-neoplastic respiratory diseases, vascular diseases, lung cancer, and all causes of death considered together.[22-25] These findings are consistent among groups of patients, but it is not possible to predict the symptoms or mortality of individual patients accurately on the basis of FEV_1 alone.

Interpretation of Lung-Function Tests

Test quality remains the most important concern in lung-function testing. Variability (noise) is greater in pulmonary-function tests than in most other clinical laboratory tests because of the inconsistency of efforts by patients.[26] The American Thoracic Society (ATS), the European Respiratory Society, and other organizations have published standards designed to minimize the variability in these tests[27-44] (Table 2). The elements that lead to high-quality test results are accurate equipment, good test procedures, an ongoing program of quality control, appropriate reference values, and good algorithms for the interpretation of results. It is tempting to assume that all equipment on the market is accurate. However, a 1990 evaluation of spirometers revealed that only 57 percent met the standards of the ATS for accuracy.[42] Purchasers should insist on evidence that an instrument meets the ATS performance recommendations.[27] A quality-control program for spirometers that uses a calibrated 3.0-liter syringe and a few other simple checks[32] can be conducted easily in a physician's office. Monitoring the accuracy of instruments that measure diffusing capacity, lung volume, and blood gases is more difficult. These machines are best used in settings where there are larger volumes of patients.

The interpretation of lung-function tests usually involves comparing values measured in patients with reference values from studies of populations of healthy nonsmokers. There are substantial differences between the equations used to predict normal lung function, because of differences among the populations studied as well as technical and procedural differences. It is important to select equations for reference use that are well matched with the patients served in a particular office or laboratory. The ATS has published guidelines for making these choices.[33] Physicians unfamiliar with selecting reference values and choosing the lower limits of normal ranges should consult a local pulmonary-testing laboratory with expertise in this area.

The first step in interpreting a lung-function test is to assess and comment on test quality. Spirometric tracings should be examined to make sure they represent adequate effort by the patient, are reproducible, and contain no artifacts that would alter the test results (Table 3). If the requirements for quality are not met, tests should be interpreted (Table 4) with caution. Some technical problems are so important that

Table 2. Sources of Information on the Measurement and Interpretation of Pulmonary-Function Tests.

Type of Information	Reference
Adults	
Practical, how-to manuals or guides	Morris et al.,[38] Enright and Hyatt,[40] Miller,[39] Wanger,[41] Clausen[37]
Standards	
Equipment and procedures	
Spirometry	American Thoracic Society,[27] European Respiratory Society,[28] Morris et al.,[38] Nelson et al.[42]
DLCO	American Thoracic Society,[29] European Respiratory Society[28]
Lung volumes and mechanics	European Respiratory Society[28]
Personnel	Gardner et al.[30]
Computers	Gardner et al.[31]
Quality control	Gardner et al.,[32] Clausen[37]
Reference values and interpretation	American Thoracic Society,[33] European Respiratory Society,[28] Morris et al.,[38] Clausen[37]
Disability or impairment	American Medical Association,[43] American Thoracic Society[44]
Children	
Overall guidelines	Quanjer et al.,[34] Taussig et al.,[35] Zapletal et al.[36]

Table 3. Technical Requirements for Spirometry of Good Quality.*

At least 3 acceptable tests

Full inhalation before start of test
Satisfactory start of exhalation
  Evidence of maximal effort
  No hesitation
No cough or glottal closure during the first second
Satisfactory duration of test
  At least 6 seconds
  Up to 15 seconds in patients with airflow obstruction
No evidence of leak
No evidence of obstruction of the mouthpiece

Reproducible results

For FVC and FEV_1, the 2 largest values should be within 5 percent or 0.1 liter (whichever is larger) of each other
  If these criteria are not met, continue testing
  If the criteria are not met after 8 trials, stop testing and proceed with the interpretation, using the 3 best acceptable tests

Selection of test values for interpretation

Select from tests of acceptable quality
Select the largest values for FVC and FEV_1, regardless of the test used
For indexes of average or instantaneous flow, use values from the test with the largest value for FVC and FEV_1 combined

*Adapted from the statement of the American Thoracic Society,[27] with the permission of the publisher.

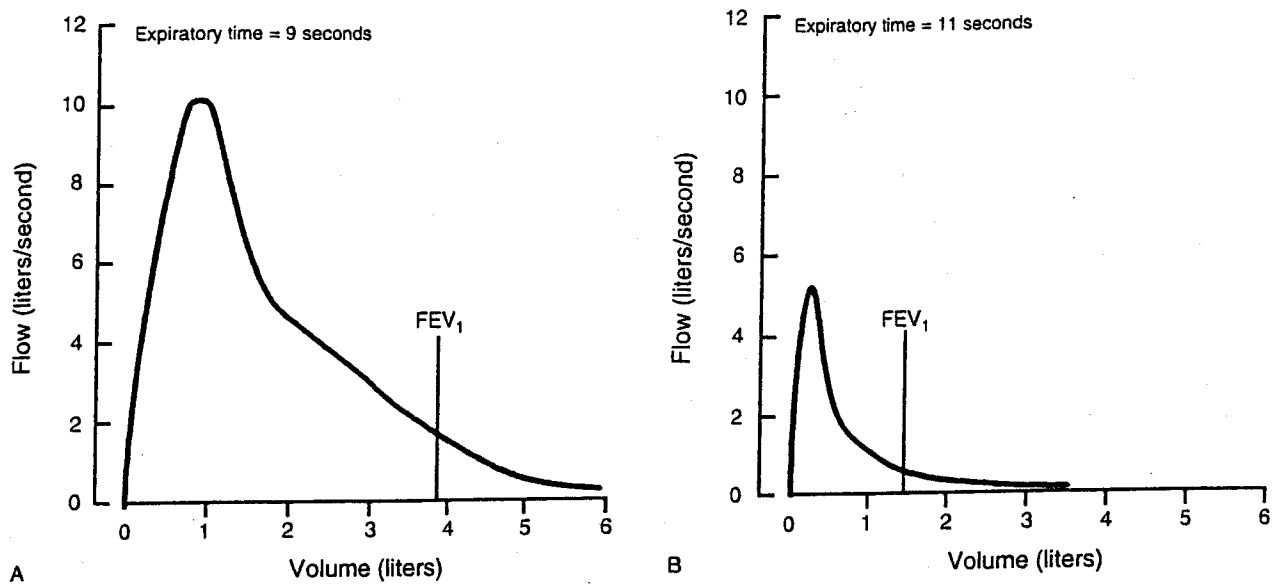

Figure 2. Expiratory Flow–Volume Curves for Patients with Mild and Severe Airflow Obstruction.

Panel A shows the curve for a 45-year-old man 184 cm tall with mild airflow obstruction. The initial effort is good, with early, well-defined peak expiratory flow. The concave character of the descending curve indicates the presence of airflow obstruction. $FEV_1/VC\%$ is reduced at 64 (predicted value, 80), but FEV_1 is normal (92 percent of predicted), indicating that the obstruction is mild. The expiratory flow approaches but does not reach zero, a subtle but important element to look for on the tracing; it may be the only evidence of a problem with the test, because total expiratory time is not seen on the flow–volume curve.

Panel B shows the curve for a 47-year-old man 183 cm tall with severe airflow obstruction. Although peak expiratory flow is reduced, the peak is well defined, indicating a good initial effort. There is a sudden drop in flow after the peak, and the tail of the expiration curve is long. The subject's $FEV_1/VC\%$ is 40. The marked reduction in FEV_1 (34 percent of predicted) indicates the presence of severe airflow obstruction.

changes in FVC and FEV_1 over time.[33] Treating a patient with a bronchodilator medication is a clinical, not a laboratory, decision. A response to this therapy in the laboratory makes a clinical response to therapy more likely; nevertheless, the lack of such a response does not preclude a clinical response to long-term bronchodilator therapy. If the clinical evaluation suggests that such therapy may be effective, it can be instituted and followed by a reevaluation, both clinical and spirometric, in four to six weeks. As when patients are monitored in other ways, patterns of change are more apparent with serial measurements.

Table 5. Response to Bronchodilator Therapy and Changes over Time.*

Measure of Response	Percent Change in FVC or FEV_1 Required for a Substantial Response†	Comment
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Classifying the severity of disease involves several complex issues. A general discussion and specific guidelines are provided in the statement by the ATS.[33]

Conclusions

There are good reasons to seek quantifiable data about lung function. Interpreting the results of pulmonary-function testing requires careful attention to the equipment used, the patient's performance, and the reference values chosen. In cases in which disease or lung injury may develop over time, a person's own base-line values provide the best reference data.

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REVIEW ARTICLES

CURRENT CONCEPTS

PULMONARY-FUNCTION TESTING

ROBERT O. CRAPO, M.D.

PULMONARY-FUNCTION tests provide objective, quantifiable measures of lung function. They are used to evaluate and monitor diseases that affect heart and lung function, to monitor the effects of environmental, occupational, and drug exposures, to assess risks of surgery, and to assist in evaluations performed before employment or for insurance purposes. The indications for pulmonary-function tests are summarized in Table 1. Spirometric examination, the most widely used such test, is the focus of this paper. Spirometry is the measurement of the movement of air into and out of the lungs during various breathing maneuvers. Such examinations should be readily available and routinely used in medical offices and hospitals where patients with heart and lung diseases are treated. Other common tests of lung function include the measurement of lung volumes, airway resistance, carbon monoxide diffusing capacity, and arterial-blood gases.

DIAGNOSTIC INDICATIONS

Pulmonary-function tests are useful in diagnosing and managing pulmonary diseases. The recommendations of the National Asthma Education Program indicate that such testing is essential in the diagnosis and management of asthma because of evidence that both patients and physicians have inaccurate perceptions of the severity of asthma that contribute to delays in treatment.[1] Indeed, underestimation of the extent of airflow (airway) obstruction is associated with increased mortality in asthma.[2]

Pulmonary-function tests can identify abnormalities of lung function that might otherwise be overlooked and can exclude the possibility of some respiratory disorders such as chronic obstructive pulmonary disease. Physicians cannot identify obstructive or restrictive patterns reliably from history taking and physical examination alone.[3-5] When physicians ordering lung-function tests were asked to predict the results, they correctly predicted an obstructive pattern 83 percent of the time.[4] However, predictions of normal or restrictive patterns were correct only about half the time.[4] Besides identifying abnormalities, lung-function tests allow the severity of an abnormality to be quantified and the presence of reversible airflow obstruction to be determined.

Pulmonary-function testing is sometimes indicated when there may be more than one explanation for a patient's symptoms. For example, a smoker who presents with dyspnea and obvious signs of congestive heart failure may also have obstructive lung disease. Failure to recognize and treat both disorders may limit the therapeutic response.

SCREENING AND MONITORING

Lung-function tests are included in many evaluations of fitness and some routine physical examinations. Such testing may provide interesting information, but in the absence of symptoms, physical findings, or risk factors its clinical usefulness is questionable. There is little evidence to support a policy of screening the general population with spirometry.[6] Some subgroups (e.g., cigarette smokers and people exposed to known agents of lung injury, such as asbestos or diisocyanates) are at higher risk of lung disease; screening and monitoring are appropriate for them.[6,7] It has been suggested that about 15 percent of cigarette smokers have an accelerated decline in the maximal volume of air exhaled, after a maximal inhalation, in the first second of a forced exhalation (i.e., the forced expiratory volume in one second, or FEV_1); ultimately, this condition leads to airflow obstruction and the possibility of early disability and death from chronic obstructive pulmonary disease.[8] Although the rates of loss of FEV_1 in smokers and nonsmokers overlap, nonsmokers tend to lose FEV_1 at a rate of 20 to 30 ml per year, whereas "sensitive" smokers (those with an accelerated decline in FEV_1) lose FEV_1 at a rate of more than 60 ml per year. In people under 35 years of age, cessation of smoking is associated with improved lung function; for those older than 35, the accelerated decline in lung function slows to the normal rate associated with aging.[8-10] Smokers with one normal spirogram cannot rest easy; they may still have an accelerated loss of lung function that is detectable only by serial measurements. Smokers may be more likely to stop smoking if they are informed of such functional abnormalities.

Serial measurement of lung function (monitoring) may be useful in tracking pulmonary expressions of diseases, quantifying responses to therapy, and making early diagnoses of lung injury after occupational exposures and drug or radiation therapy. Many diseases, including heart failure, rheumatoid arthritis, inflammatory bowel disease, and vasculitis, affect the lungs either directly or as a result of the adverse effects of treatment.[11] Monitoring lung function allows the physician to identify and quantify pulmonary involvement in such diseases. For example, serial measurement of vital capacity (VC) may help a physician

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Table 1. Indications for Pulmonary-Function Tests.

Diagnostic
To evaluate symptoms, signs, and abnormal results of laboratory tests
Symptoms: cough, dyspnea, wheezing, orthopnea, or chest pain
Signs: overinflation, expiratory slowing, cyanosis, chest deformity, wheezing, or unexplained crackles
Abnormal results of laboratory tests: hypoxemia, hypercapnia, polycythemia, or abnormal chest radiographs
To measure the effect of disease on pulmonary function
To screen persons at risk for pulmonary disease
Smokers
Persons with occupational exposure to injurious substances
Some persons at the time of a routine physical examination
To assess preoperative risk
To assess prognosis
Monitoring
To assess effectiveness of therapeutic interventions
Bronchodilator therapy
Steroid treatment for asthma, interstitial lung disease, and the like
Management of congestive heart failure
Other
To provide information on the course of diseases affecting lung function
Pulmonary disease, such as obstructive airways disease and interstitial lung disease
Cardiac disease, such as congestive heart failure
Neuromuscular disease, such as Guillain–Barré syndrome
To assess current status of persons with occupational exposure to injurious substances
To detect adverse reactions to drugs with known pulmonary toxicity
Evaluation of disability or impairment
To assess patients as part of a rehabilitation program
Medical
Industrial
Vocational
To assess risks for an insurance evaluation
To assess the condition of persons for legal reasons
Social security or other program involving government compensation
Personal-injury lawsuits
Other
Public health
Epidemiologic surveys

quantify a patient's response to therapeutic agents in congestive heart failure. In the Framingham study, decreases in VC were a better predictor of heart failure than were symptoms, examinations, or radiographic findings.[12] Improvements in VC may also indicate recovery from congestive heart failure.[13]

Numerous drugs are associated with lung injury.[14,15] The role of pulmonary-function testing in monitoring for drug toxicity is not clearly defined. In the case of amiodarone hydrochloride, an antiarrhythmic agent, it is quite controversial, but monitoring of lung function may confirm or provide an early indication that an adverse pulmonary reaction has begun. The development of pulmonary fibrosis can be monitored with lung-function testing in patients undergoing cancer chemotherapy or radiation therapy involving lung parenchyma. Lung-transplant recipients are commonly monitored with lung-function tests to detect early evidence of bronchiolitis obliterans.[16,17]

Monitoring is useful only when adequate base-line studies are available for comparison. A change from a patient's base-line value is more likely to indicate pulmonary injury than is the traditional comparison of values measured in the patient with reference values obtained from population studies. Changes from base line that are as small as 5 to 10 percent may be substantial for a person and could be missed if only reference values are used in the comparison. Consider, for example, a 40-year-old man who is 175 cm tall. His predicted VC, based on reference values, is 4.99 liters (normal range, 3.79 to 6.11). If his VC at base line was 6 liters, it could decrease by up to 37 percent before his test results fell below the normal range.

The frequency and kinds of pulmonary-function tests vary with the situation. If the primary involvement is in the airways (for example, in a lung-transplant recipient at risk of bronchiolitis obliterans), spirometric testing is adequate. If involvement of the lung parenchyma is likely (for example, in a patient receiving bleomycin), lung volumes and the carbon monoxide diffusing capacity (DLCO; also known, especially in Europe, as "transfer factor") should also be measured. In congestive heart failure, lung volumes are primarily affected, and VC is the best index to monitor.

Preoperative Evaluation

Although the role of preoperative pulmonary-function testing remains controversial,[18] its goals are now more clearly defined.[19-21] They include helping to identify patients for whom the risk of surgery is prohibitive and helping to identify patients at increased risk of pulmonary complications, for whom better-informed decisions about preoperative and postoperative care can then be made.

There is general agreement that at the least, the preoperative pulmonary testing of patients for whom lung resection is being considered should include spirometry and measurement of arterial-blood gases. The abnormalities that suggest an increased risk of postoperative pulmonary complications and the need for further evaluation are as follows: VC less than 50 percent of the predicted value, FEV_1 less than 2 liters or less than 50 percent of predicted, or the presence of substantial hypoxemia or hypercapnia. Studies designed to predict postoperative FEV_1 from ventilation or perfusion scans and, in some cases, DLCO and exercise studies may help in further defining the risk.[19-21] Patients whose predicted postoperative FEV_1 is less than 0.8 liter or 40 percent of the predicted value are at very high risk.

For other surgery, the risk of postoperative pulmonary complications generally declines as the distance from the chest to the surgical site increases. Upper abdominal and thoracic operations not involving lung resection are associated with increased risks of pulmonary complications. Smokers and people with signs and symptoms suggestive of lung disease

are most likely to benefit from preoperative screening with spirometry and blood gas analysis.[21] Lower abdominal and head-and-neck surgery are associated with lower surgical risks. Spirometric testing and blood gas analysis are likely to help only patients without prior lung-function tests whose preoperative evaluation suggests the presence of pulmonary disease.[21]

Risk and Prognosis in Patients with Known Lung Dysfunction

Low levels of lung function, even in patients who have never smoked cigarettes, are associated with a poor prognosis in patients with heart and lung disease. Studies consistently find that reduced lung function (usually FEV_1) is associated with an increased risk of death from chronic obstructive pulmonary disease, non-neoplastic respiratory diseases, vascular diseases, lung cancer, and all causes of death considered together.[22-25] These findings are consistent among groups of patients, but it is not possible to predict the symptoms or mortality of individual patients accurately on the basis of FEV_1 alone.

Interpretation of Lung-Function Tests

Test quality remains the most important concern in lung-function testing. Variability (noise) is greater in pulmonary-function tests than in most other clinical laboratory tests because of the inconsistency of efforts by patients.[26] The American Thoracic Society (ATS), the European Respiratory Society, and other organizations have published standards designed to minimize the variability in these tests[27-44] (Table 2). The elements that lead to high-quality test results are accurate equipment, good test procedures, an ongoing program of quality control, appropriate reference values, and good algorithms for the interpretation of results. It is tempting to assume that all equipment on the market is accurate. However, a 1990 evaluation of spirometers revealed that only 57 percent met the standards of the ATS for accuracy.[42] Purchasers should insist on evidence that an instrument meets the ATS performance recommendations.[27] A quality-control program for spirometers that uses a calibrated 3.0-liter syringe and a few other simple checks[32] can be conducted easily in a physician's office. Monitoring the accuracy of instruments that measure diffusing capacity, lung volume, and blood gases is more difficult. These machines are best used in settings where there are larger volumes of patients.

The interpretation of lung-function tests usually involves comparing values measured in patients with reference values from studies of populations of healthy nonsmokers. There are substantial differences between the equations used to predict normal lung function, because of differences among the populations studied as well as technical and procedural differences. It is important to select equations for reference use that are well matched with the patients served in a particular office or laboratory. The ATS has published guidelines for making these choices.[33] Physicians unfamiliar with selecting reference values and choosing the lower limits of normal ranges should consult a local pulmonary-testing laboratory with expertise in this area.

The first step in interpreting a lung-function test is to assess and comment on test quality. Spirometric tracings should be examined to make sure they represent adequate effort by the patient, are reproducible, and contain no artifacts that would alter the test results (Table 3). If the requirements for quality are not met, tests should be interpreted (Table 4) with caution. Some technical problems are so important that

Table 2. Sources of Information on the Measurement and Interpretation of Pulmonary-Function Tests.

Type of Information	Reference
Adults	
Practical, how-to manuals or guides	Morris et al.,[38] Enright and Hyatt,[40] Miller,[39] Wanger,[41] Clausen[37]
Standards	
Equipment and procedures	
Spirometry	American Thoracic Society,[27] European Respiratory Society,[28] Morris et al.,[38] Nelson et al.[42]
DLCO	American Thoracic Society,[29] European Respiratory Society[28]
Lung volumes and mechanics	European Respiratory Society[28]
Personnel	Gardner et al.[30]
Computers	Gardner et al.[31]
Quality control	Gardner et al.,[32] Clausen[37]
Reference values and interpretation	American Thoracic Society,[33] European Respiratory Society,[28] Morris et al.,[38] Clausen[37]
Disability or impairment	American Medical Association,[43] American Thoracic Society[44]
Children	
Overall guidelines	Quanjer et al.,[34] Taussig et al.,[35] Zapletal et al.[36]

Table 3. Technical Requirements for Spirometry of Good Quality.*

At least 3 acceptable tests

Full inhalation before start of test
Satisfactory start of exhalation
  Evidence of maximal effort
  No hesitation
No cough or glottal closure during the first second
Satisfactory duration of test
  At least 6 seconds
  Up to 15 seconds in patients with airflow obstruction
No evidence of leak
No evidence of obstruction of the mouthpiece

Reproducible results

For FVC and FEV_1, the 2 largest values should be within 5 percent or 0.1 liter (whichever is larger) of each other
  If these criteria are not met, continue testing
  If the criteria are not met after 8 trials, stop testing and proceed with the interpretation, using the 3 best acceptable tests

Selection of test values for interpretation

Select from tests of acceptable quality
Select the largest values for FVC and FEV_1, regardless of the test used
For indexes of average or instantaneous flow, use values from the test with the largest value for FVC and FEV_1 combined

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they prevent any interpretive statements from being made; other problems reduce but do not totally eliminate the amount of interpretable information. For example, a set of spirograms may contain good information about VC but not about FEV_1.

Figures 1 and 2 show spirograms from a normal subject and two patients with airflow obstruction. With computerized equipment, more than 20 different spirometric variables can be reported. It is important to resist the temptation to use more than a few such variables in the basic interpretation. Increasing the number of variables used in the test increases the number of false positive results.[33] In spirometry, there are several basic variables. VC is the maximal volume of air that can be exhaled after a maximal inhalation or the maximal volume of air that can be inhaled after a maximal exhalation. It can be measured as two variables: forced vital capacity (FVC) and slow vital capacity (SVC). Two other variables are FEV_1 and $FEV_1/VC\%$ (calculated as $FEV_1/VC \times 100$). In most cases these variables suffice to provide all the information needed to interpret a spirogram.

Two basic types of lung dysfunction can be defined by spirometry: obstructive patterns and restrictive patterns. The primary criterion for airflow obstruction is a reduced $FEV_1/VC\%$. Other measurements of flow can be used to support conclusions based on this variable or to assist in making decisions when $FEV_1/VC\%$ is borderline.

A restrictive pattern means that lung volumes are small. The primary criterion for this diagnosis is a reduction in total lung capacity (TLC), the volume of air in the lungs at the end of a maximal inhalation. However, the presence of restriction is commonly inferred from a decreased VC. VC may also be reduced in the presence of airflow obstruction, especially when exhalation time is short. When there is airflow obstruction and VC is reduced, the possibility of restriction can usually be eliminated with evidence of overinflation from the physical examination or chest radiograph. When there is any question about the cause of a reduced VC, TLC should be measured. Even though restriction is defined by a reduced TLC, VC has frequently been demonstrated to be more useful in following the course of restrictive chest diseases.

Table 5 lists the criteria of the ATS for evaluating a response to the administration of a bronchodilator in the laboratory and assessing the importance of

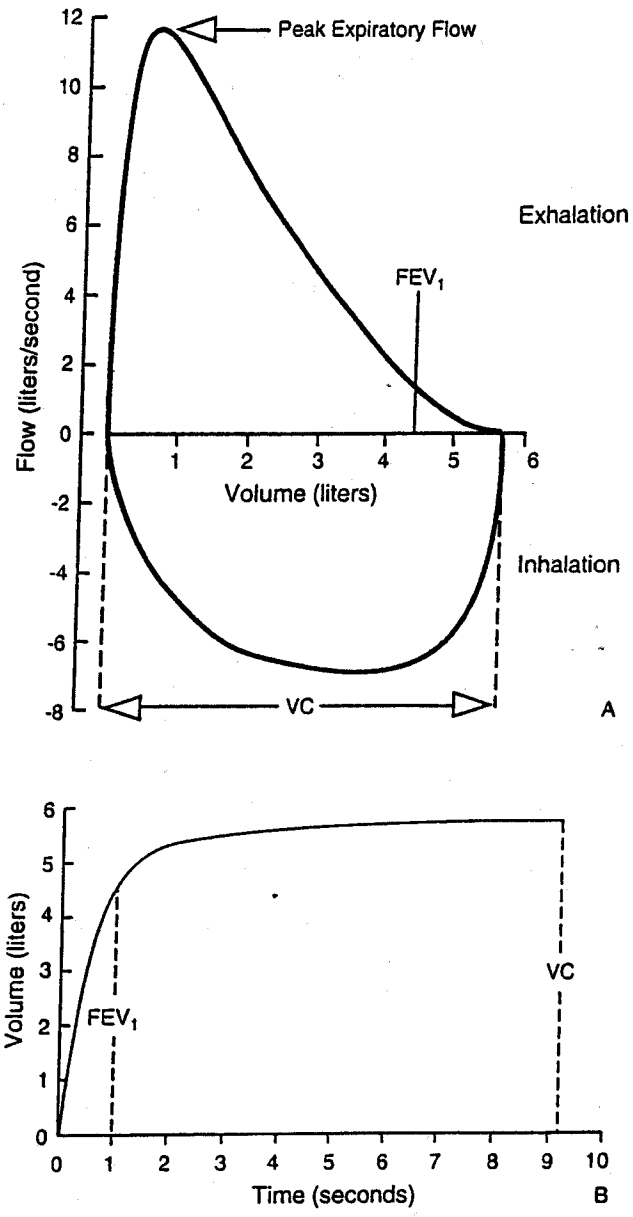

Figure 1. Spirometric Flow–Volume (Panel A) and Volume–Time (Panel B) Curves for a Healthy 52-Year-Old Man 188 cm Tall.

In the flow–volume curve the well-defined peak in expiratory flow shows good initial effort. The slightly concave appearance of the expiratory portion of the curve appears with aging alone. In a 20-year-old person, the same pattern could indicate the presence of airflow obstruction. In the volume–time curve good initial effort is shown by the sharp increase in volume from time zero. The long, slow increase in volume shows the age-related decrease in flow at end-expiration. Total expiratory time can be seen only in the volume–time curve.

Table 4. Guidelines for the Interpretation of Spirometry.*

Choose statistically acceptable lower limits of normal.
Evaluate and comment on test quality.
Use FVC, FEV_1, and $FEV_1/VC\%$ as the primary guides for interpretation. (Increasing the number of variables in the interpretation increases the incidence of false positive results.)
Values that are well above or well below the lower limits of normal can be interpreted with confidence. Interpret borderline values with caution, using clinical information to make decisions.
The primary indicator of airflow obstruction is a reduced $FEV_1/VC\%$.
Once obstruction is diagnosed, classify the severity using FEV_1 expressed as a percentage of the predicted value.
Determine the response to bronchodilator therapy (see Table 5).
A restrictive pattern may be cautiously diagnosed from the spirometric examination when VC is reduced and $FEV_1/VC\%$ is normal. However, the definitive finding for a restrictive pattern is a reduced TLC.
The severity of restriction should be based on TLC if that value is available, and otherwise from VC.
Restriction cannot be diagnosed from the spirometric examination in the presence of moderate-to-severe airflow obstruction.

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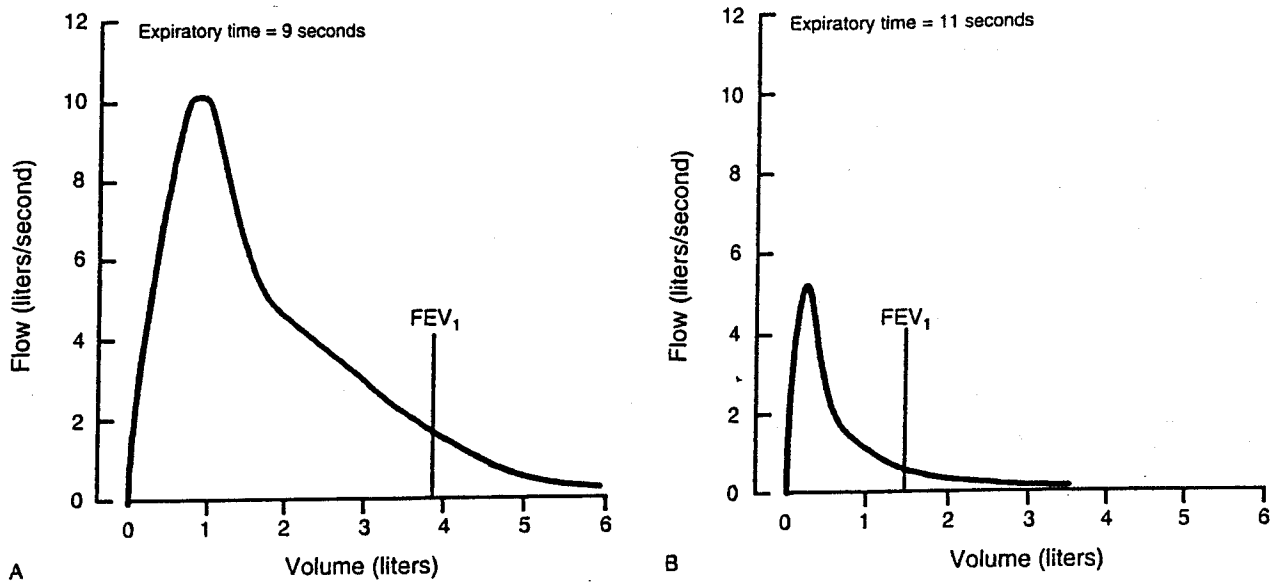

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Chapter 38

MECHANICAL DYSFUNCTION OF THE RESPIRATORY SYSTEM

$\epsilon = \frac{\text{int work}}{\text{energy expenditure}}$

J. Julio Pérez Fontán

The normal function of the mammalian respiratory system requires the constant motion of gas in and out of the lungs. This motion is achieved by means of a pumplike mechanism in which the respiratory muscles act on the chest wall (rib cage and abdomen) to expand and compress the lungs. As often happens with systems that contain moving parts, most diseases of the respiratory system both in children and in adults involve some sort of mechanical dysfunction. Moreover, it is the increased energy demands imposed by such dysfunction that are usually responsible for the majority of the disease's signs and symptoms and, ultimately, for the development of respiratory failure. Therefore, any review of the pathophysiology of respiratory disease must include first a basic understanding of respiratory mechanics in health and disease. This chapter is intended to provide such an understanding, focusing on the factors that determine both respiratory work and energy expenditure. Accordingly, the first portion of the chapter takes the reader from the forces responsible for the volume-pressure behavior of the lungs and chest wall to how this behavior relates to the work of breathing in both normal and disease conditions. The second portion analyzes the elements that influence the translation of the work of breathing into energy expenditure, with special attention to those that define the efficiency of the respiratory system. Throughout the discussion, the unique characteristics that make the developing respiratory system more susceptible to mechanical dysfunction are highlighted.

DETERMINANTS OF RESPIRATORY WORK

The respiratory system as a thermodynamic system

The respiratory system is a well-specified thermodynamic system. As such, its condition can be well described at any time by state variables such as pressure, volume, or temperature. Furthermore, the relationships between each variable and the others can be summarized in a mathematical formulation known in thermodynamics as the equation of state. These equations provide information about the general function of the system and allow predictions of its behavior, should the state variables change.

Similar to other thermodynamic systems, changes in the state of the respiratory system must be analyzed in terms of energy gains and losses. The first law of thermodynamics establishes that when a certain amount of energy (ΔQ) is added to a system by an external source (e.g., metabolism of fuels supplied by the circulation to the respiratory muscles), the resultant change in the system's internal energy (ΔU) and any external work performed by the system (ΔW) must satisfy the following relationship:

$$\Delta Q = \frac{1}{\epsilon}(\Delta U + \Delta W) \quad (1)$$

where the symbol ϵ represents the thermodynamic efficiency of the system. Because the internal energy of a gas depends on its temperature, and heat changes generated during breathing are rapidly buffered by the circulation, $\Delta U \approx 0$, leaving

$$\Delta Q = \frac{1}{\epsilon}\Delta W \quad (2)$$

The external work done during a small breathing excursion (dW) can be approximated by comparing the respiratory system to a cylindrical piston pump. If a constant force F acts on the pump's piston and causes it to undergo a linear motion, dx, the amount of work done by the force, can be computed as

$$dW = F\,dx \quad (3)$$

In practical terms, however, it is much easier to measure the pressure inside the pump's cylinder (P) than to measure F. Because $P = F/A$ (where A is the section area of the piston) and the volume displacement of the piston is $dV = A\,dx$, we can write

$$dW = P\,A\,dx = P\,dV \quad (4)$$

which, when integrated between volumes V_0 and V_1 to obtain work, yields:

5

$$W = \int_{V_0}^{V_1} P\, dV$$

In simpler terms, the work done by the respiratory system and consequently the energy that must be supplied to the respiratory muscles to do this work are defined by the system's volume-pressure relationships.

Volume-pressure relationships

The volume changes of the respiratory system can be easily measured. If we ignore the small amount of compression and expansion of the gas inside the lungs, the volume changes undergone by the lungs (ΔV_L), the chest wall (ΔV_W), and the thorax as a whole (ΔV_{TH}) during breathing are equivalent.

6

$$\Delta V_L = \Delta V_W = \Delta V_{TH}$$

The simple reason for this equality is that the lungs and chest wall are linked by a noncompressible boundary (the pleural space), which, under normal conditions, makes it impossible for them to change volume independently of each other and of the thorax as a whole.

The pressures needed to inflate the lungs (P_L, transpulmonary pressure), chest wall (P_W), and thorax (P_{TH}) are, however, different from each other. Each of these pressures can be defined as the pressure difference across the specific component:

7

$$P_L = P_m - P_{pl}$$

8

$$P_W = P_{pl} - P_B$$

9

$$P_{TH} = P_m - P_B$$

where P_m is the pressure measured at the mouth, P_{pl} is the representative pressure at the pleural surface, and P_B is the atmospheric pressure (conventionally considered to be the zero reference). By adding Equations 7 and 8, it is clear that

10

$$P_{TH} = P_L + P_W$$

which indicates that the pressure necessary to produce a certain volume change in the thorax is equivalent to the sum of the pressures that would be necessary to produce the same volume change in the lungs and in the chest wall if each of these two components were inflated independently.

Forces acting on the respiratory system

Pressure changes within the respiratory system are the result of several kinds of forces acting on the lungs and chest wall. Elastic forces are volume dependent and result from the tendency of the tissues to recover their original shape after undergoing deformation. Resistive forces are flow dependent and originate for the most part from the friction of the gas against the airway walls. Viscoelastic forces are time dependent and caused primarily by molecular rearrangements after the tissue has been subjected to a deforming force. A mucus droplet, for example, exhibits a viscoelastic behavior when it slowly stretches under its own weight. Similarly, catsup acts as a viscoelastic substance when it stubbornly refuses to leave the bottle until it has been shaken several times. Finally, inertial forces are acceleration dependent and result from the changes in the velocity of the gas and tissue contained in the thorax during breathing.

The various forces listed in the previous paragraph can be classified as nondissipative and dissipative, depending on whether the energy derived from them stays or leaves the system. Elastic forces, for instance, are nondissipative because the energy needed to overcome them during inspiration is accumulated in the thorax and then used to empty the lungs during expiration. Inertial forces are also nondissipative because the energy required to accelerate gas and tissue at the beginning of a breath is recovered as they decelerate in the middle of the breath. Resistive and viscoelastic forces, in contrast, are dissipative: the energy needed to overcome them is lost as heat or used to produce molecular rearrangements in the lung tissue and lung-gas interface. Dissipative forces are responsible for the hysteresis (different behavior between inspiration and expiration) of the volume-pressure relationships of the respiratory system.

Nondissipative forces

Respiratory inertial forces are negligible in the child during normal breathing. We will therefore only discuss the elastic forces.

Static volume-pressure relationships. Elastic forces are purely dependent on the volume of the thorax and are therefore most easily studied when this volume is stationary. Under such conditions, there is no flow of gas in the airways, and the pressure at the mouth (P_m) is equivalent to the pressure in the alveoli (P_A). Equations 7, 8, and 9 can therefore be rewritten (assuming that $P_B = 0$) as

11

$$P_{L,el} = P_A - P_{pl}$$

12

$$P_{W,el} = P_{pl}$$

13

$$P_{TH,el} = P_A$$

where $P_{L,el}$, $P_{W,el}$, and $P_{TH,el}$ represent the elastic pressures or recoils generated by the lungs, chest wall, and thorax, respectively.

The volume-pressure behaviors of the lungs, chest wall, and thorax are complex and cannot be described in a simple mathematical fashion. The volume-pressure relationship of the lungs, for example, has a sigmoid shape, with pressure increasing rapidly with respect to volume at low and high volumes and more slowly at middle volumes (Fig. 38-1). Being a continuous function, however, each relationship has a defined slope at each thoracic volume (dV/dP). This slope defines the *compliance* of the thorax, lungs, or chest wall, depending on whether dP is replaced by dP_{TH}, dP_L, or dP_W. Whereas a summary examination of Fig. 38-1 reveals that

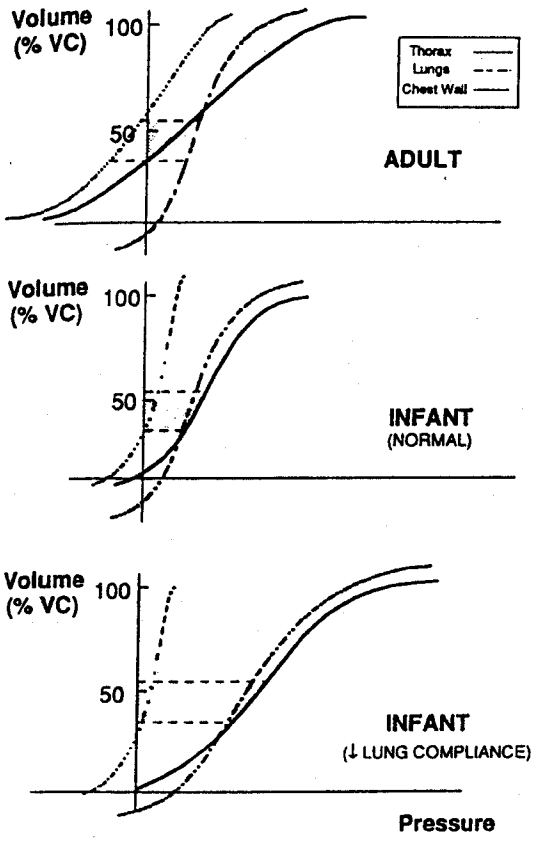

Fig. 38-1. Schematic representation of the static volume-pressure relationships of the thorax, lungs, and chest wall in the adult, normal infant, and infant with decreased lung compliance. Volume, on the ordinates, is shown as percent of vital capacity. Pressure, on the abscissa, represents the pressure across the thorax, lungs, and chest wall. The volume-pressure relationships of the lungs are similar in the adult and the normal infant. The volume-pressure relationship of the chest wall, however, is steeper in the infant, indicating a greater chest wall compliance. The stippled area between the volume-pressure curve of the thorax and the volume axis represents the elastic work done by the respiratory muscles for a breath starting at functional residual capacity (FRC).

compliance is not constant for any of these volume-pressure relationships over the entire volume range, dV/dP is relatively constant at normal breathing volumes, and we can safely consider

$$\Delta P_{el} = \frac{\Delta V}{C} \qquad 14$$

where ΔP_{el} represents the change in elastic recoil pressure of the lungs, chest wall, or thorax for a lung volume excursion ΔV, and C is the compliance of the corresponding component. At high and low thoracic volumes, dV/dP decreases in a volume-dependent manner, and volume-pressure behaviors within the respiratory system cannot be described using a linear notation.[45]

The elastic recoil of the thorax is equivalent to the total pressure that the respiratory muscles need to generate in order to produce a certain volume change and, as we have seen, can be calculated as the sum of the elastic recoils of the lungs and chest wall (Equation 10). Each specific recoil acts to change the lungs and chest wall volumes until they reach a certain *relaxation volume*, for which the recoil becomes zero (the intercept of the volume-pressure relationships with the ordinate in Fig. 38-1). Just as they have different volume-pressure relationships, the lungs and the chest wall also have different relaxation volumes. In the adult human, the relaxation volume of the lungs is lower than residual volume (the volume of gas contained in the lungs at the end of a forced expiration). The relaxation volume of the chest wall, by contrast, exceeds 50% of the vital capacity (the maximal volume of gas that can be inhaled from residual volume). Such discrepancy in the relaxation volumes of the lungs and chest wall has several consequences. First, it forces the relaxation volume of the thorax to occupy a position intermediate between the relaxation volumes of the lungs and the chest wall (at approximately 35% of vital capacity). Under most circumstances, this volume coincides with the functional residual capacity (FRC), the volume contained in the lungs at the end of a tidal expiration. Second, the outward recoil of the chest wall contributes to the expansion of the lungs, thereby reducing the work that the respiratory muscles need to perform during normal breathing (Fig. 38-1, *top*). Finally, at normal breathing volumes, the opposing actions of the lungs and chest wall recoils create a negative pressure at the boundaries of the lung tissue with the chest wall and the intrathoracic structures.[34]

The static volume-pressure relationships of the lungs and chest wall vary depending on their state of maturation and health (Fig. 38-1). In the infant, the chest wall generates remarkably little outward recoil within the normal range of breathing volumes.[1,18,41] Because, during development, the inward recoil of the lungs varies little with respect to lung size and age,[13,14,46] the relaxation volume of the thorax is proportionally smaller than that of the adult (as shown in Fig. 38-1 by the lower intercept of the volume-pressure relationship of the thorax and the ordinate). If, as it happens in the adult, the FRC coincided with this relaxation volume (which, based on the balance of pressures, can be estimated at 15% of vital capacity compared to 35% in the adult), then the infant would be at definite disadvantage in terms of alveolar stability and oxygenation. The newborns of most mammalian species, however, have developed strategies to maintain their FRC above the relaxation volume of the thorax. These strategies are generally directed at interrupting expiratory flow before expiration is complete and include shortening of the expiratory time,[38] contraction of adductor muscles of the glottis to retard exhalation,[16] and persistence of the tonic activity of the inspiratory muscles during expiration.[37] Being so dependent on the pattern of breathing, the FRC of the newborn and small infant is very vulnerable to changes in muscle coordination and tone. As an example, the decrease of tonic activity of the respiratory[37] and laryngeal muscles[19] associated with REM sleep may cause a substantial reduction in thoracic lung volume at these ages.[21] Similarly, muscle weakness, anesthesia, deep sedation, and central nervous system depression in general tend to lower FRC below levels compatible with alveolar stability. Under such circumstances, alveoli close, and both the shunt fraction and the work of breathing rise.

In addition to its effects on the FRC, the reduced outward recoil of the chest wall in the infant reduces the chest wall's

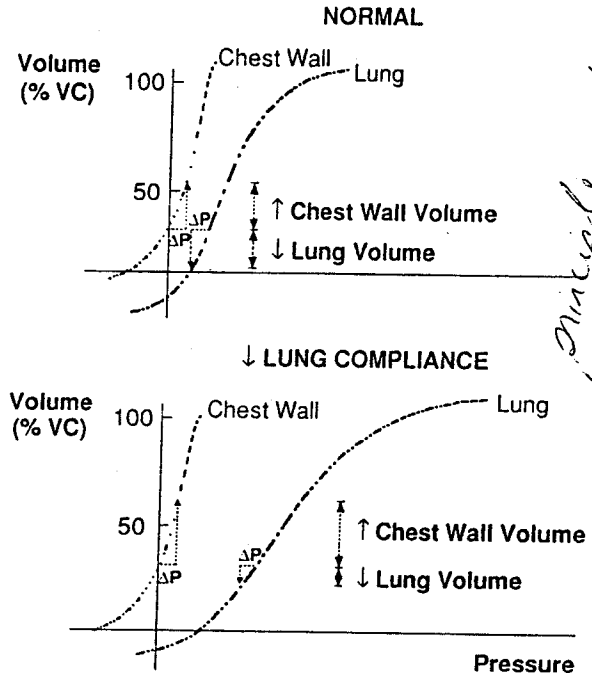

Fig. 38-2. This figure illustrates the mechanical interdependence of the lungs and chest wall by comparing the effects of a pneumothorax on their respective volumes when lung compliance is normal *(top)* and reduced *(bottom)*. Volumes, on the ordinates, are shown as a fraction of vital capacity *(VC)*; pressures, on the abscissa, represent the distending pressures of the lungs (mouth − pleural pressure) and chest wall (pleural − atmospheric pressure). The introduction of a volume of gas into the pleural space raises pleural pressure by a magnitude ΔP, which depends on both the volume introduced and the volume-pressure characteristics of the chest wall. The increment in pleural pressure decreases both the distending pressure and the volume of the lungs and increases both the distending pressure and the volume of the chest wall.

contribution to lung expansion (Fig. 38-1, *middle* and *bottom*). It also limits the amplitude of the pleural pressure variations during breathing, an effect that may explain the surprising cardiovascular tolerance of many infants to the application of high levels of positive airway pressure. Because the volume-pressure relationship of the infant's chest wall is much steeper than that of the thorax, relatively large changes in thoracic pressure ($P_m - P_B$) are accompanied by only small variations of the chest wall pressure ($P_{pl} - P_B$). Consequently, large changes in mouth (or ventilator) pressure (P_m) have only a limited effect on pleural pressure (P_{pl}), which is the relevant pressure surrounding the intrathoracic vessels.

Lungs–chest wall interactions. As we have seen, the volume-pressure relationships of the lungs and chest wall are necessarily linked. Under normal conditions, lungs and chest wall cannot change volume independently and are simultaneously influenced by variations in the pressure at their boundary (P_{pl}). This lungs–chest wall interdependence is well illustrated by the effect of a pneumothorax on the volumes of the lungs and chest wall (Fig. 38-2). When a certain volume of air penetrates into the pleural space, the most immediate effect is an increase in the pleural pressure (dP). This increase causes the elastic recoils of the lungs and chest wall to change in a similar magnitude. The change, however, is in opposite directions: the recoil of the lungs ($P_m - P_{pl}$) decreases in a magnitude dP, whereas the recoil of the chest wall ($P_{pl} - P_B$) increases in a magnitude dP. As a result, the volume of air originally introduced in the pleural cavity is partitioned between a collapse of the lungs and an expansion of the chest wall, the terms of the partition being dictated by the respective volume-pressure relationships of the lungs and chest wall. If the compliance of the chest wall exceeds the compliance of the lungs (as is the case in the infant), then the volume of the chest wall expansion exceeds that of the lung collapse. The difference is even greater when lung compliance is reduced by disease. Then (Fig. 38-2, *bottom*) the chest wall absorbs the majority of the volume change while the lungs barely change their volume. This simple analysis explains why noncompliant lungs do not collapse when a pneumothorax develops (Fig. 38-3), a finding that is often mistakenly attributed to the "stiffness" of the lung parenchyma.

Dissipative forces

Dynamic volume-pressure relationships. Until now, we have considered only the pressure changes that take place when the thoracic volume changes in a stepwise manner. These changes are, as we have seen, the result of the elastic behavior of the lungs and chest wall. The analysis of the volume-pressure relationships of the thorax and its components becomes more complicated if we also consider the pressure changes generated by gas flow and by the movement of the lung and chest wall tissue as the lungs inflate and deflate. Flow-dependent or resistive pressure changes in the respiratory system result from a variety of physical forces. These include the viscous friction of the gas agains the airway walls (frictional pressure losses) and the density-dependent forces generated by gas turbulence and acceleration (convective pressure losses). Because of their dissipative nature, viscoelastic pressure losses are often included as part of the total resistive losses. Although generally less relevant than flow resistance, viscoelasticity can contribute a sizable portion of the pressure changes within the respiratory system in both health and disease.[3,26,39,40] Its discussion, however, is beyond the scope of this chapter.

Regardless of their physical nature, resistive pressure losses occur only when there is flow ($\dot{V}$). The relationship between resistive pressure (P_{res}) and $\dot{V}$ in the respiratory system is often assumed to be linear:

$$P_{res} = R\,\dot{V} \qquad (15)$$

where R represents the flow resistance of the thorax, lungs, or chest wall. However, similar to elastic recoil, resistive pressure losses cannot be described with a single constant. In practice, R exhibits a complex dependence on flow rate, lung volume, and the phase of the respiratory cycle. Understanding this dependence is essential for the recognition of airway obstruction.

Airway dynamics. The airways behave like collapsible tubes rather than rigid pipes. At any time, the diameter of an airway is determined by both the compliance of the airway wall and the pressure difference between the column of gas inside the airway and the tissue surrounding the airway (airway transmural pressure). Airway compliance is modulated by airway smooth muscle tone and may vary

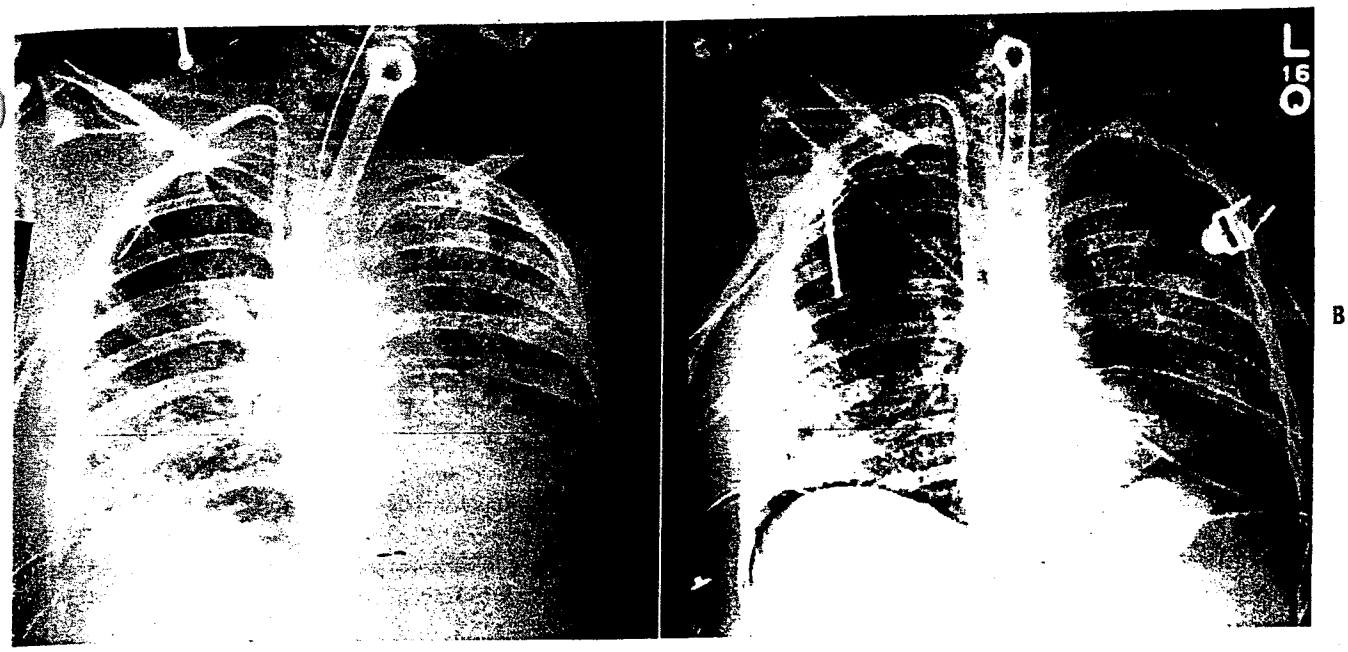

Fig. 38-3. These two chest radiographs illustrate the effect of a pneumothorax on the volumes of the lungs and chest wall in a 7-year-old child whose lung compliance was reduced by the adult respiratory distress syndrome (ARDS). In **A**, there are diffuse infiltrates, and a chest tube has been placed in the right pleural space, but no pneumothorax is present. In **B**, obtained shortly thereafter, the patient has developed left tension and smaller right subpulmonic pneumothoraces. Consistent with the principles explained in Fig. 38-2, note how, despite the increased recoil of the lungs and the elevated pleural pressure, the left lung experiences only a small decrease in volume. Note also how the left side of the rib cage appears to expand substantially to accommodate the volume of the pneumothorax.

during breathing. For instance, the smooth muscle of intrapulmonary airways contracts during inspiration to stiffen the airway wall[42] and limit airway deformation.

Airway transmural pressure varies during breathing. Its variations are the result of the different effects of inspiration and expiration on the pressures inside and outside the airways. The pressure inside all airways undergoes qualitatively similar changes during each phase of the breathing cycle. During inspiration, for instance, a gradient of increasingly negative pressures is created from the mouth, where pressure is zero (or atmospheric), to the alveolar spaces, where the pressure must be negative (or subatmospheric) for inspiration to occur. The inside pressure, however, is always negative, independent of the position in the airway. During expiration, alveolar pressure becomes positive, and the gradient is inverted, with the pressures inside the airways being always positive, but diminishing toward the mouth. The pressure surrounding the airways, in contrast, is influenced in a different fashion by inspiration or expiration, depending on whether the airways are extrathoracic or intrathoracic. Extrathoracic airways are included in the tissues of the neck, where the pressure can be considered to be zero (as tissue gravitational forces are dispersed to the skeletal support of the neck); most of the intrathoracic airways are embedded in the lung tissue. Radial elements transmit the stresses (or pressures) generated by the tissue recoil to the airway wall, which, similar to the pleura, acts as a boundary between the lung tissue and the chest wall. Therefore, just like other intrathoracic airways, the pressure outside the intrapulmonary airways can be considered similar to the pleural pressure[25,34] and relates to lung volume in a manner that depends on the pressure-volume characteristics of the chest wall (Equation 12).

From the previous discussion, it follows that the effect of inspiration and expiration on airway caliber differs between the extrathoracic and intrathoracic airways. During inspiration, the extrathoracic airways (pharynx, larynx, and extrathoracic portion of the trachea) narrow because their inside pressure decreases while their outside pressure is constant. The intrathoracic airways, however, become dilated because their surrounding pressure decreases more than their inside pressure. Conversely, during expiration, the extrathoracic airways dilate as their inside pressure becomes positive with respect to atmospheric pressure, and the intrathoracic airways narrow as their inside pressure decreases with respect to pleural pressure.

It is important to understand that the narrowing of the intrathoracic airways during expiration is contingent upon the existence of a pressure gradient from the alveoli to the mouth. As predicted by Equation 11, alveolar pressure (P_A) must always exceed pleural pressure (P_{pl}) by a magnitude equivalent to the elastic recoil of the lungs ($P_{L,el}$):

$$P_A = P_{L,el} + P_{pl} \qquad 16$$

As the gas progresses downstream during expiration, frictional pressure losses lower the pressure inside the airways. Eventually the cumulative pressure losses can be as large as $P_{L,el}$, and the pressure inside the airways becomes equal to P_{pl}. Beyond this *equal pressure point*,[35] airway transmural pressure is negative (i.e., the pressure outside exceeds the pressure inside the airway) and acts to collapse the airway.

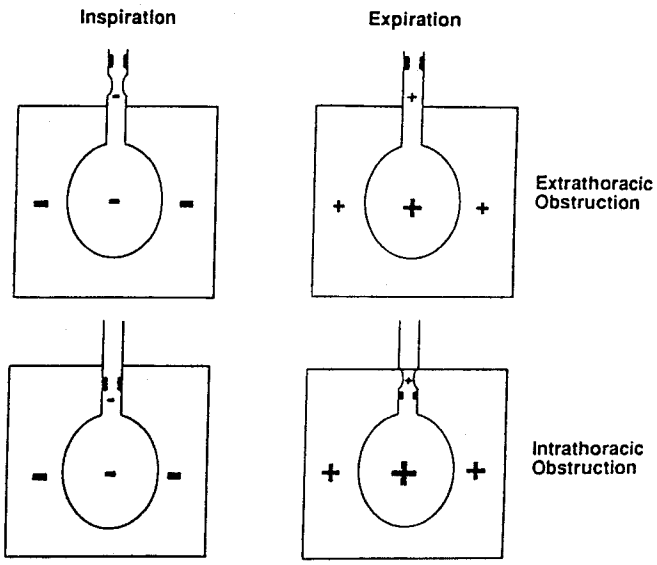

Fig. 38-4. Schematic representation of the effects of inspiration and expiration on the dimensions of the airways during extrathoracic and intrathoracic airway obstruction. Extrathoracic airway obstruction worsens during inspiration because the highly negative pressure inside the airway is unopposed by the atmospheric pressure outside the airway. Intrathoracic obstruction worsens during expiration because the positive pleural pressure outside the airways exceeds the pressure inside the airways downstream from the obstruction point. (Adapted from Pérez Fontán JJ and Lister G in Toulukian RJ, Pediatric trauma, ed 2, St Louis, 1990, Mosby–Year Book Inc.)

Depending on the airway's compliance and diameter, airway collapse can lead to *expiratory flow limitation,* a situation in which gas flow can no longer increase, even if the subject makes a greater effort to raise alveolar pressure. In practice, flow limitation in the lungs is not only caused by the coupling of airway compliance and viscous pressure losses as described. Wave-speed flow limitation results from the fact that the velocity of gas flow through an airway cannot exceed the critical velocity with which disturbances in pressure travel in the direction opposite to the flow.[10,51] This critical velocity, which in an artery equals the velocity of the pulse wave, is directly proportional to the diameter of the airway and inversely proportional to the airway wall compliance. Regardless of its mechanism, viscous or wave speed, flow limitation occurs at lower flows in the presence of airway obstruction and at low lung volumes, when airway diameter is minimal.

Airway obstruction. Airway obstruction causes an exaggeration of the normal breathing changes in airway caliber (Fig. 38-4). Consequently, the dynamic consequences of the obstruction depend on its location (extrathoracic or intrathoracic) and on the direction of flow (inspiratory or expiratory). When the obstruction is extrathoracic (e.g., croup or glossoptosis), the subject must create a more negative pressure inside the airway segment downstream from the obstruction to overcome the increased resistance during inspiration. Therefore, this segment of the airway will tend to collapse, worsening the obstruction and producing a characteristic turbulent noise (inspiratory stridor) as gas passes through it. The obstruction is somewhat relieved during expiration because the pressure inside the airway segment, now upstream from the obstruction, must become more positive with respect to atmospheric pressure to force gas flow through the obstruction.

When the obstruction is intrathoracic (e.g., tracheobronchomalacia or asthma), there is also a change in the pressure within the airways at the level of the obstruction. During inspiration, the pressure inside the airways downstream from the obstruction is more negative than that inside the airways upstream. It still must be less negative than both alveolar and pleural pressure (Equation 16), and therefore the transmural pressure remains positive. During expiration, in contrast, the pressure inside the airway segment located between the obstruction and the thoracic outlet becomes lower than pleural pressure. This causes these airways to collapse and produces the typical findings of wheezing, expiratory delay, and dynamic hyperinflation.

Airway dynamics during positive pressure ventilation. The application of positive pressure in the airways changes the balance of pressures that determines airway caliber. The pressure inside the extrathoracic airways increases with respect to the outside, atmospheric pressure, and therefore these airways undergo dilation. The pressure inside the intrathoracic airways also increases with respect to pleural pressure in a magnitude determined by the increase in lung volume and recoil produced by the positive pressure. For this reason, positive end expiratory pressure (PEEP) has been proposed as a therapy to decrease airway resistance and gas trapping in patients with intrathoracic airway obstruction.[4,27,29] Although beneficial in some patients, in other patients PEEP increases lung volume, interferes with cardiovascular function, and ultimately decreases oxygen delivery to the tissues.[50] The individual variations in the response to PEEP of patients with airway obstruction may simply reflect differences in the mechanisms of dynamic hyperinflation. Marini has proposed that in patients who have gas trapping without expiratory flow limitation, proximal airway pressures (and thus also PEEP) are transmitted to the alveoli. As a result, the hyperinflation worsens.[27] In patients who have both gas trapping and expiratory flow limitation, in contrast, low levels of PEEP are not transmitted across the flow-limiting point, and therefore alveolar pressure and lung volume do not change. The pressure inside the airways downstream from the flow-limiting point increases, however, and may cause the limiting point to move toward the periphery of the lung, improving the emptying of proximal lung regions. The small diameter and high compliance of children's airways favor the development of flow limitation. Therefore, although PEEP is not recommended in every patient, its judicious use may be considered an alternative to improve the mechanical function of the lungs of some selected infants and children with obstructive airway disease.

Restrictive and obstructive respiratory disease

As we have seen, inertial pressure losses are relatively insignificant at normal breathing frequencies in children, and viscoelastic pressure losses are usually lumped together with resistive pressure losses. Therefore, the pressure that the respiratory muscles must generate to produce a certain volume excursion of the thorax (P_{TH}) can be simply considered to be the sum of elastic ($P_{TH,el}$) and resistive ($P_{TH,res}$) components.

$$P_{TH} = P_{TH,el} + P_{TH,res} \quad (17)$$

Combining this equation with Equations 14 and 15, we obtain a simplified form of the equation of motion of the respiratory system.

$$P_{TH} = \frac{\Delta V_{TH}}{C_{TH}} + R_{TH}\dot{V} \quad (18)$$

where ΔV_{TH}, C_{TH}, and R_{TH} represent the volume change, compliance, and resistance of the thorax, respectively.

Integration of either Equation 17 or 18 with respect to V_{TH} leads to the following expression for the total work done by the respiratory muscles (W_{TH}):

$$W_{TH} = W_{el} + W_{res} \quad (19)$$

where W_{el} and W_{res} are the works done to overcome elastic and resistive forces, respectively. When applying these formulations, it is important to consider that elastic and resistive forces do not always act in the same direction. During inspiration, the respiratory muscles must generate the force to overcome both elasticity and resistance, and W_{TH} always has a negative value (indicating that the work must be done by the respiratory muscles). During expiration, however, the elastic recoil of the lungs normally provides the force needed to overcome resistance, and $W_{TH} = 0$. In the presence of airway obstruction, however, the absolute value of W_{res} often exceeds that of W_{el}, causing W_{TH} to have a negative value. Under such circumstances, the expiratory muscles must do the balance of the expiratory work.

The term *restrictive respiratory disease* encompasses all those conditions in which W_{el} is primarily increased. Restrictive disease is caused by a decrease in thoracic compliance. Whether originating in the lungs or the chest wall, a decrease in thoracic compliance has two important mechanical consequences. First, the work of breathing increases, but only during inspiration; expiration continues to be passive, and, in fact, takes place at a faster rate as elastic recoil increases. Second, the relaxation volume of the thorax and the FRC decrease (see Fig. 38-1). This decrease in lung volume, which further reduces lung compliance, may be more pronounced in the infant, whose resting relaxation volume is already low. At low lung volumes, alveoli are very unstable and tend to collapse. To prevent this collapse, infants and small children who suffer from restrictive respiratory disease often close their glottis toward the end of expiration, causing each breath to end in a grunt. Positive end-expiratory pressure (PEEP) and continuous positive airway pressure (CPAP) are effective therapeutic modalities to achieve the same objective of preserving the end expiratory inflation volume.[12,15,22,24,47] Deep lung inflations during positive pressure ventilation may also maintain unstable alveoli open for a short period of time.[33] This effect of volume history on alveolar volume decreases the work needed for the spontaneous breaths following the inflation and explains some of the beneficial effects of intermittent mandatory ventilation in patients with restrictive lung disease.

Obstructive respiratory disease includes all those conditions in which W_{res} is predominantly increased. The small caliber and high wall compliance of the developing airways[28] make the infant and child more susceptible to developing airway obstruction. Under normal breathing conditions the small caliber of the airways represents no mechanical disadvantage because gas flows are low (see Equation 15). When obstruction develops, however, airway resistance increases as an exponential function of the reduction in airway diameter. Because the same absolute decrease will cause a much greater proportional reduction in airway diameter in a small than in a large airway, obstructive lesions tend to have more severe consequences in children than in adults. In addition, developing airways are more compliant than adult airways, and therefore similar decreases in transmural pressure cause them to collapse more easily.

DETERMINANTS OF RESPIRATORY ENERGY EXPENDITURE

The respiratory system has a surprising ability to compensate for its mechanical dysfunctions. However, compensation does not come cheap. It raises the work of breathing in almost every instance, usually by combining increases in the force of contraction of the respiratory muscles with changes in ventilatory pattern. If the increase in work is sufficient to overcome the additional restrictive and obstructive loads applied on the respiratory system, minute alveolar ventilation and arterial P_{CO_2} are maintained within normal limits and respiratory failure is averted. If, in contrast, the metabolic and contractile machinery of the respiratory muscles cannot meet the greater work demands, CO_2 is retained and respiratory failure ensues.

In the final analysis, the success or failure of the compensatory effort is a simple matter of balance between the energy resources available to the respiratory muscles and the energy demands imposed upon these muscles. The energy resources are relatively well defined and limited by the blood supply of the muscles, their ability to metabolize substrates, and the internal efficiency of the muscle's metabolic apparatus.[43] The energy demands on the respiratory muscles are more variable, however, and depend on the work load that these muscles need to perform per unit of time (i.e., the power that they must generate) and the overall efficiency with which the work is performed.

Power of breathing and breathing frequency

Unlike work, which is a function of the volume-pressure characteristics of the thorax, respiratory power (work/time) is influenced by the pattern of breathing. It has been held for some time that, at any given time, each subject has an optimal breathing frequency at which minimum power is needed to attain a certain minute alveolar ventilation.[9,30,36] Although this view has been challenged more recently by those who believe that breathing frequency is adjusted to minimize average muscle force rather than power,[8,31] it is a common clinical observation that different mechanical derangements result in distinctive patterns of breathing. These patterns generally agree with the principle of minimal power expenditure. For instance, patients with restrictive lung disease breathe rapidly and shallowly. In contrast, patients with airway obstruction breathe more slowly and prolong their inspiration or expiration, depending on whether the obstruction is extrathoracic or intrathoracic. By simply inspecting the effort and frequency of the breathing movements, the clinician can therefore assess not only the severity but also the specific nature of a patient's respiratory dysfunction. It

is important to remember, however, that the low thoracic compliance of infants and small children mandates a relatively high breathing frequency at rest, even in the presence of airway obstruction. Nevertheless, severe tachypnea in a child with obstructive disease should always raise suspicions of an associated restrictive impairment. This distinction is best clarified by the following examples. A breathing frequency of 40 breaths/min can be considered low for a 3-month-old infant who has severe respiratory difficulty from bronchiolitis and is consistent with a predominantly obstructive dysfunction. A frequency of 100 breaths/min in the same infant, on the contrary, would be indicative of a predominantly restrictive dysfunction, caused by either parenchymal involvement in the disease (e.g., pneumonitis or collapse) or severe distention of the lungs and chest wall caused by pulmonary hyperinflation.

Breathing efficiency

In thermodynamic terms, *efficiency* is defined as the proportion of the free energy available within a system that is transformed into external work (Equation 2). For the respiratory system,

$$\text{Efficiency} = \frac{\text{Breathing power}}{\text{Respiratory muscle energy consumption}} \qquad 20$$

In practice, the breathing power (work/time) is calculated from the volume-pressure relationships of the thorax. The energy consumption of the respiratory muscles is estimated from their oxygen consumption, which is in turn computed as the difference between the total body oxygen consumptions measured during spontaneous and supported ventilation. Some obvious sources of energy consumption are not included in the breathing power and reduce the respiratory system's efficiency. For example, the work of breathing does not account for isometric activity of the respiratory and postural muscles, which is not proper work (no volume change) but consumes energy. Other forms of volume-pressure work are usually not taken into account when calculating respiratory efficiency. The work performed to inflate the chest wall, for instance, cannot be determined during spontaneous breathing when contraction of the muscles changes the wall's passive properties. Similarly, the work done to deform the rib cage is difficult to measure and often ignored. It is thus not surprising that the published efficiencies tend to be artifactually low. Notwithstanding these limitations and oversights, the low efficiency values (8% to 25%) reported in adult humans during rest, exercise, and voluntary and CO_2-induced hyperventilation[6,7,36] leave little doubt that the respiratory system is a rather inefficient machine.

As defined by Equation 20, the poor overall efficiency of the respiratory system implies that, during each breathing cycle, a substantial amount of energy derived from metabolic substrates is dissipated as heat and cannot be converted into volume-pressure work. Respiratory disease can increase this energy dissipation by various mechanisms leading to efficiency values as low as 1% to 3%.[7,17,49] Disease-induced alterations in chest wall configuration, for example, can limit the force generation by the muscles, thus interfering with the transformation of chemical energy into mechanical energy. Configurational changes also modify the spatial relationships of the muscles and can interfere with the transformation of mechanical energy into work. Finally, disease-related alterations in the contractile state of the muscles produced by fatigue or poor nutrition further decrease muscle force and the work of breathing without decreasing muscle energetic demands.

Alterations in chest wall configuration

Diaphragmatic configuration. The amount of force developed by a muscle depends on its resting length. An optimal resting length for which maximal force is developed can be defined for each muscle. In the case of the diaphragm, the optimal length is attained at thoracic volumes close to the normal FRC. At these volumes, the muscle has the shape of a dome-capped cylinder (Fig. 38-4), a configuration that has several advantages.[11] First, diaphragmatic contraction shortens the cylinder in the axial direction,[5] producing a pistonlike motion that displaces more volume than if the diaphragmatic dome simply became flatter (assuming the same degree of fiber shortening). Second, the descent of the diaphragmatic dome increases the surface of contact between the rib cage and the lungs. Therefore, the increase in lung surface produced by lung inflation can be accommodated without changing the shape of the lung or the chest wall. Finally, at normal breathing volumes, the sides of the diaphragmatic cylinder are apposed to the internal surface of the rib cage. This area of apposition establishes a mechanical link between intraabdominal pressure and lung volume.[32] As the diaphragm contracts during inspiration, intraabdominal pressure increases, pushing the lower portion of the rib cage forward and laterally. Thus, diaphragmatic contraction has an additional contribution to lung inflation at low energy cost and may help to stabilize the lower rib cage against inspiratory distortion.

The configuration of the chest in the infant and small child minimizes these advantages. At these ages, the lower portion of the infant's rib cage has large anteroposterior and lateral diameters.[48] As a result, the insertions of the diaphragm are spread out, and the muscle does not have a cylindrical shape (Fig. 38-5). Shortening of the muscle fibers can therefore only increase the radius of the dome, and the volume excursion of the lungs is proportionally less in comparison to the adult. Moreover, the lack of a substantial area of apposition of the diaphragm and rib cage abolishes the inspiratory and stabilizing effects of intraabdominal pressure on the rib cage.

In a similar manner, thoracic hyperexpansion and abdominal distention widen the diameters of the lower portion of the rib cage and spread out the diaphragmatic insertions. The length of the muscle fibers is diminished to a suboptimal length, and the force generated during inspiration is decreased (Fig. 38-5). Abdominal distention has the additional disadvantage of raising intraabdominal pressure, which opposes diaphragmatic contraction and raises the work that the muscle has to do.

Rib cage distortion. Until now, we have assumed that the rib cage and abdomen have the same configuration during both spontaneous breathing and passive inflation-deflation maneuvers. This assumption implies that all the various parts of the chest wall move with a single degree of freedom and that there are no volume shifts between parts. However, it has been known for quite some time that, under certain conditions, rib cage and abdomen can change volume independently of one another and even in opposite directions.[23] Under those conditions, the chest wall has multiple degrees of freedom and can undergo regional distortion.

Regional chest wall distortion results from the coupling

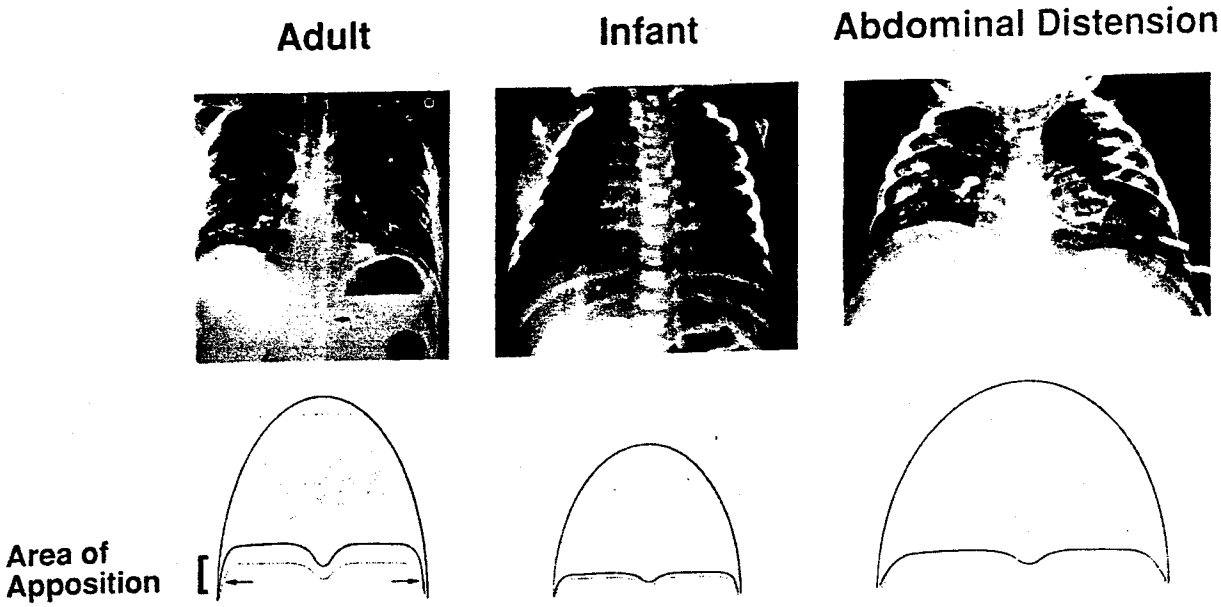

Fig. 38-5. This figure presents anteroposterior radiographs and drawings of the chest to compare the shapes of the diaphragm in the adult, infant, and child with abdominal distention. In the adult, the diaphragm has the shape of a cylinder with a domed cap.

of changes in pressure (pleural or intraabdominal) and the local compliances of the rib cage and abdominal wall. Rib cage distortion is more pronounced during inspiration, when pleural pressure decreases with respect to atmospheric pressure, forcing the thoracic wall inward in the expiratory direction. This inward movement of the rib cage causes visible retractions in areas where the chest wall normally has no bony support (intercostal, subcostal, or suprasternal spaces) or where the support has been abnormally weakened (e.g., costal fractures). Abdominal distortion, in contrast, usually involves alterations in the contractile state of the diaphragm or the abdominal wall muscles. When one hemidiaphragm becomes paralyzed, for example, the negative pleural pressure generated by other inspiratory muscles pulls the paralyzed muscle upward, into the rib cage, during inspiration. As a result, the abdominal wall of the affected side moves paradoxically in the inward direction, and the chest wall becomes distorted. As another example, contraction of the abdominal muscles stiffens the abdominal wall, raising intraabdominal pressure and shifting all volume changes to the rib cage during both inspiration and expiration.

The developing chest wall is particularly susceptible to distortion. As we have seen, the rib cage is very compliant in the newborn (see Fig. 38-1).[18,41] Although this high compliance facilitates enormously the passage through the birth canal, it also promotes inward distortion of the rib cage during inspiration. In addition, the intercostal muscles, whose main contribution to breathing is to stabilize the rib cage by contracting simultaneously with the diaphragm, appear to have decreased tone at early ages, especially during REM sleep and in preterm infants.[21] Finally, the lack of a substantial area of apposition between the diaphragm and the rib cage removes the stabilizing effect of the intraabdominal pressure on the lower rib cage. Accordingly, infants tend to develop chest wall retractions in the presence of minimal mechanical lung dysfunction.

Chest wall distortion represents a pressure-induced change in volume, and therefore it constitutes a form of work. Not being an inspiratory activity, distortional work is usually not computed as part of the work of breathing. This work, however, has a measurable energy cost, and thus it may be viewed as a source of respiratory inefficiency. Both the distortional work and its energy cost can be better understood if we analyze the volume-pressure relationships of the thorax in the particular case of rib cage retractions during inspiration. Regardless of whether such retractions are present, at any point in time, the volume change of the lungs (ΔV_L) must be equivalent to the sum of the volume changes of the rib cage (ΔV_{rc}) and abdomen (ΔV_{ab}).

21

$$\Delta V_L = \Delta V_{rc} + \Delta V_{ab}$$

Consequently, if ΔV_L is to remain constant, decreases in ΔV_{rc} caused by rib cage retractions during inspiration must be accompanied by a proportional increase in ΔV_{ab}. If, as often occurs, ΔV_{rc} is negative, then ΔV_{ab} becomes greater than ΔV_L. Because the volume displacement of the diaphragm approximates ΔV_{ab}, chest wall retractions inevitably result in an increase in the diaphragmatic excursion (Fig. 38-6). Considering that diaphragmatic work (W_{di}) is the integral of transdiaphragmatic pressure (intraabdominal − pleural pressure or $P_{ga} - P_{pl}$; P_{ga} is gastric pressure, which is often used to estimate intraabdominal pressure) with respect to the excursion volume of the diaphragm (V_{ab}) and the work done on the lungs (W_L) is the integral of transpulmonary pressure ($P_{tm} - P_{pl}$) with respect to tidal volume,

22

$$W_{di} = \int_{V_0}^{V_1} (P_{ga} - P_{pl})\, dV_{ab}$$

23

$$W_L = \int_{V_0}^{V_1} (P_{tm} - P_{pl})\, dV_L$$

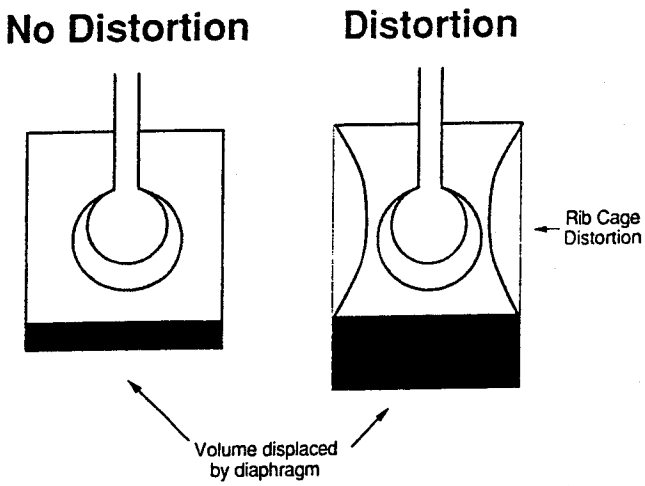

Fig. 38-6. Schematic representation of the effect of inward distortion of the rib cage on the volume displaced by the diaphragm. During a nondistorted inflation *(left)*, both rib cage and abdomen undergo expansion. In the presence of rib cage retractions *(right)*, however, the diaphragm must offset the inward motion of the rib cage to maintain tidal volume constant. As a result, the diaphragmatic volume displacement is greater in the distorted than in the nondistorted state.

it is clear that W_{di} substantially exceeds W_L because P_{ga} is greater than P_m and dV_{ab} is greater than dV_L. It is also clear that W_{di} is greater when there are retractions than when there are no retractions because the latter increases dV_{ab}. Using this analysis, Heldt and McIlroy have demonstrated that the volume displacement of the diaphragm may be up to twice the tidal volume of the lungs in premature infants without apparent lung disease.[20] These investigators suggested that the resultant increase in diaphragmatic work could be responsible for the poor weight gain and development of fatigue of infants recovering from the respiratory distress syndrome.

Alterations in contractile state of the respiratory muscles. Respiratory efficiency is also affected by the functional state of the respiratory muscles. Sustained supranormal activity is likely to result eventually in decreased contractile force and a lower minute alveolar ventilation, a condition often classified as muscle fatigue.[44] When muscle fatigue is present, the energy consumption of the muscle may be increased with respect to the actual work performed. Similar decreases in contractility without a decrease in energy consumption can be present in a variety of clinical situations. Some result from an imbalance between the energy demands of the muscle's contractile machinery and its substrate availability (e.g., shock).[2] Others are simply the expression of the inadequate coupling of the excitation-contraction processes inside the muscle cell or the chronic depletion of the muscle's energetic resources due to malnutrition.

CONCLUSION

Although the developing respiratory system has obvious mechanical disadvantages, the reader should not be left with the idea of infants and children as constantly on the brink of respiratory failure. Quite the contrary, they have a remarkable capability to tolerate respiratory disease. This capability is in great part based on a very proficient system of mechanical compensation. The information contained in this chapter is intended to provide an overview of the factors involved in both mechanical dysfunction and its compensation. Understanding these factors should permit a more rational approach to the therapy of respiratory disease in the critically ill child.

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American Thoracic Society/European Respiratory Society

Respiratory Mechanics in Infants: Physiologic Evaluation in Health and Disease

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THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE EUROPEAN RESPIRATORY SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS (JUNE 1992) AND THE ERS EXECUTIVE COMMITTEE (SEPTEMBER 1992).

Respiratory disease is now the number one cause of morbidity and mortality in infants worldwide. Advances in neonatal care are continuing to increase the rates of survival of prematurely born infants with respiratory disease. Rapid progress in the basic sciences is providing new diagnostic and therapeutic approaches for the management of respiratory disease. In the first 18 months of life the respiratory system undergoes extraordinary functional developmental changes. Until recently, however, our knowledge of the normal mechanical properties of the developing human lungs and airways during this period of rapid growth has been extremely limited. Similarly, it has been difficult to assess the effects of disease and the responses to therapeutic interventions in infants.

In the last decade many new and innovative methods for assessing pulmonary function in infants have been developed, while older, classic techniques have continued to evolve. Studies using these methods have already provided valuable insights into the normal process of growth and development of infant lungs and airways. The effects of various prenatal and postnatal biologic, mechanical, and environmental insults that disrupt this normal process and result in dysfunction are also now being characterized quantitatively using these measures.

Tests of pulmonary function in infants are now being used worldwide. Although our understanding of the physiologic basis for many of these measurements remains incomplete, they are yielding important new information about the respiratory problems of infancy. The marketing of commercial devices has made the technology for these measurements widely available. However, procedural guidelines and equipment standards for these tests have not yet been developed. Given the worldwide importance of respiratory disease in early life and the new therapeutic approaches originating from advances in the basic sciences, there has been a growing need for a coordinated effort to understand, develop, and standardize methods for assessing pulmonary function in infants. This process was initiated in 1989 with the report of European Society for Clinical Respiratory Physiology on the standardization of lung function tests in pediatrics (1). This review encompassed many aspects of infant lung function testing, including the measurement of lung volumes, respiratory mechanics, and FEF in infancy.

This Statement was prepared by a joint committee of the ATS Assembly on Pediatrics and the ERS Paediatrics Assembly. Members of the Committee are: Julian L. Allen; Ephraim Bar-Yishay; A. Charles Bryan; Jeffrey Budd; Robert G. Castile (Chair); Allan L. Coates; G. Michael Davis; Sandra England; Claude Gaultier; S[illegible] Godfrey; Michael Grunstein; Peter LeSouëf; Robert B. Mellins; Wayne J. Morgan; Etsuro K. Motoyama; Michael Silverman; Peter D. Sly; Janet Stocks; Robert S. Tepper; Warren J. Warwick.

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in order to further this process, a group of experts in the field of infant respiratory mechanics convened under the auspices of the American Thoracic Society and the European Respiratory Society in January 1991. Their aim was to (1) determine what was known about currently available tests and (2) define what further information needed to be learned before the process of standardization could begin. The purpose of this Statement is thus to summarize what is known and agreed upon by investigators in this field, and thereby provide the scientific basis for the future standardization of infant pulmonary function tests.

Tests of pulmonary function in infants are summarized in four sections: MEASURES OF FORCED EXPIRATORY FLOW, MEASURES OF COMPLIANCE AND RESISTANCE, MEASURES OF LUNG VOLUME, and OTHER TESTS (including measures of tidal volume and respiratory pattern, chest wall motion, and gas mixing). Each section is organized under the general subheadings of INTRODUCTION, METHODS (what is known), CURRENT CONTROVERSIES (what is not known, uncertain, or controversial), and FUTURE DIRECTIONS (what needs to be known). A critique of the available reference values is presented for each category of measures.

MEASURES OF FORCED EXPIRATORY FLOW

Introduction

The maximal expiratory flow volume (MEFV) relationship was first described by Hyatt and coworkers in 1958 (2). In the years since, research has established that maximum expiratory flow (MEF) on the descending portion of the MEFV curve is independent of effort (flow limitation) and reflects airway caliber upstream (peripheral) from the airway segment subjected to flow limitation (3, 4). The measurement of MEF has been standardized and has come to play a central role in the clinical evaluation of lung function as a sensitive test of abnormalities in the intrathoracic airways. The ability to measure MEF reproducibly has expanded our knowledge of normal and abnormal human lungs, thus contributing greatly to the diagnosis and treatment of lung disease in adults and older children.

In the last decade, two methods have evolved to allow the forced expiratory flow-volume relationship to be examined in infants. The first, the forced deflation technique, was initially described in 1977 (5). In this technique the lungs are inflated to a pressure of 40 cm H_2O and then deflated rapidly to residual volume (RV) by a sudden exposure to negative pressure. The advantage of the forced deflation method is that it generates increased flows over the entire range of the vital capacity (VC). The disadvantage of this technique is that it requires endotracheal intubation as well as deep sedation and muscle relaxation. These requirements limit its use to intensive care or surgical settings. The second technique, rapid thoracoabdominal compression (RTC), was described in 1978 (6) and later modified (7). In this technique, forced expiratory flows are produced by the sudden application of a compressive pressure to the thorax and abdomen at end-tidal inspiration. The advantage of the RTC method is that it is relatively noninvasive and can be performed in the clinical setting with neither intubation nor deep sedation (8). This technique has the disadvantage of producing only a partial expiratory flow-volume (PEFV) maneuver. Also, it is unclear at present whether or not flow limitation is achieved using this method.

Much controversy remains regarding the comparability of the forced flows produced by these two methods in infants with the flows measured in adults and older children during voluntary forced expiratory maneuvers. Nonetheless, the results of studies using these techniques document their value as research tools. The use of forced expiratory flow measurements to assess lung function in infants has extended our understanding of the normal growth and development of the lungs during infancy (9–11) and helped to describe the pulmonary abnormalities seen in acute and chronic infantile lung diseases (12–18). Both methods have also helped to define the onset of and recovery from bronchopulmonary dysplasia (BPD) in prematurely born infants. Much remains to be learned, however, about the treatment and management of both the acute and the chronic aspects of the pulmonary sequelae of premature birth. Measurements of forced expiration are central to the management of lung disease in older children and adults with cystic fibrosis (CF). RTC measurements have been used in infants with CF (19, 20) to define the severity of disease at diagnosis and to measure the short-term effects of antibiotic and bronchodilator therapy.

Studies using various bronchodilator and bronchoconstrictor stimuli have shown that normal infants and infants with wheezy bronchitis, CF, or neonatal lung disease have significant airway reactivity (14–27). Bronchoconstrictors, however, have produced substantial decreases in flow in a large percentage of otherwise healthy infants (21, 22), and bronchodilators have produced paradoxic decreases in forced flows in some wheezy infants (25). Although the significance of these changes in forced expiratory flow after bronchial challenges are not yet fully understood, further application and development of forced expiratory methods should help to define the origins of infantile and childhood asthma.

Forced expiratory flow measurements have revealed not only levels of dysfunction and responses to therapy in infants with respiratory disease, but also characteristics of normal infants who are at increased risk for later respiratory problems. Epidemiologic population studies have suggested that altered airway function precedes and predicts recurrent wheezing and an increased incidence of lower respiratory illness in infancy (11, 28). Studies in normal infants have further suggested a significant negative effect of maternal smoking during pregnancy on infant lung function (24, 29).

Although the current methods of measuring forced expiratory flows in infants have provided much information, many concerns still exist regarding the techniques and the interpretation of the measurements obtained (30–33). Further research to develop and standardize these tools, however, should improve their utility.

Methods

Forced deflation technique. This technique is limited to infants and children who already have an endotracheal tube or a tracheostomy. The subject must be deeply sedated or under general anesthesia with or without muscle relaxation. For the test procedure (5, 14), the lungs are inflated manually with a breathing bag to +40 cm H_2O of airway pressure, defined as total lung capacity (TLC), and held for 2 to 3 s. Manual inflation is performed four times to recruit lung volume from previously closed or atelectatic segments and to establish a consistent volume history. On the fourth inflation, after TLC has been reached and maintained for a few seconds, an air-tight slide valve is pushed open, suddenly exposing the endotracheal tube via a pneumotachograph to a 100-L capacity, constant negative pressure source (−40 cm H_2O). The valve is held open until the expiratory flow ceases at RV or for a maximum of 3 s (FEV_3). In healthy infants RV is reached (i.e., FVC is produced) within 1 to 2 s.

Immediately, the slide valve is pushed closed, reconnecting the endotracheal tube to the breathing bag. The lungs are reinflated to TLC with an oxygen-enriched gas mixture several times to ensure full reexpansion before tidal ventilation is resumed. Throughout the forced deflation procedure, the subject is con-

tinuously monitored with a pulse oximeter to assure adequate oxygenation.

The flow signals and integrated volume signals are plotted instantaneously on a storage oscilloscope to produce an MEFV e. The maneuver is repeated until three virtually identical FV curves are superimposed on the oscilloscope screen. Alternatively, flow signals may be A/D converted, and the MEFV curves produced by a computer.

With this technique, MEFV curves and FVC are highly reproducible unless previously collapsed airway segments are successively recruited by lung inflation. MEF is measured at 25% and 10% of FVC from RV (MEF_{25} and MEF_{10}, respectively) and the ratios of MEF_{25}/FVC and MEF_{10}/FVC are calculated as indices of the ate constant of the upstream airway segment (34). Flows are measured low in the VC (MEF_{25}, MEF_{10}) to help ensure that flow limitation has been achieved. Flows > 30% of VC appear not to be at ow limitation. Further, artifact introduced by the endotracheal ube acting as a critical orifice may also occur at lung volumes mid-VC.

In eight healthy infants undergoing elective surgical procedures nder general endotracheal anesthesia, the deflation negative ressure applied at TLC was decreased successively from −40 m H_2O to −10 cm H_2O to determine the pressure necessary to roduce flow limitation (Motoyama EK, unpublished observations, 990). At 25% FVC from RV, which is near FRC, the negative pressure necessary to produce flow limitation ranged from −25 to −30 m H_2O. In contrast, infants with lower airway obstruction (15) required much less pressure to produce flow limitation at FRC. Accordingly, a deflation negative pressure of −40 cm H_2O has been sed routinely to ensure flow limitation at and below 25% of VC all infants studied as well as to determine TLC in the forced on technique.

pid Thoracoabdominal Compression Technique

r an RTC maneuver, infants are usually sedated with 50 to 100 g/kg of chloral hydrate given orally. The RTC technique produces ced expiratory flows by applying a sudden pressure to the tho- and abdomen at end-tidal inspiration using an inflatable oracoabdominal jacket connected to a positive-pressure reser- r (8, 32). Compression is usually maintained for 1 s, but a longer e may be required in some infants with severe obstruction. Flow measured at the mouth using an appropriately sized pneu- tachograph with a face mask. To reduce potential leaks, either roleum jelly or a silicone putty sealant is applied to the face sk before placement. Flow signals are integrated to obtain vol- e signals, and the flow-volume plot is displayed in real time an oscilloscope screen or computer monitor. Before the RTC neuver, a reproducible end-expiratory point, or FRC, is estab- ed on the volume axis by at least three tidal breaths. RTC at l-inspiration then produces a PEFV curve with exhalation con- ing to a point below FRC. FRC has been the most commonly d reference point (8) for the measurement of forced expira- flow by this technique. The jacket compression pressure is dily increased until no further increase in flow at this FRC t is observed.

The compression jacket should have a noncompliant outer sur- and an inflatable inner surface, and it should cover the en- thorax and abdomen. The jacket should be wrapped snugly e infant, with the arms outside (35), but not so tightly decreases FRC. The jacket should be inflated rapidly, so peak jacket pressure is reached in 50 to 100 ms. In normal ts the PEFV maneuver may be completed within 200 ms. For reason, the frequency response of flow and pressure measuring devices should be linear through at least 10 Hz. The true frequency content of PEFV maneuvers, however, remains to be studied in depth, and the value of 10 Hz is probably an underestimate. Nonlinearity in the frequency response can result in overestimation or underestimation of rapidly changing flows. Furthermore, in computer-based systems the digital sampling rate needs to be at least 64 Hz with 12-bit resolution, to allow adequate frequency response and accurate digital integration.

The jacket pressures used to produce forced expiratory flows in infants have ranged from 40 to > 80 cm H_2O. In many infants with significant airway obstruction, reproducible PEFV curves can be generated using a jacket pressure of 40 cm H_2O or less. Additional increases in jacket pressure in such infants have been shown to decrease flow (9, 36). In normal infants, jacket pressures of 80 cm H_2O or more may not produce flow limitation. Pressures of up to 100 cm H_2O have produced steadily increasing flows in some infants. Most investigators have placed a limit on the maximal jacket pressure to be used. As the pressure actually transmitted to the pleural space is probably influenced by such factors as the construction of the jacket and how tightly the infant is wrapped in the jacket, it is impossible currently to specify a maximum compression pressure that will guarantee flow limitation in all infants. Thus, the jacket compression pressures used to produce forced expiratory flows should always be reported. Furthermore, some authors have suggested that the efficiency of jacket pressure transmission is variable and should be measured and reported as well (36).

Because it is uncertain whether this technique produces flow limitation at wave speed, most investigators have judged the quality of the resultant PEFV curves in terms of their shape. An "acceptable" PEFV curve is generally triangular, with the flow-volume relationship rising sharply to a peak and then falling smoothly to a point below the initial end-expiratory volume. Irregular or jagged curves are usually considered to have been distorted by pharyngeal or glottic closure. This problem can often be remedied by gently extending the infant's neck. Infants frequently inspire before the completion of chest compression. Curves that end near, at, or above the resting end-expiratory volume are generally considered to have been distorted by inspiratory effort and are unacceptable.

How best to compute the values of flow measured at FRC is unclear. In most studies the intrasubject coefficients of variation (CV = SD/mean × 100) for technically acceptable flows measured at FRC have been approximately 10 to 15% within a single test session (9). It seems reasonable to attempt to obtain three maximal measurements varying by no more than 10% and to report the final result as the mean of those three values. Some have argued on a physiologic basis that only the highest flow achieved should be reported, as this flow must represent the flow nearest to maximal flow. To the degree that the flows produced by the RTC technique exceed those during tidal breathing, they may provide a useful forcing function to evaluate the respiratory system even if flow limitation is not reached.

Current Controversies

Forced deflation technique. The use of the forced deflation method in obtaining MEFV curves has been limited to a small number of institutions and essentially the same technique as originally described (5, 14). As a result, controversies in terms of procedural standards have not emerged. The potential controversies include the following: Various sedatives, anesthetics, muscle relaxants, and adjuvant medications may affect bronchomotor tone, compliance, and lung volume. Inhaled anesthetics, such as halothane

and isoflurane, and anticholinergic drugs, such as atropine, are potent bronchodilators, affecting different segments of the airway system, whereas morphine and the muscle relaxant d-tubocurarine are potential bronchoconstrictors by causing histamine release. Although clinically significant alterations in vital signs with the forced deflation method have not been reported, repeated maneuvers may result in hypocapnia, affecting vascular and bronchomotor tone. Further, the positive pressure used to inflate the lungs may impede venous return to the right side of the heart, especially in hypovolemic subjects. Continual monitoring of vital signs with pulse oximetry and other means is indicated.

The use of an endotracheal tube may influence the site of flow limitation and prevent movement of the choke point upstream during deflation. The effect of the endotracheal tube needs to be studied; however, measuring flow at a low lung volume (MEF_{25}, MEF_{10}), may avoid this problem in infants. In older children and adolescents care needs to be taken to ensure that the tube is not acting as a critical orifice preventing flow limitation in the tracheobronchial lumen. In patients in the intensive care unit, the fraction of inspired oxygen (FIO_2) should be increased during a forced deflation maneuver, to ensure optimal hemoglobin saturation and tissue oxygen delivery. When different gas mixtures (increased FIO_2, nitrous oxide, helium) are used. the calibration of the pneumotachograph should be adjusted for the alteration in gas physical properties. Finally, the impact of altered volume history on lung function in infancy needs to be delineated. Measurements of MEF after repeated recruitment of airspaces may not represent airway function at steady state. Further, the impact of altered volume history on airway and parenchymal characteristics needs to be defined in infants with and without lung disease.

Rapid thoracoabdominal compression technique. Controversy surrounds almost all aspects of the RTC method. The most critical question, however, is whether or not physiologically determined flow limitation is reliably produced by RTC. Flow limitation is usually documented using isovolume pressure-flow curves in adults (2). These have not been successfully obtained in normal infants, however. Although flow-limited isovolume pressure curves have been demonstrated during RTC maneuvers in infants with severe airway obstruction, flow limitation in normal infants has not been clearly or consistently documented using this standard method. In infants with BPD, most of whom were near flow limitation during tidal breathing, a clear plateau in the pressure-flow curve relationship was observed with a minimal increase in the pressures applied to and transmitted across the chest wall (37, 38). In infants with less severe airway obstruction or normal airway function, higher intrathoracic pressures are required to produce flow limitation at FRC and a plateau in the isovolume pressure-flow relationship. Using the forced deflation technique, airway pressures of −25 to −30 cm H_2O are required to produce consistent flow limitation at low lung volumes near FRC (25% FVC) in intubated, anesthetized, paralyzed infants with normal lung function (see METHODS: FORCED DEFLATION TECHNIQUE). Measurements of intrathoracic pressure during a dynamic RTC maneuver suggest that only approximately 25% of the applied jacket compression pressure is transmitted to the pleural space at FRC (7, 37, 39). This means that even with jacket pressures of 80 cm H_2O only about 20 cm H_2O is transmitted across the chest wall to produce the flows observed. Thus, it is not surprising that most investigators are uncertain of the ability of RTC to produce flow limitation in normal infants. When infants undergo RTC under assumed static, relaxed conditions (obstruction at the mouth), from 60 to 80% of jacket pressure appears to be transmitted through the thorax (36). It has been suggested (30, 33) that this difference in transmission between dynamic and static conditions may be explained by reflex inspiratory activity induced by sudden thoracoabdominal compression. Diaphragmatic contraction or an increase in chest and abdominal wall resistance may account in part for the inefficient transmission of pressure during a dynamic RTC maneuver.

As an alternative method of assessing flow limitation during RTC, the superimposition of an oscillatory pressure wave obtained at the chest wall has been studied (40). The disappearance of flow oscillations measured at the mouth is proposed to signal the onset of physiologic flow limitation in the airways. Although this technique looks promising, additional measurements of intrathoracic pressure and simultaneous corroboration of flow limitation using isovolume pressure-flow curves will be necessary to document its validity. To date, flow limitation as evidenced by a maximal flow plateau in the isovolume pressure-flow curve has not been consistently demonstrated during RTC in normal infants (41). Although flow limitation is not produced in all infants, the results of studies in both normal infants and those with airway obstruction document the utility of the RTC technique. Without true flow limitation, however, comparisons between and within individuals are problematic.

A potential source of error in PEFV measurement that has not been investigated in infants is the use of integrated flow at the mouth to describe volume. Because of intrathoracic gas compression in subjects with obstructive lung disease, the flow-volume relationship may be systematically altered unless volume is measured by plethysmography (42, 43).

Increased upper airway resistance may represent another source of interference in the measurement of intrathoracically determined flows. Care must be taken to prevent nasal compression, and the head and neck must be positioned to minimize pharyngeal narrowing. Reflex glottic closure may cause problems in some infants. Compression of the chest wall in lambs elicits glottic closure, and most investigators have observed rapid decreases in flow during RTC maneuvers that are compatible with glottic closure (32, 33, 44). Although glottic closure at FRC makes it impossible to determine flow at FRC, the effect of earlier or partial glottic closure remains poorly defined (45).

Levels of end-expiratory lung volume are actively controlled in infants and consequently may be variable. Variations in end-expiratory level of lung volume or FRC may affect measurements of flow at FRC. Measured flows are likely to increase if end-expiratory level increases and to decrease if end-expiratory level decreases. This problem is particularly acute when the response to bronchodilator or bronchoconstrictor agents is being evaluated. Measuring lung volume by gas dilution or plethysmography may help to limit the variability, but is only a partial solution to the problem because of the additional errors inherent in volume measurements.

The flow-volume relationship produced by the RTC method, even if flow is limited, represents only a small, low-lung-volume segment of the full MEFV curve. This segment is highly variable and extremely sensitive to even minor changes in airway function. Many of the problems encountered in the RTC method might be solved if techniques were developed to measure the flow-volume relationship in infants over a larger portion of the VC range, as in the forced deflation method. Preliminary efforts using the expiratory volume clamping technique and positive-pressure inflation through a face mask in sedated infants appear to offer promise (46).

Standardization of the RTC techniques presents many problems, and much remains to be learned about the effects of seemingly minor procedural changes on the flow-volume curves produced. In all reported studies, the methods used should be

pecified in detail, as such variations in procedure may explain e sometimes large discrepancies in results from different labora-

eference Values and Interpretation

ecause of the difficulty of recruiting normal subjects and the lack standardized procedures, adequate reference values for these chniques are lacking.

Forced deflation technique. Although no reference values are ailable for the forced deflation technique, limited data have been ublished (5, 14–17). In six otherwise healthy newborn infants un- r general anesthesia for elective surgery (16), the mean (± SD) EF_{25} was 49 ± 16.2 ml/kg/s, and the mean MEF_{25}/FVC was 1.12 0.27/s. In four sedated and intubated preterm newborn infants th a mean gestational age of 27.7 wk and no apparent lung dis- se (14), the mean MEF_{25} was 95 ± 27.7 ml/kg/s, and the mean EF_{25}/FVC was 1.67 ± 0.38/s. When adjusted for weight and lung lume, the values in the preterm infants were much higher than ose in full-term newborns (16, 17).

Rapid thoracic compression technique. Limited reference lues are available for the RTC method. Only two studies have ported flow measurements generated by RTC in large numbers normal infants. In 1986, forced expiratory flow measurements ken in 120 normal infants from Tucson, Arizona, were reported , and in 1990, a report of 148 measurements in 72 normal in- nts from Boston, Massachusetts, was published (10). In the Tuc- n series, flow measured at FRC was related to body length by e equation: flow at FRC (ml/s) = 4.5 × length (cm) − 123. In ston series the relationship was: flow at FRC (ml/s) = 9.67 gth (cm) − 399.8. The results from these two studies ap- ar to differ, as the second equation reflects a more rapid in- ease in flow measured at FRC with increasing body length than es the first. The measured flows in infants less than 3 months age were similar in both studies. In the Tucson study, most in- nts measured were less than 3 months of age (< 60 cm in length). e Tucson study also reported flow measurements from five nor- al full-term and six normal premature newborns, which were gher than those in normal infants 1 to 3 months of age, a find- g that remains unexplained. The increased flows in newborns, upled with the relative paucity of measurements from infants nger than 65 cm (older than 6 months), in the Tucson study ap- ar to account for the slower increase in measured flow at FRC h increasing length by comparison with the results from Bos- n. Although most infants tested in the Boston study were also unger than 6 months of age, this study included more mea- rements taken in the second 6 months of life. Very few mea- rements were taken in the second year of life in either study. us, the data from both studies appear to serve as predictors normal RTC-generated flows at FRC in young infants, but the ston study, which predicts significantly higher flows in infants nonths of age and older, probably provides more reasonable edicted values in older infants.

That flows measured at FRC in older infants are higher than edicted by the Tucson study is confirmed by an independent of measurements taken in normal infants in Indianapolis, In- These 22 infants, whose average age was 13 months and was 72 cm, had average flows at FRC of 273 ml/s (20). This ue is close to the 296 ml/s prediction for 72-cm infants from Boston data, but is significantly higher than the 201 ml/s predic- n from the Tucson data. Jacket compression pressures aver- ed 45 cm H_2O in the Tucson study and were approximately 80 H_2O in the Boston study. The reasons for these differences unclear, as the same criteria for increasing jacket pressures until flow at FRC reached an apparent maximum were used in both studies.

At present, the Tucson and the Boston data provide preliminary reference values for forced expiratory flow by RTC in infants less than 6 months of age. From 6 months of age onward, the Boston data are probably the better reference. Limited data are available on forced flows produced by the RTC method in infants in the second year of life. Predicted values in this age range are based primarily on extrapolation.

Future Directions

Three primary concerns remain in the understanding of the physiology of forced expiratory flow. First, methods to determine or achieve flow limitation in healthy infants need to be developed. Second, these methods need to be standardized and applied in population studies to define the normal development and growth of the lungs and to provide useful reference values. Third, potential sources of variation in the measurements need to be characterized and limited. This effort will entail studies of transmission pressure, isovolume pressure-flow relationships, the impact of chest wall tone, and upper airway resistance. A critical comparison of MEF values obtained by the RTC technique during sedation with values obtained by the forced deflation technique during anesthesia and paralysis in the same infants (41) would help to solve a number of these questions.

The effect of variations in lung volume on the flows measured in both the RTC and the forced deflation techniques needs to be addressed. Functional residual capacity may be dynamically determined, and hence be variable, in infants, thus altering the flow measurements obtained. End-expiratory lung volume (relaxation volume) under anesthesia or muscle relaxation is much lower than dynamic FRC. Thus, MEF at relaxation volume during forced deflation cannot be equated with MEF at FRC during RTC. Studies involving the use of bronchodilators or bronchoconstrictors may systematically alter lung volume, thus altering volume-based flow measurements. An accurate, noninvasive method of rapidly tracking this volume change is needed.

Methods designed to increase the volume at which flow is initiated should be further developed. Two promising techniques are the use of volume clamping to raise lung volume progressively, breath by breath, and the rapid inflation technique, in which the lungs are inflated before the PEFV maneuver by positive pressure applied through a face mask. By generating a larger segment of the MEFV curve, these methods might better characterize the kinetics of volume elimination.

Two goals must be achieved before MEF measurements can be recommended for general use. First, the procedures for both the RTC and the forced deflation techniques need to be standardized. Until this is accomplished, investigators must supply detailed descriptions of their methods, including not only flow production techniques but also curve selection criteria. Second, a longitudinal study using standardized methods in a large number of normal infants needs to be undertaken to generate normal prediction equations over the first 18 months of life. The population studied also needs to include sufficient proportions of infants of differing race and gender to develop specific equations for different population groups. Further, the upper age at which useful MEFV measurements can be performed needs to be determined.

MEASURES OF COMPLIANCE AND RESISTANCE

Introduction

In adults, compliance and resistance are rarely measured directly, and pulmonary function is assessed using standardized, indirect

tests from which abnormalities of these mechanical characteristics are inferred. In infants and young children, however, these standardized tests are difficult to perform because they require the subject's cooperation and coordination. Therefore, a number of innovative approaches have been devised to measure compliance and resistance directly in infants.

Using these techniques, valuable clinical and physiologic information has been obtained in many laboratories. For example, the normal development of the lungs and the chest wall have been assessed by measuring compliance and resistance during maturation. Compliance measurements have been used to investigate the efficacy of surfactant replacement therapy in neonates and of steroid therapy in interstitial lung disease in young children, and to differentiate the severity of disease in infants with CF. Resistance measurements have been used to assess the severity of infant respiratory diseases and the efficacy of bronchodilator therapy. The studies with bronchodilators have revealed that, contrary to established beliefs, significant bronchoconstriction can occur even in preterm infants studied during the first weeks of life.

At present, instruments to perform some of the measurements of compliance and resistance are commercially available. Nevertheless, there remains considerable controversy over the optimal methods to be used and the interpretation of the data obtained. Thus, although the techniques to be described have great potential for providing sound clinical data on pulmonary function in infants, a number of problems must be resolved before they can be confidently recommended for wide clinical use.

Methods

General Considerations

Techniques for measuring compliance and resistance can be classified as passive or quasistatic and dynamic. All require measurements of airflow, volume, and pressure. Dynamic mechanics are measured during either spontaneous or, less frequently, mechanically assisted ventilation, and passive mechanics are measured during maneuvers that silence the respiratory muscles.

In most techniques, the description of the mechanical properties is derived from the general equation of motion of the lung: $Pdr = (1/C \times V) + (R \times \dot{V}) + (I \times d^2V/dt^2)$, where Pdr is the driving pressure for the system, C is compliance, R is resistance, I is inertance, V is volume, $\dot{V}$ is flow, and d^2V/dt^2 is acceleration. The principal assumption is that the system follows a linear function such that unique values exist to describe it. Although this assumption may be tenable in the V_T range for normal infants, the function of the respiratory system during disease is less well described by a linear pattern. A further basic assumption for all methods is that the inertance is negligible, thus simplifying the equation to the compliance and the resistance terms. This assumption has not been tested in infants at high respiratory rates, when inertance may make a larger contribution. The measurement of pressure at the airway opening (Pao) relative to barometric pressure (P_B) represents the driving pressure across the total respiratory system (airways, lungs, and chest wall) and in relation to volume and flow yields respiratory system compliance (Crs) and resistance (Rrs). Rrs and Crs can both be partitioned into lung and chest wall components by measuring the relevant driving pressure for each component. The measurement of lung compliance (C_L) and resistance (R_L) requires the measurement of transpulmonary pressure (Ptp, the difference between pleural pressure [Ppl] and Pao), with Ppl usually approximated as esophageal pressure (Pes). Esophageal pressure is measured with either a water-filled catheter or an air-filled esophageal balloon on a catheter. The catheter is placed either through the nose (in intubated infants) or through the mouth. Nasal insertion substantially increases the contribution of nasal resistance to the total measured resistance in nonintubated infants.

The physical characteristics of esophageal balloons for infants have been extensively investigated (47). Balloons with a diameter of 5.5 to 7.7 mm and a length of 3.5 to 5.0 cm are recommended for use, after their pressure-volume characteristics have been established and the optimal operating volume has been determined from the passive compliance curve. Balloon thickness also affects the pressure-volume characteristics. Water-filled esophageal catheter systems are easier to pass into the esophagus than are balloon-tipped catheters, and, in certain cases, an existing nasogastric catheter can be withdrawn into the esophagus and used to measure changes in esophageal pressure. The existence of a hydrostatic pressure gradient between the transducer and the catheter tip makes it impossible to measure absolute pressures, but the difference can be minimized by positioning the transducer in the supine infant at the mid-axillary line. Because of the possibility of partial obstruction, multiple orifices are needed in the catheter. The fluid column must be kept free of bubbles ("degassed"), as the quality of the measurement depends upon minimizing the compliance of the measuring device. Using 8-French catheters, the system has been shown to have an adequate frequency response and to provide useful clinical information (48–50).

During an inspiratory effort against an occluded airway, when there is no airflow ($\dot{V} = 0$), the change in alveolar pressure (ΔPalv) is approximated by the change in Pao (ΔPao). Pleural pressure differs from Palv by the static elastic recoil pressure, but during occlusion, when $\dot{V} = 0$, the change in Ppl (ΔPpl) should equal ΔPalv and, hence, ΔPao. Therefore, if the change in Pes (ΔPes) = ΔPao, Pes is the equivalent of Ppl. The "occlusion test" (51) has been used to demonstrate that this relationship is valid under inspiratory occlusion conditions in normal adults and in normal infants (48). Esophageal pressure measurements are unreliable in a subject with esophagospasm or previous surgical trauma to the esophagus. A satisfactory occlusion test requires < 5% difference between ΔPao and ΔPes (52).

The functional properties of the chest wall (Cw, Rw) can be determined from the pressure across the chest wall (Pw = Pes − P_B). Under normal functional conditions, Pw is the combination of the static elastic properties and the effect of the pressure generated by the activity of the muscles in the chest wall. Accordingly, the passive mechanical properties of the chest wall can be derived only when the muscle pressure is inhibited (passive conditions).

A pneumotachograph is normally used to measure airflow, which is integrated to obtain volume. The flow range of the pneumotachograph should encompass the maximal flow of the infant. Because any attachments to the pneumotachograph contribute to its characteristics, linearity and frequency should be ascertained in the entire system through which the infant respires. In intubated patients, the endotracheal tube itself offers a significant resistance to $\dot{V}$ (53) and increases the difficulty of obtaining a leakproof seal (54). Nasal adapters have been used (55), but they significantly augment the large component of resistance contributed by the nasal airway (56, 57). As an alternative method a face mask may be used, but it introduces sources of error including small unapparent leaks (54) and stimulation of the trigeminal nerve distribution (58). Evidence of a competent mask includes no change in flow or volume with airway occlusion and a return to the preocclusion end-expiratory volume baseline after release of the occlusion (52, 59).

Three important concerns related to the use of the pneu-

motachograph are (1) that the increase in dead space can increase P_{aCO_2} and change both V_T and respiratory rate; (2) that the pneumotachograph increases resistance; and (3) that failure to calibrate with the gas composition being breathed by the subject can cause error in the flow measurements. A low-dead-space system has recently been described (60).

The transducers used to measure the relevant pressures should have appropriate frequency response characteristics to 10 Hz, and the phase response characteristics should be the same for all signals (61–63).

Infants should be tested in quiet sleep when respiration is regular, and rapid eye movement (REM) and gross body motion are absent (64). Sleep state is an important but rarely monitored variable that may profoundly alter the measurements. For instance, FRC has been suggested to decrease with active sleep (65) in full-term but not in premature infants (66). Although the absolute changes in lung volume in full-term infants have not been confirmed in subsequent studies (67), variations in lung volume during active sleep are apparent. Diaphragmatic muscle tone is inhibited and postural (intercostal and abdominal) muscle recruitment and laryngeal braking of expiratory airflow are greatly reduced in active sleep (68–70). Posture may also influence respiratory mechanics. The supine posture has been suggested as a standard for the measurement of Pes (68). The absolute Pes, by balloon measurement, is affected by posture, although changes in pressure are unaffected (71, 72) except in anesthetized patients or those with unilateral lung disease (72). Sedation with chloral hydrate (25 to 100 mg/kg) is popular and appears not to interfere with the measurements (73, 74), although both this technique and the alternative, sleep deprivation, may alter upper airway tone (75), thus increasing upper airway resistance and the risk of obstruction.

Because infants almost always breathe through the nose during testing, upper respiratory tract infections, allergic rhinitis, and other factors may influence the results obtained. If baseline measurements are desired, testing should be delayed until several weeks after resolution of upper respiratory tract pathology.

Dynamic Techniques

The Mead-Whittenberger technique (78) was used in many of the original studies of respiratory mechanics in infants. In this technique, Pes is measured to obtain measurements of C_L, C_w, R_L, and R_w. The original analysis was performed by deriving compliance at the points of zero flow at the end of inspiration and expiration as $C_{dyn} = \Delta V/\Delta P$, assuming that compliance is linear over the V_T range. Using points of equal volume in the midvolume range, one during inspiration and the corresponding volume during expiration, the assumption is that the elastic forces are equal but opposing (78), and therefore $R_{dyn} = \Delta P/\Delta \dot{V}$.

The major assumption for these measurements is that the C_{Ldyn} and R_L are constant throughout both phases of respiration: an assertion that may be true over the normal V_T range in newborns but becomes more suspect with progressive lung hyperinflation (79). With hyperinflation, C_{Ldyn} may be constant within the V_T range but may differ from the values at lower lung volumes. Studies in infants with lung disease have demonstrated the nonlinearity of R_L (80, 81). The limitation of assuming a single value for C_{Ldyn} becomes apparent when the variability of pressure-flow curve shapes in infants is examined (82). Furthermore, the larynx actively modulates the expiratory flow and resistance (83) in nonintubated patients. Nevertheless, given the limitations of the model, the technique has been used for the repeated assessment of newborns.

Another approach to analyzing the same data is the method of multiple simultaneous equations, in which all values of flow, volume, and pressure are fit to a linear model. Although this is the most popular computerized method, it requires considerable data filtering (84) as well as an arbitrary selection of breaths for analysis and an arbitrary end point. Despite these limitations, the technique has proved effective for clinical use and trend monitoring.

Another analysis variation is least-squares regression, in which the plot of Pdr versus $\dot{V}$ (the Pdr/$\dot{V}$ loop) is fit with a linear regression of the data points, such that the slope of the line is the resistance (85). Before the regression line is determined, pressure is corrected for tissue elastance such that the plotted pressure = Pdr − (C × V), to eliminate the viscoelastic component of the driving pressure. This method also assumes a linear relationship of the data.

A variation on this technique has been described in infants (85, 86) in which the relationship is plotted as P/V versus $\dot{V}$/V, where the intercept of the regression line is P/V (the reciprocal of compliance, elastance = 1/C) and the slope is the resistance. Again a linear relationship is assumed, although there is deviation from linearity at the extremes of the equation. An advantage of the regression techniques is the separate description of inspiratory and expiratory resistances. In ventilated infants or children, however, the expiratory values are influenced by the characteristics of the ventilator. Furthermore, valves in the breathing circuit introduce high-frequency noise in the flow and pressure signals.

Measurements of Pao and analysis of the data by a regression technique are frequently used in acute clinical situations in intensive care units to describe the respiratory system in infants receiving mechanical ventilation during a disease process. The measurements are relatively simple to make, but the calculation of results is more difficult because of the interference pattern induced by the mechanical action of the valves in the ventilator.

Dynamic lung resistance values derived in the same infants using each of the various linear methods of analysis have recently been compared (87). The Mead-Whittenberger technique consistently yielded higher values than the regression techniques, presumably because inspiratory and expiratory resistances both contribute to, and expiratory resistance normally exceeds the inspiratory value.

In addition to methods that use the equation of motion for the respiratory system, several other techniques are available for measuring dynamic mechanics.

(1) Body plethysmography. This technique to measure airways resistance (Raw) was first described by DuBois and coworkers (88). In adults and older children, the technique is applied during shallow panting to alleviate confounding variables such as changes in lung volume and temperature differentials between inspiration and expiration. As this is impractical in infants, the most commonly used technique involves rebreathing from a bag containing heated, humidified, oxygen-enriched gas at BTPS (55, 89). This is a sophisticated technique requiring substantial training. This method has the advantage of providing both simultaneous measurements of lung volume and resistance and pressure-flow curves. Inspection of the latter can give valuable information regarding changes in resistance throughout the respiratory cycle (90). The limitations of plethysmographic measurements are detailed in MEASURES OF LUNG VOLUME.

(2) Forced oscillation. This technique has been well reviewed in published reports (91). It has been applied in infants by several investigators (92, 93). The approach is to impose oscillatory changes in pressure and therefore flow at the airway and to mea-

sure resistance from the oscillatory relationship. Recently this technique has been improved through the use of multiple frequencies of oscillations. However, the predominance and variability of the contribution of upper airway compliance and resistance when pressure is applied at the mouth have limited its clinical use.

(3) Interrupter technique. Airways resistance in ventilated infants can be approximated by the quotient of the initial decrease in pressure during rapid occlusion of the airway in ventilated infants divided by the flow just preceding occlusion (94). In this technique, the calculation of compliance can be made using essentially the multiple occlusion approach (see PASSIVE AND QUASISTATIC TECHNIQUES). The technique allows for the calculation of both airflow and viscous tissue resistance and is being developed for use in infants. It is considered to be in the developmental stage and is of use only in intubated infants.

Passive and Quasistatic Techniques

All the techniques to be described in this section provide measurements of Crs and, in some cases, Rrs but do not permit partitioning of these values into chest wall, lung, and airway components. However, Cw is so high (4- to 5-fold greater than CL [49]) in infants that Crs is nearly equivalent to CL. For all these techniques, it is assumed that the respiratory muscles are totally relaxed at the point of measurement.

The most widely used passive or quasistatic approaches are the multiple occlusion technique for compliance and the flow-volume technique for compliance, resistance, and time constant. Both techniques rely on the assumption that the Hering-Breuer inflation reflex, producing complete relaxation of both inspiratory and expiratory pump muscles, can be elicited during airway occlusion and that Pao comes into equilibrium with Palv during the occlusion.

(1) Multiple occlusion. In the multiple occlusion technique (59, 95), pressure is measured at the mouth or outlet of an endotracheal tube during brief airway occlusions on multiple spontaneous breaths. The occlusions are performed at different volumes above end-expiratory level, and the individual measurements are plotted as volume versus pressure. The slope of the least-squares linear regression fit to these data is the measured Crs.

This technique has been extended to include measurements outside of the VT range by "volume clamping" (96), in which the expiratory side of the breathing circuit is kept occluded during several successive breaths. This procedure allows lung volume to increase progressively above the normal VT, thereby progressively activating the Hering Breuer reflex. Pressure and volume are measured during the expiratory pause following each successive inspiration, and compliance is calculated from curve fitting of the pressure-volume relationship.

(2) Passive flow-volume. The passive flow-volume technique, as originally described for infants (85) and later extended (97), involves measuring the pressure measurement during occlusion of the airway at end-inspiration and fitting a straight line relationship to the flow-volume curve obtained during the subsequent passive expiration. Thus, both compliance and resistance can be obtained from a single breath, and multiple measurements are made to confirm the result. This technique is particularly well suited to intubated, acutely ill patients because it is relatively noninvasive and easy to use. However, it is applicable only if the flow-volume curve is truly linear over the expired volume range.

(3) Weighted spirometer. Another technique that has received some attention is the weighted spirometer approach for measuring compliance (98). The infant or child breathes through a face mask into a closed-system spirometer. After control measurements are obtained, a weight is placed on the spirometer. By imposing a force upon the spirometer bell, the weight increases end-expiratory pressure, thus increasing FRC. Compliance is calculated as the quotient of the change in volume divided by the applied pressure. Several considerations are important in the use of this technique. The compliance of the spirometer system must be a reasonably small percentage of the total compliance or, alternatively, must be measured and subtracted from the abovementioned quotient. The cheeks and the upper airway should be positioned so that their compliance does not change when the weight is applied. To the extent that lung compliance is increased with increasing lung volume, the size of the weight may correlate with compliance. Finally, the weight imposes a load on the respiratory system that may elicit compensatory mechanisms, altering respiratory volumes and timing.

When the passive and quasistatic techniques are used, any muscle activity, either inspiratory or expiratory, can alter the results. Furthermore, clinically undetectable laryngeal narrowing during expiration ("grunting") may modulate the flow signal (82, 99) and alter the measurement of resistance. Because of this problem, the passive flow-volume technique should be used with caution to measure resistance in nonintubated infants. One way to check for laryngeal influences is to compare the value obtained with the value measured by some other technique, such as multiple occlusion. Laryngeal modulation of airflow usually results in extrapolation of a falsely elevated end-expiratory volume from the passive flow-volume curve and, therefore, calculation of a falsely elevated compliance value.

Current Controversies

The measurements obtained by the various techniques described are difficult to interpret, and further work is required to define their validity in normal infants and in those with lung disease. Compliance is interpreted differently in acute versus chronic lung disease. In an infant with acute lung disease, assessed in the short term, the intrinsic elastic properties of the tissue are assumed to be a constant, and therefore compliance is proportional to changes in lung volume. This assumption is only partially true. If compliance is increasing because volume is being recruited, a situation likely to occur in the immediate postnatal period, elastic recoil will probably decrease simultaneously because of a decrease in surface tension. Despite this, compliance does appear to reflect the gas exchange surface and correlates closely with the course of acute lung disease. In infants with chronic lung disease it is hoped, but not yet proved, that compliance can be used to identify changes in elastic recoil. However, if specific compliance (compliance corrected for FRC) is not measured, the measured Crs may still reflect changes in lung volume. Both RL and CL are volume dependent, but the degree to which changes in lung volume affect compliance and resistance measurements using the techniques described above requires investigation.

Respiratory system resistance is dominated by the upper airways and hence measured values may not reflect modest changes in lower airway resistance. The situation is further complicated in infants by high nasal resistance, active expiratory glottic adduction, or the presence of an endotracheal tube. Although it has been proposed based on morphometric and *in vitro* physiologic evidence (100) that the peripheral airway resistance in infants is proportionately higher than that in adults, this view has not been substantiated by subsequent evidence (5–7, 34). It thus seems likely that the upper airway still accounts for a large proportion of the resistance in infants. Therefore measurements of resistance in infants are considered to be of greatest value to examine spe-

cific upper airway pathology, tracheal stenosis, tracheomalacia, or the response to bronchodilator therapy. Because Rrs measurements are dominated by the upper airways, only relatively large changes in Raw due to bronchodilators are accurately detected.

A major point of discussion (101) has been the validity of Pes measurements in infants with chest wall distortion (102) due to respiratory disease or prematurity and in intubated infants (103, 104). Some investigators have found that Ptp can be determined, even in the presence of severe lung disease (49, 50), to measure the dynamic lung mechanics. The conditions under which measurements of Pes (and thus of Ptp) can be used in newborns remain to be clarified.

All the measurements described may be significantly altered by spontaneous variability in the subject and by the measurement conditions. There are insufficient data for any of the techniques to define the intrasubject or intersubject variability. Many criteria have been suggested for judging the acceptability of data, but no standardized criteria have been developed. For example, what constitutes a sufficiently good straight-line fit to flow-volume and pressure-volume curves? Can methods be developed to quantify more accurately the curvilinear flow-volume and pressure-flow relationships often seen in passive and dynamic measurements made in infants with severe lung disease? Although several nonlinear models have been described (105) they have not achieved popularity. A nonlinear expression may describe the relationship of compliance and resistance better but could be difficult to transform into useful clinical information. A linear slope does not necessarily indicate relaxation of the respiratory muscles. An even, descending slope could represent balanced respiratory muscle contraction.

Those techniques that involve the measurement of a relaxed pressure during occlusion require sufficient time for relaxation of inspiratory muscles and equilibration of pressure throughout the lung, the time constant of which increases with increased airway resistance. However, the longer the occlusion is held, the more likely is the recruitment of expiratory or inspiratory muscle activity. Further, the degree to which expiratory laryngeal narrowing and diaphragmatic braking influence resistance and compliance values measured by the passive flow-volume technique in nonintubated infants needs to be investigated.

Reference Values and Interpretation

Although correction for size is often based on body weight or length, the best basis for comparison of measurements from different subjects is the lung volume at which they were obtained. While this approach appears to be valid in older infants, it must be viewed with caution in neonates (89). Given normal intrauterine growth, expression per unit body weight is reasonably precise in the immediate postnatal period (50). However, because elastance decreases and conductance increases linearly with lung volume, which itself is a power function of somatic growth in normal infants, the range of reference values needs to be expressed per unit lung volume. The reference values to be reported here are not definitive, because none is based on a large population of subjects studied either cross-sectionally or longitudinally during infancy and childhood. Furthermore, few reports are available of values obtained using different techniques in the same subjects (99, 106, 107), providing insufficient data to allow for comparison of all techniques over all age ranges.

Dynamic lung compliance values for infants and newborns (both full-term and preterm) range from 1.1 to 2.0 ml/kg/cm H_2O, and specific dynamic compliance ranges from 0.04 to 0.08 ml/cm H_2O/ml FRC or volume of thoracic gas (Vtg) (95, 108–115). The larger range of specific compliance may be explained by the consistently lower values of FRC measured by helium dilution relative to Vtg measured by plethysmography (see MEASURES OF LUNG VOLUME). The reported values of passive compliance in infants and newborns range from 1.0 to 1.6 ml/kg/cm H_2O (85, 95–98, 116, 117), and the specific passive compliance reported in one study of healthy preterm infants was 0.06 ml/cm H_2O/ml FRC (95). In a longitudinal study of five full-term infants studied four times each between 4 and 55 wk of age using the passive flow volume-technique, Crs = 0.87 + 26.3 × height^3 (118), and in another study over the age range of 3 to 54 months using the multiple occlusion technique the relationship was Crs = 0.88 × weight(kg)$^{1.09}$ (119). Coefficients of variation of 10 to 13% for Crs (107, 120, 121) and 28% for CLdyn (122) have been reported.

Although few studies of Cw have been done in infants, values measured in preterm infants exceed those in full-term infants (6.4 versus 4.2 ml/cm H_2O/kg under quastistatic conditions in paralyzed, ventilated infants [123]). During relaxed expiration after end-expiratory occlusion in nonparalyzed preterm infants, Cw ranged from 2.4 to 3.8 ml/cm H_2O/kg (49). Dynamic Cw has been assessed in one study of preterm infants (124). Mean Cw was 7.8 ml/cm H_2O during tidal breathing in infants weighing 890 to 1,700 g. During airway occlusion in the same infants, Cw decreased to 0.89 ml/cm H_2O, probably because of chest wall muscle activity.

Values for Raw are high at birth but decrease rapidly during the first year of life (89). Because of this rapid change, specific airway conductance (SGaw = 1/[Raw × Vtg]), where Vtg is the volume of thoracic gas) is recommended as a more constant parameter during development. Specific airway conductance is approximately 0.3/cm H_2O·s at birth in full-term infants, then decreases to 0.2/cm H_2O·s, the normal value used in older children and adults. Values as high as 0.6 have been reported for preterm infants (112). The initial investigations (55, 89) reported values of inspiratory airway resistance at two-thirds of the tidal flow range. More recent studies (82, 90) have used computerized techniques describing Raw throughout the respiratory cycle, but there are insufficient reference values for use outside the two-thirds flow range. Resistance values using passive and quasistatic techniques in infants have been reported as Rrs = 0.047 − 0.036 × height^3 (118) or Rrs = 5.36 × weight(kg)$^{-0.75}$ (125). Reported coefficients of variation are 11 to 15% for Rrs (107, 120, 121) and 56% for RL in one study (122).

Future Directions

As discussed earlier, a number of techniques have been developed and successfully applied in infants to measure the resistance and static and dynamic compliances of the lungs and the respiratory system. Each technique has inherent strengths and limitations, and none has clearly predominated in efficacy under all circumstances of study: subject size and age, ease of technique application, presence of an endotracheal tube, and so on. Thus, an important need exists to further evaluate these methods with respect to standardizing the procedures on the basis of studies designed to determine optimal methods to circumvent the technical problems and interpretation controversies described; assessing the reproducibility of the measurements obtained; determining the influence of such factors as sedation, sleep state, and anesthesia; and obtaining values for normal infants and young children over a wide age range. The validity of assumptions regarding respiratory muscle activity following airway occlusion needs to be tested in healthy and sick infants. The influence of possible active respiratory muscle responses during passive and quasistatic measurements needs to be defined.

For the techniques used to measure compliance proposed fu-

ture directions for research include: assessment of the relationship between C_L and Crs and of the age-related changes in the contribution of Cw; evaluation of age-related changes in the relationship between passive or quasistatic compliance and dynamic compliance; determination of the shape and position of the inflation and deflation limbs of the pressure-volume curves of the lungs, chest wall, and respiratory system outside the V_T range; and incorporation of measurements of absolute lung volume (e.g., Vtg or FRC) as a means of obtaining volume-specific indices of compliance.

The methods used to measure flow resistance in infants are as diverse as the compliance techniques. In this regard, some proposed future directions for research include: assessment of the relationships between R_L, Raw, and other measures of Rrs in healthy infants and those with pulmonary disorders; partitioning of the contribution of nasal resistance from that of the lungs and chest wall; partitioning of the airway resistance from that contributed by the viscoelastic properties of the lungs and chest wall; evaluation of the utility and limitations of derived measurements of resistance based on analysis of the flow-volume relationships during "passive" lung deflation in healthy infants and infants with obstructive or restrictive lung disease; and incorporation of measurements of absolute lung volume as a means of correcting flow resistance per unit of lung volume.

MEASURES OF LUNG VOLUME

Knowledge of lung volume can play an important role in the respiratory care of infants and young children and assist in interpreting measurements of resistance, compliance, and forced expiratory flow.

Functional residual capacity, that is, the volume of air in the lungs and airways at end-expiration, is mechanically determined by the balance between the outward recoil of the chest wall and the inward recoil of the lungs. It corresponds approximately with 40% of TLC and 25% of VC in older subjects. Some evidence suggests that FRC is closer to RV in infants, such that airway closure may occur during tidal breathing. During early infancy, FRC may be dynamically increased above the passive level determined by the characteristics of the lungs and the chest wall (126–128). The mechanisms underlying this phenomenon include laryngeal braking and postinspiratory diaphragmatic activity, which prolong the expiratory time constant, combined with a relatively short expiratory time (i.e., rapid respiratory rate). Infants with airway disease may exhibit a similar but more marked phenomenon in which increased Raw prolongs the expiratory time constants, contributing to hyperinflation of the lungs.

FRC is the only lung volume that can be measured accurately, repeatedly, and reliably in infants. Other lung volumes such as TLC and RV have been estimated from measurements of VC during crying (129–132), but these estimates have an unacceptable degree of reproducibility for routine use. Similarly, although TLC and RV have been estimated from forced inflation and deflation maneuvers (5, 15, 18), such techniques require the presence of an endotracheal tube and are used mainly for research. Consequently, this section concentrates on the measurement of FRC in infants.

The assessment of FRC in infants has contributed important information about the growth and development of the lungs in health (9, 10, 89, 131, 133) and disease. FRC may be reduced by abnormal alveolar development (134–136), by atelectasis, or by decreased lung or increased chest wall compliance (137–141). Increased FRC may be caused by abnormal alveolar development (142) but more commonly occurs in relation to gas trapping associated with airway obstruction (143). From a clinical point of view, measurement of FRC in infants may be valuable in the management of controlled ventilation (143, 145), and in the evaluation of potential hyperinflation and treatment efficacy in airway disease (143, 146–148).

The two physical principles that are routinely applied to the measurement of FRC in infants are whole body plethysmography and gas dilution. Whole body plethysmography is based on Boyle's law, as originally described by DuBois and associates (149), and measures thoracic gas volume, Vtg. The helium dilution and the nitrogen washout techniques are based on the conservation of mass principle. All three techniques have been used in infants since the early 1960s, and substantial information has accumulated to define the normal range of lung volumes over the first year of life (150) as well as the changes observed with disease.

Despite increasing interest in the assessment of lung volume by a variety of imaging techniques (151–154), these methods have yet to be fully validated. Consequently, this discussion focuses on the three most widely used techniques for assessing FRC in infants: whole body plethysmography, helium dilution, and nitrogen washout.

Methods

Whole Body Plethysmography

In 1956, DuBois and colleagues (149) described a technique of measuring Vtg by determining the change in volume when a gas undergoes isothermal compression, as assessed by Boyle's law: $P_1V_1 = P_2V_2$. In practice, a subject is placed in a rigid, closed container (a plethysmograph) and makes respiratory efforts against an occlusion at the airway opening, which rarefy and compress the thoracic gas. The resultant changes in the subject's body volume can then be measured either directly, by a spirometer (the volume displacement plethysmograph [155]), or indirectly, by measuring the small pressure changes occurring within the container (the pressure plethysmograph). If the changes in Pao (which in the absence of airflow are equivalent to the changes in Palv) are related to the changes in volume, the initial Vtg can be calculated by applying Boyle's law as follows: $(P_B - P_{H_2O}) \times Vtg = (P_B - P_{H_2O} + \Delta P) \times (Vtg - \Delta V)$, where P_B is the barometric pressure in kPa (mm Hg), P_{H_2O} is the saturated water vapor pressure at 37° C (6.27 kPa [47 mm Hg]), ΔP is the change in Pao during the occluded respiratory maneuver, and ΔV is the resulting change in Pao during the occluded respiratory maneuver, and ΔV is the resulting change in volume of the thorax. Water vapor pressure is subtracted from all pressures because it relates only to temperature (going in and out of the vapor state as temperature changes) and thus, under saturated conditions, does not behave as a compressible gas. Ignoring the negligibly small product of $\Delta P \times \Delta V$ and solving the equation for Vtg gives: $Vtg = (P_B - 6.27) \times \Delta V/\Delta P$. This method was rapidly adapted for use in infants (156–158) and continues to be used in research centers throughout the world. Although most published results have been based on the pressure plethysmograph (89, 158, 159), the successful use of an integrated flow plethysmograph was recently reported in infants (160).

The major advantage of plethysmography is that it measures all the gas in the thorax, including gas that is not in direct communication with the airway, thus allowing the assessment of gas trapping in obstructive lung diseases (146, 161). Furthermore, this technique can produce rapid, reproducible, and accurate measurements of FRC in infants (89). However, the equipment required is expensive and cumbersome, requires considerable operator training, and is not applicable in the intensive care unit. Conse-

quently, its application has been largely restricted to research establishments. In recent years, computerized techniques have been used increasingly to facilitate data collection and analysis (80, 90, 162), and several user-friendly systems now exist.

The plethysmographic technique is based on four assumptions: *(1) There is no gas flow, and hence no flow-resistive loss in pressure, during respiratory efforts against the occluded airway; consequently, Pao equals Palv.* This assumption has been challenged in some studies in adults. These studies have suggested that the upper airway acts as a shunt capacitor during airway occlusion, allowing gas to flow back and forth in the airway, so that changes in Ppl exceed changes in Pao, leading to an overestimate of Vtg (163–165). Although, theoretically, this phenomenon could occur in all subjects, only those with significant airway obstruction have been shown to have sufficient airway resistance to cause losses in pressure. Panting at slower frequencies (i.e., around 60/min^{-1}) reduces the error (166) but may not completely eliminate it (163). Infants do not "pant" during airway occlusion and indeed tend to make fewer respiratory efforts (rarely more than 30/min^{-1}) than when breathing spontaneously.

(2) The pulmonary parenchyma is sufficiently elastic that changes in pressure are transmitted across the parenchyma to all gas-containing spaces, with no pressure gradient across the tissue. Although this assumption is probably reasonable in most adults, it has been challenged in infants. Values of Vtg that were much lower than expected from clinical findings have been observed in infants recovering from bronchiolitis (167, 168). These studies suggested that the lungs of these infants have regions of such high resistance and low compliance that they act as rigid spheres, so that the gas contained escapes rarefaction and compression during occlusion. Other potential problems in estimation of Vtg in sick infants have also been reported (169, 170). These reports suggested that a better approximation of swings in Palv during occlusion may be obtained by esophageal manometry, but this remains controversial (170–172).

(3) The changes in pressure and volume are isothermal. The proximity of the tissue to the gas in the respiratory system is such that heat generated during occluded respiratory maneuvers is rapidly lost to the body, and changes in volume within the subject are isothermal (173). Moreover, during rarefaction and compression of the gas inside the plethysmograph, heat may or may not be lost to the walls of the container, and therefore plethysmographic pressure changes may be either adiabatic or polytropic. The plethysmograph must be calibrated at the approximate frequency of respiratory efforts during occlusion to compensate for any error introduced by polytropic conditions (162, 174).

(4) Only gas in the thorax undergoes rarefaction and compression. The volume of gas in the gastrointestinal tract is assumed to be either insignificant, uncompressed, or both. This assumption was confirmed in adults (163) and in sick infants (168, 170) and appears to be valid in healthy infants (168, 170), because the changes in intraabdominal pressure are small relative to the changes in Pao during respiratory efforts against airway occlusion.

Detailed descriptions of plethysmographic measurements of Vtg in infants have been reported (89, 160, 168, 175, 176). In the first month of life measurements can be made during natural sleep, but in older infants sedation is usually required. Although in adults Vtg is conventionally calculated from the slope of box pressure (displacement volume) versus Pao ($\Delta V/\Delta P$), for calculations in infants the additional use of time-based traces is strongly recommended. The latter approach makes it possible to assess any variations in end-expiratory level more accurately, to correct for thermal or metabolic drifts during airway occlusion, and to occlude the airway at any phase of the tidal breath (e.g., at end-inspiration) and subsequently correct to the end-expiratory level.

The sleeping infant is placed inside the plethysmograph, and a face mask attached to a pneumotachograph and shutter is sealed around the nose and mouth. The seal can be tested by recording at least five tidal breaths before occlusion to establish a stable end-expiratory level, then briefly closing the shutter at end-inspiration. Any increase in the volume baseline after release of the occlusion or decay of the Pao signal during occlusion suggests a leak (59, 175). Ideally, the mask should be held in place with strapping to support the cheeks and hence reduce the risk of shunting to the upper airways during the occlusion. After leaks have been eliminated, the plethysmograph is closed.

If a pressure plethysmograph is used, it is allowed to reach thermal equilibrium (as indicated by minimal drift of the box pressure signal). At least five tidal breaths (more if end-expiratory level is unstable) should then be recorded before the airway is occluded. Thoracic gas volume is conventionally measured by closing a shutter at end-expiration and allowing the infant to make two to four respiratory efforts against the occlusion, from which the relationship of box volume to changes in Pao (ΔPao) is established. In practice, occlusion is frequently performed at end-inspiration, with subsequent subtraction of the volume above end-expiratory level at the moment of occlusion. This procedure improves the signal-to-noise ratio, is better tolerated by most infants, and reduces the incidence of glottic closure, which can invalidate results. The appropriate volume at which to occlude is still under debate (see CURRENT CONTROVERSIES) (170, 177). In healthy infants, measurements made at end-expiration and end-inspiration (corrected to end-expiratory level) usually agree within 5%, thereby providing a simple *in vivo* method of validating the accuracy of the measurements.

During the occlusion, the changes in box volume and Pao should be strictly in phase. A loop appearing on the *x-y* display usually indicates a leak in the system or glottic closure. Three to five separate occlusions should be made in each infant. All measurements should be obtained during quiet sleep (64).

The thermal characteristics of the box must be accounted for during calibration (see above, Assumption 3). This can be achieved by replacing the volume of the infant with bags of saline and dynamically calibrating the instrument at the frequency observed during respiratory efforts against the occlusion (174). Alternatively, a computerized correction factor can be used (162).

Although no standardized approach to reporting Vtg values in infants has been established, it seems reasonable to report the mean value of at least three separate, technically satisfactory measurements. In healthy infants, Vtg measurements tend to be very reproducible, with a coefficient of variation of < 5% (176). The variability may be greater in infants with respiratory disease (178), those who are not in quiet sleep (179), or those without a stable end-expiratory level before occlusion.

Helium Dilution Technique

The helium dilution technique is the most widely used method for determining FRC in infants (9, 10, 130, 131, 133, 180–183). This technique is based on the principle of gas equilibration between an unknown long volume (VL) and a known volume (Vgas) containing helium as an indicator gas. Gas mixing is brought about by ventilatory movements. Assuming mass balance, the unknown lung volume can be derived from the change in helium concentration. That is, if C_1 is the helium concentration at the start of the experiment and C_2 is the concentration when gas mixing is complete, then $Vgas \times C_1 = (Vgas + VL) \times C_2$ and $VL = [Vgas \times$

$(C_1 - C_2)]/C_2$. Detailed descriptions of the helium dilution technique for the measurement of FRC in infants have been reported (129, 130). The equipment needed to perform the test is simple, reliable, relatively cheap (compared with plethysmography), and suitable for bedside measurements, but still requires considerable operator training to achieve reliable results consistently.

After a stable end-expiratory level has been established, the infant is switched into a spirometer breathing circuit that contains a known volume of gas with a known concentration of helium, and this mixture is rebreathed until equilibration is complete (concentration of helium is stable). The system must include a rapid and accurate helium analyzer, a CO_2 scrubber, a water absorption system, and an efficient circulating pump for fast response and prevention of rebreathing. The spirometer is normally attached via a face mask. Although measurements can be made in intubated infants, a leak-free connection is difficult to achieve because cuffed endotracheal tubes are rarely used in this age group (184). The calculated volume at FRC must be corrected for any inspired volume above end-expiratory level at the moment the infant is switched into the spirometer circuit and for the dead space of the apparatus, and must be converted to BTPS conditions. To improve the resolution of the measurement, the volume of the spirometric system should be as small and as close to the infant's lung volume as possible. Commercially available 1-L spirometric bells should suffice for older infants and toddlers, but a smaller size is recommended for neonates. The circuit must contain sufficient air to accommodate large sighs (two to three times normal V_T). The system should be calibrated by adding several known increments of volume over the range of lung volumes being measured.

The helium analyzer should be operating within its linear range and be accurate within 1% of full-scale deflection. It must be calibrated specifically for each F_{IO_2} used. Spirometer temperature should be monitored internally and kept constant, as the helium analyzer is sensitive to changes in temperature. When connected to the enclosed system, the spirometer should be carefully balanced with the fan on, so that the system pressure remains as close as possible to atmospheric pressure. A useful method of checking for leaks in the system is to weight the spirometer bell temporarily and note any downward drift in the volume trace. During the measurements, oxygen must be added to keep the volume of the circuit constant. A fluctuating volume in the circuit may result in substantial errors in calculated FRC.

The time to equilibration is usually 20 to 60 s in healthy infants and young children (131), but may be considerably longer (3 to 5 min) in those with airway disease. Thus, rebreathing should be continued until helium concentration has been stable for at least 30 s. All helium should be cleared from the lungs before measurements are repeated. The interval required depends upon the mixing time for the particular subject. A leak in the system will cause a continuous decrease in helium concentration, and a small decrease may be difficult to distinguish from that due to poor mixing or inappropriate oxygen supplementation. Common practice is to average at least two FRC values within 10% of each other. As prolonged rebreathing is necessary in some infants with airway disease, this technique can require a lengthy testing period.

Helium dilution measurements of FRC have been reported to be reproducible in healthy infants (mean CV ± SD = 4 ± 2.8%) (131). Gas dilution techniques assume full equilibration of all lung units with the airway opening, and hence may underestimate true resting lung volume in subjects with gas trapping due to airway obstruction. Resting lung volume may also be underestimated if the F_{IO_2} is high, possibly as a result of increased alveolar oxygen transfer with subsequent reduction in alveolar volume (182).

Nitrogen washout technique. A third method of estimating FRC is to measure the volume of nitrogen washed out of the lungs when the infant rebreathes from a reservoir of nitrogen-free gas. In the original studies the equipment used was fairly simple, but the more recent techniques rely on mass spectrometers, which are technically demanding to maintain. As with the helium dilution technique, the apparatus needs to be sized appropriately for the subject. If the amount of washed out nitrogen is measured and the initial concentration of alveolar nitrogen is known, then the lung volume at which the washout started can be derived. If washout starts at FRC, then FRC equals the volume of nitrogen washed out divided by the initial nitrogen concentration in the lungs.

The difficult aspect of this technique is the accurate measurement of the volume of nitrogen washed out. In the two most commonly used methods, the volume of nitrogen is either measured from the expired gas in a collection bag or obtained by continuous integration of nitrogen concentration in the expired gas (185–187). A closed-circuit technique has also been described in which the infant rebreathes from a bag for a short time (188), but this method is limited and assumes conditions that are difficult to verify. At end of washout the nitrogen concentration and volume of the bag are measured.

In the expired gas collection method, the expired nitrogen volume is calculated as the product of the nitrogen concentration and the bag volume. Any inaccuracy in the measurement of the bag volume or, more commonly, the final nitrogen washout concentration, will cause significant errors. Because the final nitrogen concentration is very low, having been diluted with large amounts of oxygen, an error of < 1% in its measurement will cause substantial error. The resolution, and thus the accuracy, of the method depends on the initial alveolar nitrogen concentration. Thus, when an infant is breathing gas with a relatively high F_{IO_2} (i.e., low F_{IN_2}), the volume of nitrogen to be washed out will be very small, which may adversely affect results. At $F_{IO_2} > 0.7$ to 0.8, virtually no nitrogen is washed out of the lungs, and the technique cannot be used.

Using rapidly responding gas analyzers (or mass spectrometers) to obtain instantaneous nitrogen concentration and a computer to integrate flow signals, an open-circuit system can be created without a collection reservoir (185, 187). This system is potentially suitable for measurements in the neonate because its dead space is very low. Recent adaptations of the open-circuit technique have used a constant background flow of oxygen, to eliminate changes in instantaneous flow rate, and incorporated a mixing chamber in the exhalation circuit prior to the sampling port for nitrogen analysis (to minimize the effect of respiratory phase on estimation of nitrogen concentration) (191). In this method, the volume of nitrogen is proportional to flow rate through the system, and extreme care is needed to ascertain that flow rates remain truly constant. It is also important to ensure that the background flow remains higher than peak inspiratory flow of the subject.

Other potential problems with the nitrogen washout technique include those associated with analyzer response time, lag time between flow rate and gas concentration, and sampling rate. Corrections must be made for the nitrogen flushed from the tissues and blood. The latter usually causes < 5% error within a typical washout period of 2 to 3 min (187, 190) but may be larger if washout is prolonged in infants with lung disease. In the usual adult methods, end-tidal nitrogen concentration is measured continuously and required to decrease to < 2%, because concentrations higher than 2% tend to overlook the effects of extremely slow spaces. Final nitrogen concentrations of < 1% tend to exaggerate the effect of normal nitrogen diffusion from pulmonary blood

to the alveolar space. In some methods the final concentration is derived from exponential analysis of only a few breaths, but this has been used in only one study in infants (191).

The nitrogen washout has recently been adapted for use in ventilated infants (144). A second ventilator, with settings identical to those being used for the infant, is set up to deliver pure oxygen. At FRC, the patient is switched to the second ventilator and washout starts. The technique is accurate and reproducible but has the same disadvantages of the other nitrogen washout methods just described. As with all gas dilution techniques, results may be invalidated by leaks and accurate measurements may be feasible only if a cuffed endotracheal tube is in place.

Current Controversies

Measures of lung volume in infants remain controversial with respect to the conditions and techniques of measurement, the characteristics of the equipment, and apparent physiologic artifacts. In addition, the relative limitations and advantages of plethysmography versus the gas dilution techniques, and recommendations regarding the best test to use in specific clinical or research situations have yet to be clearly defined. Controversies about the presentation of results and the use of reference values are discussed in REFERENCE VALUES AND INTERPRETATION.

Measurement conditions. Measurements of FRC are usually made in sleeping, supine infants who, if more than 1 month of postnatal age, have been sedated with chloral hydrate. Alternative sedatives such as phenobarbital suppositories have been used, but infrequently. Anesthesia with a volatile gas such as halothane has been reported to reduce lung volume markedly (137, 138) in all age groups, although ketamine does not (192). Sedatives in the doses usually given for lung function tests appear to have little effect on respiratory pattern, resting lung volume, or the amount of time spent in quiet sleep (193–196), but caution is required in patients with upper airway obstruction because chloral hydrate may decrease upper airway muscle tone. The use of sleep deprivation to achieve such measurements is not recommended because it may disturb the breathing pattern (76).

Sleep state may affect lung volume measurements. In one report, Vtg measured by plethysmography was approximately 30% lower during active sleep than during quiet sleep (197). Only six infants in the first week of life were studied, however, and subsequent studies using both gas dilution and plethysmography have failed to demonstrate any significant change in lung volume with sleep state (66, 67, 179, 183). Nevertheless, the increased variability of end-expiratory level and the difficulty of obtaining reliable estimates of FRC during active sleep are such that measurements should ideally be confined to quiet sleep. Since the proportion of active sleep in relation to the total sleep time is at least 50% in full-term infants, and even greater in preterm infants, the time available for lung function studies is limited. Failure to monitor sleep state may contribute to the discrepancies between various published studies. Further research is required to define the influence of phasic versus tonic active sleep on lung volume.

In the absence of unilateral lung disease, measurements of FRC appear similar in the lateral and supine positions (72). In adults, significantly lower values of FRC are observed in the supine compared with the upright or sitting position, but this relationship has not been established in infants. For practical reasons, infants are always studied lying down, and this needs to be kept in mind when FRC measurements are compared between infants and older subjects.

Equipment and technical procedures. A great difficulty in comparing and interpreting results from different centers is the lack of standards for equipment, methods, and calculation procedures. Most equipment for measuring lung volumes in infants is homemade, and the necessary specifications for comparative conclusions are rarely presented in published reports. Substantial differences currently exist with respect to the thermal and frequency characteristics of the equipment, the response time of gas analyzers, and the dead space and resistance of the apparatus. The frequency response of measuring equipment should be adequate to at least five times the basic frequency of the respiratory maneuvers being measured (i.e., at least 10 Hz for measurements in infants). However, a standardized approach to simple, accurate methods of assessing the frequency response of infant lung function equipment has yet to be defined (172).

In the past few years, efforts have been made to introduce some degree of standardization into measurement techniques (130, 175, 198), but criteria for technically satisfactory data have not been established clearly enough for recommendations to gain widespread acceptance. With respect to the helium dilution technique, the primary areas of controversy include the optimal ratio of spirometer size to lung volume, the recommended duration of rebreathing (i.e., how "equilibration" is defined in health and disease), and whether extrapolation of helium concentration should be used in the presence of a relatively small but constant decline in helium concentration (175). With respect to the nitrogen washout technique, methods of overcoming the potential practical and theoretical difficulties have only recently been described (144, 189), and numerous methodologic variations still exist between different centers using this technique. Further work is required before a standardized approach can be adopted.

With all the techniques there is controversy regarding how many measurements should be made in each infant and how the results should be expressed. Obtaining three to five repeat measurements is relatively simple and quick with plethysmography. This is less feasible with the gas dilution techniques because of the duration of rebreathing or washout required and the necessary interval between tests. An acceptable result should be based on the mean of at least two measurements within 10% of each other.

Apparent physiologic artifacts. Once body size has been accounted for, plethysmographically determined values of FRC (Vtg) appear similar throughout life, and are comparable to measurements made in other mammalian species. By contrast, the gas dilution techniques, especially nitrogen washout, yield consistently lower values of FRC. This discrepancy between lung volumes measured using plethysmographic versus gas dilution techniques appears to be greater in healthy infants than in older children and adults. Further carefully designed comparative studies are required to elucidate the true magnitude of this difference and the reasons underlying it.

Particularly puzzling and controversial is the apparent underestimation of Vtg by plethysmography in infants with chronic wheezing after bronchiolitis (168). By contrast, the plethysmograph appears to measure Vtg accurately in infants with other types of obstructive lung disease including CF and acute bronchiolitis (136, 143, 147, 199). Further studies are required to resolve this specific controversy.

A further controversial aspect of plethysmography is the observation that different Vtg values may result from occlusions at end-inspiration and end-expiration. Whereas several groups have found this to be the case in infants with airway obstruction, others do not believe the problem exists (167, 170, 177, 200). Whether the differences are real, and if so, which occlusion volume should be used, remains to be determined.

Reference Values and Interpretation

Although numerous reports of reference values for lung volume ancy have been published and recently summarized (150), repancies remain between different studies and techniques. Problems in the appropriate use of reference values arise because ew of the published studies are based on more than 50 healthy nfants and the data are generally cross-sectional. Furthermore, he characteristics of the reference population may differ from hose of the study group with respect to the age, body size, gen- ler, or ethnic origin, as well as the equipment and techniques used.

In healthy newborn infants, body weight and length may be equally good predictors of lung size. At this age, normalization ased on body weight may be preferable because length may be nore difficult to measure accurately, especially in sick preterm nfants. Beyond the neonatal period, body length appears to be better predictor of lung volume, being less influenced by differ- nces in body fat in healthy infants and less dependent on the elative undernourishment that may accompany disease states uch as CF. Lung volumes must be expressed in relation to predic- on equations based on length, not as a simple ratio, because xpression of lung volume as milliliters per centimeter of length esults in "false ratios" and gross misinterpretation of results (198, 01). Although lung volumes are commonly expressed as "per- ent predicted" (202, 203), this approach necessitates the use of ome arbitrary cut-off point for normality, which precludes the in- rpretation of a subject's result with respect to the range of values und in the reference population. The relative advantages of al- rnative approaches such as the use of percentiles and stan- ardized residuals (146, 204, 205) need to be addressed. It is es- al that statistically correct methods of prediction be used, ever method of normalization is chosen.

Numerous studies have reported values for FRC in healthy in- nts using both gas dilution and plethysmography. Many of these udies have confined measurements to the neonatal period, ereby precluding calculation of prediction equations based on ody weight or length. However, lung volume has frequently been pressed per kilogram of body weight. Using this approach, the ean values of FRC measured by gas dilution techniques have nged from 20 to 24 ml/kg in infants as old as 18 months of age 10, 131, 133, 181, 187, 190); the lowest values were obtained ing the nitrogen washout technique. In contrast, mean values Vtg have ranged from 29 to 34 ml/kg in infants as old as 1 yr 5, 89, 113, 159, 206, 210). The results of many of these studies ve had wide scatter.

Most studies of FRC in infants have reported similar values boys and girls (9, 10, 131, 133), but one of these suggested a all difference due to gender in younger infants, FRC being larger boys than in girls (133). Insufficient data have been collected ascertain whether race is an important determinant of lung vol- e during the first year of life, although clear evidence supports s in older children (208, 209).

ture Directions

ernational collaborative efforts are urgently needed to stan- rdize equipment and techniques for the assessment of lung umes in infants, with special emphasis on the areas outlined RRENT CONTROVERSIES. With the increasing commercial ility of equipment for infant lung function testing, it is par- larly important to establish firm guidelines that can be adopted manufacturers. These guidelines should address suitable ipment characteristics, such as frequency response, thermal racteristics, size, dead space and resistance of apparatus, sam- g speed, and response time of gas analyzers. In the mean- time, manufacturers should provide complete details of their equipment, including evidence of performance tests or the means by which the user can perform such tests.

Future work is required to assess the reproducibility of each technique in both healthy and sick infants and to assess the relative limitations and advantages of the various methods of assessing lung volume in specific research and clinical situations. Methods of assessing the *in vivo* accuracy of the three techniques need to be developed, together with a consensus on what constitutes technically acceptable data. Once standards have been established there is a need to obtain valid reference values during the first 2 yr of life. The development of training programs in infant lung function testing, by means of postgraduate courses or within designated laboratories, could greatly facilitate the process of standardization and establishment of common criteria for quality control.

In healthy infants, measurements of FRC by gas dilution are consistently lower than those obtained by plethysmography. The physiologic basis of this phenomenon must be clarified by carefully designed comparative studies.

Further studies are required to clarify how factors such as the chest wall, the respiratory muscles, and the central control of breathing influence breathing strategy in infants, how such factors evolve during the first year of life, and the extent to which they may influence lung volume measurements. To achieve this, simpler, noninvasive methods are needed to assess sleep state and respiratory muscle function, including that of the upper airways.

Improved methods and equipment for bedside investigations of lung volume in sick, intubated, or ventilated infants are required. Although the use of radiographic assessments of lung volume may be limited by the undesirable X-ray exposure, techniques such as echoplanar imaging and computed tomography hold considerable potential for future clinical use because they are less labor intensive, are easily repeatable, carry minimal risk other than the high dose of radiation, and require no sedation (151–154). However, considerable further development and validation will be required before such techniques can be applied routinely.

OTHER TESTS

Introduction

This section covers three categories of pulmonary function tests performed during tidal breathing: (*1*) measures of VT, respiratory rate, and tidal breathing patterns, (*2*) measures taken at the chest wall surface, and (*3*) measures of gas mixing. These tests are included because they represent standard or promising new measures of pulmonary mechanical function in infants that deserve further investigation. Not covered in this section are measures of gas exchange (lung diffusion, arterial-alveolar gradients, respiratory quotient, oxygen consumption, and carbon dioxide production), measures of respiratory drive (oxygen and carbon dioxide response, $P_{0.1}$), and lung scintigraphy (ventilation and perfusion scans).

Measures of VT, Respiratory Rate, and Breathing Pattern

Introduction. Although respiratory rate and clinical estimates of VT have been used for decades to assess infants with lung disease, few physiologic studies of these indices of minute ventilation have been done to define their determinants and normal values in infants. A major determinant of minute ventilation in infants appears to be the increase in metabolic demand related to growth and increasing activity. After birth in normal infants, VT

increases with weight while respiratory rate steadily declines through infancy. This change in pattern may be due to a decrease in Cw with growth (34), allowing for a more mechanically efficient increase in VT. It is unlikely to be due to alterations in CL, because specific compliance changes little during infancy (210). As will be discussed, these variables are apparently simple to measure but difficult to interpret, because the act of measurement can alter the infant's breathing pattern.

Although VT and respiratory rate offer information about how the ventilatory requirement is met in a given infant, the pattern of tidal breathing may serve as an indirect reflection of respiratory mechanics. Two recent studies suggest that tidal breathing pattern analysis in infants may be a sensitive indicator of lung disease (11, 211).

Methods. Tidal volume (VT) is most commonly measured with a pneumotachograph of the appropriate size attached to a face mask. The use of a face mask alters breathing pattern, however (212). The 2.2 ml/kg dead space of the commonly used apparatus and even slight apparatus resistances can also increase VT (213). Nasal prongs and nasal masks have been used in an effort to reduce dead space, but even newborn infants are not necessarily obligate nasal breathers (214). Other methods created to eliminate the problems of dead space and resistance include reverse plethysmography (215) and measurement of the expiratory gas dilution of a collateral flow stream (216).

Respiratory rate is often used as a nonspecific indicator of respiratory distress in infants. It is best measured during quiet sleep, usually by observing or feeling chest movements. The instrumentation techniques mentioned previously as well as capnography, nasal thermal changes, and respiratory inductance plethysmography have also been used to measure respiratory rate.

Two methods of breathing pattern analysis have been proposed. In the first, ventilation is partitioned into its "neuromechanical drive" and "duty cycle" determinants, given by the mean expiratory flow (VT/TI) or inspiratory time divided by total cycle duration (TI/Ttot), respectively (217–219). In the second method the form of tidal expiration is analyzed. For both methods, flow is measured by a pneumotachograph attached to the subject by means of a face mask. Care must be taken to obtain a leak-free seal and to avoid obstructing the nares. Flow signals are integrated to obtain volume, and a tidal flow-volume loop is displayed on an oscilloscope or a computer monitor. In one study, after a regular pattern of tidal breathing was observed as the superimposition of at least five sequential flow-volume loops, 10 breaths were sampled for analysis (11). The tidal expiratory flow pattern may then be quantitated as the ratio of the time to peak tidal expiratory flow (Tme) divided by the expiratory time (TE), Tme/TE.

Current controversies. The main controversy surrounding measurements of VT and respiratory rate in infants relates to their sources of variability. Studies have identified various sources but not their relative effects or the strength of their interactions. They include differences in state of arousal or sleep, gestational age or weight, and testing conditions. Subjects are often sedated with chloral hydrate, but this has been shown to have inconsistent effects on respiratory frequency (9, 71) and possibly on minute ventilation.

Little is known about the determinants of Tme/TE in infancy. The relationship of Tme/TE to lung function may exist because Tme/TE quantitates the degree of active tidal slowing that occurs in response to respiratory system mechanics. In other words, Tme/TE may reflect the neuromuscular response to the passive respiratory system rate constant and the resting lung volume (220–222). Slowing of expiration by postinspiratory diaphragmatic tone or laryngeal adduction seems to control TE and VT, thus adjusting the respiratory pattern to respond efficiently to demands for increased minute ventilation while maintaining a stable end-expiratory lung volume. In a patient with obstructive lung disease and a slow passive exhalation, the need for active braking might be expected to diminish, resulting in an early increase to peak expiratory flow (decreasing Tme). Further, because exhalation is slow, TE must be relatively increased to allow exhalation to be completed. Thus, Tme/TE would be abnormally low. This effect could be further augmented in severe obstruction with active exhalation with no active braking. However, this explanation for the observed relationship between low Tme/TE values and obstructive airway disease is purely speculative. Indeed, studies in adults with chronic obstructive pulmonary disease (COPD) (223) show increased laryngeal adduction, which may further prolong TE. Much work remains to be done to reveal the meaning and the limitations of this technique.

TABLE 1

PREDICTED VALUES OF RESPIRATORY RATE (BREATHS/MIN) FROM SELECTED STUDIES OF INFANTS

		Age (months)				
Source	N	Birth	3	6	9	12
Gaultier, 1979 (130)	52	48	44	39	34	29
Tepper, 1986 (8)	117	47	38	31	27	24
Taussig, 1977 (132)	34	–	31	31	31	31
Weighted mean	203	47	38	33	29	26

Reference values and interpretation. Three recent studies (8, 131, 133) providing reference values of respiratory rate in infants during quiet sleep are shown in table 1. Two of these show different rates of decrease in respiratory rate from birth to 1 yr of age, whereas the third shows little or no change from 3 months to 1 yr of age. These disparate results reflect the sources of variability inherent in the respiratory rate, some of which were not considered in the reported measurements.

Four studies (9, 10, 131, 133) reporting reference values for VT are shown in table 2. VT in the first year of life is roughly constant at 7 to 9 ml/kg. These results are much more consistent than those for respiratory rate. However, all these studies were performed with a pneumotachograph and thus the values may differ from VT values obtained without the use of a mask by inductive plethysmography.

Reference values for TI/Ttot in infants are limited. A longitudinal study of 15 normal infants reported in 1979 (224) measured TI/Ttot during quiet sleep from birth to 4 months of age. A barometric chamber method not requiring the use of a face mask was used to avoid facial stimulation. The mean TI/Ttot (0.32 ± 0.07

TABLE 2

PREDICTED VALUES OF TIDAL VOLUME (ML) FROM SELECTED STUDIES OF INFANTS

		Age (months)				
		Birth	3	6	9	12
		Weight (kg)				
		3.2	5.5	7.5	9.0	10.0
		Length (cm)				
Source	N	50	60	67	72	75
Gaultier, 1979 (130)	65	22.0	48.9	67.7	81.2	89.3
Tepper, 1986 (8)	117	24.0	51.0	69.9	83.4	91.5
Taussig, 1977 (132)	34	–	47.8	75.1	94.7	106.4
Hanrahan, 1990 (9)	148	24.4	47.9	64.4	76.1	83.2
Weighted mean	364	23.8	49.1	67.8	81.1	89.1
ml/kg		7.4	8.9	9.0	9.0	8.9

SD) did not change during the study period. The authors therefore concluded that the increase in minute ventilation seen with growth was due primarily to an increase in mean inspiratory flow rather than in the respiratory duty cycle. Challenging similarly aged infants with 2% carbon dioxide resulted in an increase in minute ventilation but no change in mean TI/Ttot (0.36) (225). In a study of 62 healthy children aged 4 to 16 yr, values of 0.40 to 0.50 have been observed (226).

Although adults with COPD have decreased TI/Ttot (227), infants with severe BPD do not (211, 228). A study of 103 healthy infants and 24 infants with BPD, using a face mask and pneumotachograph to measure flow, found that age-corrected mean TI/Ttot in the healthy babies at 3.7 months (0.43 ± 0.04 SD) did not differ from that measured in the babies with BPD (0.42 ± 0.05) (211). Indeed, it was reported (228) that hypercapnic infants with BPD had higher respiratory rates, shorter inspiratory times, and smaller VT than did normocapnic infants with BPD. Nevertheless, no significant difference in TI/Ttot was found between the groups. In contrast to the results in infants with BPD, children with chronic airway problems do have a decreased TI/Ttot and an increased mean inspiratory flow (217–219).

Abnormally shaped tidal expiratory flow-time curves, demonstrating a rapid, early expiration of VT, were first reported in infants with airway obstruction from bronchiolitis (161). The altered shape returned to normal as the disease resolved. Similarly, adults with obstructive lung disease (229) reach the peak tidal flow earlier in expiration than do normal subjects or subjects with restrictive lung disease. Reference values for Tme/TE in infants are very limited. In 103 healthy infants from Tucson, Arizona (211), studied using a face mask and a pneumotachograph to measure flow, age-corrected mean Tme/TE was 0.27 ± 0.08 SD at 3.7 months of age. The value was significantly lower (0.18 ± 0.09) in 24 infants with BPD. Reduced Tme/TE in early infancy also appears to predict later wheezing illness, suggesting that tidal expiration analysis may be useful in detecting mild to moderate levels of airway dysfunction (11).

Future directions. Rigorous studies are needed to define the determinants of tidal breathing pattern in infants in health and disease. Continued work is needed to reduce the effects of measurement conditions such as dead space, orofacial stimulation, or posture and head position, especially on VT. The interactions of sources of measurement variability such as sleep state, time since feeding, and time of day need to be better understood. Longitudinal studies of VT and respiratory rate are needed to determine the progression of these measures during normal development, taking into account gestational age, weight, and length. Measures of inspiratory timing (TI/Ttot) and drive (VT/TI) also merit further investigation in health and disease.

The observed relationship between diminished Tme/TE values and obstructive airway disease remains to be clarified. As for VT and respiratory rate, the factors governing measurement variability must be investigated. Further, these results (11, 211, 229) need to be replicated in infants with different ages, ethnicities, and lung conditions. For example, the analysis of tidal expiration in intubated neonates may be confounded because they cannot control expiratory flow by laryngeal adduction (230). If tidal breathing analysis can be shown to be useful, then this simple, noninvasive method could become a powerful epidemiologic tool.

Measures of Chest Wall Motion

Introduction

In preterm and newborn infants, Cw may exceed CL by 5- to 7-fold (231). The functional consequence of this high Cw for the infant is that the respiratory pump is less efficient in moving VT. Part of the applied pressure is used to draw in air, but another part is used to distort the chest wall (232). This is particularly true in active sleep (233). An understanding of chest wall mechanics is thus important in assessing the overall respiratory function of preterm and full-term infants. Chest wall properties that have been measured in infants include Cw (49, 231, 234), the contribution to VT of the separate rib cage (RC) and abdominal (AB) compartments (235), and the relative timing of the RC and AB compartments (synchronous, asynchronous, and paradoxic) (236, 237). This section discusses the last two measurements.

Surface measurements offer the potential for noninvasive assessment of ventilation (e.g., frequency, VT, TI/Ttot) at the chest wall (238). They may prove useful in the study of the normal physiology of the chest wall, chest wall abnormalities (e.g., thoracic deformities and neuromuscular disease), control of breathing (e.g., central versus obstructive apnea [239]), and chest wall motion. Excessive negative intrapleural pressure associated with obstructive lung disease can affect the rib cage, delaying its outward movement relative to that of the abdomen or causing paradox. Quantitation of this asynchrony appears to be a promising noninvasive approach in assessing the severity of underlying lung disease (236, 237, 240).

Methods

Respiratory inductive plethysmography (RIP) is the most widely used method to assess chest wall motion. The amplitude-frequency response of RIP has been shown to be flat to 13 Hz (232) and thus is adequate to assess breathing patterns even in very tachypneic infants. Alternative methods include the use of strain gauges and magnetometers. If calibrated, these instruments can be used to differentiate the contributions to VT of the RC and AB chest wall compartments. Care must be taken to minimize shoulder girdle motion, to place the RIP bands and strain gauges properly, and to keep them from slipping during the study, as this will affect calibration. Two methods of calibration are commonly used: an isovolume maneuver during airway occlusion (241) or a least-mean-squares regression to solve the equation $VT = I_{RC} \times k_{RC} + I_{AB} \times k_{AB}$, where I is the pen displacement in volts (V) and k is the calibration factor in milliliters per volt. Given the two unknowns (k_{RC}, k_{AB}), simultaneous equations must be solved by choosing two ventilatory strategies that differ in the RC/AB contribution to breathing. A change in body position or from quiet to active sleep is commonly used to accomplish this (242–244). A third method, a modification of the isovolume calibration equations, has recently been described that allows calibration during single-posture natural breathing (245). Most workers accept agreement of RIP and pneumotachograph measurements of VT within 10 to 20% (242–244) as evidence of adequate calibration.

Although calibration is difficult in infants, the timing (phase relationships) between RC and AB movement can be inferred without volume calibration. This can be done by calculating a "phase angle," Φ, between RC and AB motion. If the AB and RC compartments are plotted on the *x* and *y* axes, respectively, of an oscilloscope, with time as an implicit variable, the resulting "Lissajous" figure can be analyzed, and a phase angle calculated. Synchronous motion (Φ = 0°) is reflected in a closed loop with a positive slope. As asynchrony develops, the loop opens, becoming progressively wider as asynchrony increases. Counterclockwise loops indicate that outward AB motion precedes outward RC motion; clockwise loops indicate the opposite. Pure paradoxic motion (Φ = 180°) is represented by a closed loop with a negative slope. This method of analysis assumes sinusoid RC and AB wave

forms, but in most cases motion that is not purely sinusoid does not introduce substantial errors (236).

Current Controversies

Limited data are available on the relative accuracy of measurements obtained by RIP, strain gauges, and magnetometers (246). Although all three methods detect abdominal motion equally well, magnetometers may be less accurate than RIP or strain gauges in representing changes in overall chest wall volume because they are more influenced by local events (e.g., proximity to the area of apposition of the diaphragm).

The major problem with all of these methods is calibration to volume. The underlying assumption that the system has only two degrees of freedom (241) may not be true, especially in premature infants with highly distortable chest walls (247). Furthermore, calibration performed during one sleep state may not apply in a different sleep state (248). Phase relationships between RC and AB movement may be measured independently of volume calibration. However, increased chest wall asynchrony is observed in active sleep; to allow for inferences about the underlying lung mechanics from chest wall motion, the measurements should be taken during quiet sleep determined using behavioral criteria (64). Furthermore, to be most informative, phase angle values should be analyzed along with the volumetric contributions of the RC and AB compartments. For example, a phase angle of 180° with substantial RC motion has greater functional consequences for the infant than a phase angle of 180° with minimal RC motion.

Reference Values and Interpretation

Rib cage contribution to VT. The mean RC contribution to VT during quiet sleep is 35% (range = 20 to 50%) in the first 3 months and approaches adolescent values by age 1 yr (mean = 60%, range = 30 to 80%) (235). No data from preterm infants have been published.

Phase relationships of RC/AB movement. Normal chest wall motion is synchronous in full-term infants and children (mean phase shift = 8°, range = 0 to 25°) in quiet sleep (236, 237). Normal chest wall motion in preterm infants may be asynchronous, with a mean phase shift of 58° (range = 0 to 157°) in quiet sleep (outward AB motion preceding outward RC motion) (249). In this age group, chest wall motion is more synchronous in the prone than in the supine position (250). Pulmonary disease has marked effects on chest wall asynchrony that can be related to the degree of abnormality in Crs and Rrs. Again, outward AB motion usually precedes outward RC motion (251). Asynchrony improves significantly after bronchodilators in infants with lower airway obstruction (236) and after racemic epinephrine in children with upper airway obstruction (237). These changes in asynchrony correlate with the improvement in lung mechanics (236).

Future Directions

Relative to the infant lung, little is known about the infant chest wall. Promising noninvasive techniques of assessing chest wall function have recently been introduced. The methodologic issues that require further study include the relative value of RIP, strain gauges, and magnetometry and the comparison of different methods of calibration, especially in preterm infants. In calibration methods, the assumption of only two degrees of freedom needs to be critically evaluated, as does the stability of calibration between sleep states and body positions. Further development of the recently described performance index (248) will better enable workers to assess agreement between RIP and pneumotachographic measurements of VT. The accuracy of RIP in tracking changes in FRC merits study. The effects of chest wall mechanics on other measures of lung function in infants (e.g., PEFV curves by the RTC technique, esophageal manometry) need to be investigated. The accuracy of differentiating measures of chest wall volume changes to obtain flow measurements should be further assessed as a promising method of producing tidal flow-volume curves without a face mask (252).

Further reference data need to be generated to describe the changes with development in static and dynamic Cw in preterm and growing full-term infants, and in the relative magnitude and timing of RC and AB contributions to VT. The intrasubject variability of these measurements needs to be established.

Chest wall mechanics should be studied in infants with neuromuscular disease, chest wall abnormalities, and primary lung disease, and the role of chest wall instability in overall respiratory pump malfunction should be assessed. The use of the phase angle as a promising, noninvasive index of airflow obstruction needs to be further evaluated. Chest wall motion should be investigated as an indicator of control of breathing (e.g., to differentiate central from obstructive apnea). Chest wall muscle function (e.g., electromyographic activity, $P_{0.1}$, maximal inspiratory and expiratory pressure) should also be studied.

Measures of Gas Mixing

Introduction. Gas mixing is measured during tidal breathing of either washout or washin of a gas. Studies using measures of gas mixing have found them to be sensitive indicators of obstructive lung disease in infants, children, and adults. The sensitivity of these measures in infants with respiratory disease is highlighted by the results of three studies. In a study of infants with hyaline membrane disease, gas mixing measures discriminated between those infants who completely recovered with no subsequent lung disease and those who developed BPD (253). In two other studies, a measure of gas mixing discriminated between normal infants and those with CF (254) and between infants with CF with and without pulmonary symptoms (255).

Tests of gas mixing present a different view of the lungs than do the measures mentioned in previous sections in that they assess homogeneity of ventilation. The combination of measures of lung mechanics and measures of gas mixing may provide a better picture of lung function than either type of test alone. This idea is supported by a study in older subjects in which normal subjects, patients with mild or moderate asthma, and patients with CF could be discriminated only by using measures of both lung mechanics and gas mixing (256).

Methods. Measures of gas mixing are usually performed during a measurement of FRC by either nitrogen washout or inert gas equilibration. All such techniques take measurements from the resulting exponential decay curve of gas concentration. Numerous methods of analysis have been proposed and tested in adults. Some methods normalize a measurement taken at the end of the washout by lung volume—that is, the pulmonary clearance index (257) is the ratio of the ventilation required to achieve 2% end-tidal nitrogen concentration and the FRC. Because such single-point measures can be variable even in cooperative adults, they are infrequently performed in young subjects, who are commonly less cooperative and predictable.

The five measures for which data from infants or young children have been published are mixing index (258), pulmonary clearance delay (259), ventilatory efficiency (260), multiple-compartment model fitting (261), and moment analysis (262). In the first three techniques, once the diluted volume (FRC) and the diluting volume (VT) are known, the washout values for a one-compartment

ideal lung (a lung with perfect gas mixing) can be calculated and compared with the observed values. Both the mixing index and the pulmonary clearance delay compare the observed number of breaths to reach a given mixing value with the expected number from an ideal lung. The ventilatory efficiency compares the ventilatory volume needed to achieve 90% mixing in the patient's lungs to the ventilatory volume required of an ideal lung.

The final two techniques analyze the shape of the washout curve. In multiple-compartment model fitting, compartments of different time constants are derived by fitting two or more linear approximations to the log-linear plot of washout gas concentration over expired volume. In moment analysis, the distribution of the dilution number (expired volume/FRC) versus end-tidal nitrogen concentration is characterized by the moment ratios M_1/M_0 and M_2/M_0.

Current controversies. These methods have no standardized technique or terminology. Two studies have compared the sensitivity (263) and reproducibility (264) of multiple methods of performing gas mixing measurements in adults, but no such studies have been performed for infants. The question of the most appropriate method for this age group thus remains open.

When gas measurements are performed, the issues of equipment dead space, gas analyzer response, and synchronization with flow measurement require careful attention (265). In infants these issues are compounded by the smaller size and faster breathing patterns (265). The best strategy for overcoming such equipment effects continues to be debated.

Gas mixing measures are reportedly sensitive in detecting disease (263). Whether and how such measures change with age remain controversial. The lack of standardized methods or equipment impedes any generalization about normative data or demonstration of the utility of such measures in observing the course of infant lung disease.

Reference values and interpretation. A few studies have produced reference values in infants. Mixing index (i.e., the theoretic number of breaths needed to achieve 90% mixing in an ideal lung expressed as a percentage of the number of observed breaths) has a positive correlation with body length over the first year of life and averages about 61% (218). Infants with little or no disease have a pulmonary clearance delay of 47%, which corresponds to a mixing index of 68% (253). These data suggest less even mixing in infants than in adults, whose pulmonary clearance delay of 21% (259) corresponds to a mixing index of 82%. The ventilatory efficiency (i.e., theoretic ventilation to achieve 90% mixing in an ideal lung expressed as a percentage of observed ventilation) of reference subjects has been found to be about 50% in infants versus 70% in adults (267). In two similar analyses that took anatomic dead space into account, the ventilatory efficiency increased over the first day of life from 47 to 76% (185) and from 51 to 60% (268).

In multiple-compartment analysis studies newborn infants have less even ventilation than do adults, having a slow lung space that represents 10 to 20% of total alveolar ventilation (185, 253, 268, 269). These results are contradicted by one report that found more even ventilation in normal newborns than in normal adults (270). Although no results from moment analysis in infants have been published, one study in children found a significant difference in moment ratios between normal subjects and those as young as 3 yr of age with CF (271).

Future directions. The techniques for testing and analyzing gas mixing need to be standardized so that results from different studies can be compared. As the simultaneous calculation of all proposed measures of gas mixing is possible, comparative studies are needed to determine the best way to characterize gas mixing in health versus disease. The use of inert gases for gas mixing studies may yield different results from nitrogen washout with oxygen and should be evaluated. Continued work is needed to design equipment that operates quickly enough to analyze the rapid breathing patterns of infants and is small enough to provide dead spaces appropriate to the infant's size. Longitudinal studies are needed to determine how measures of gas mixing change with age and whether they are useful indicators of early lung disease in infants and young children. When these goals are met, gas mixing measures may be useful in characterizing lung function from birth to adulthood in health and disease.

Conclusion and Recommendations

It is now possible to perform a variety of measurements of respiratory mechanics in infants. These have already proved valuable in revealing the normal functional development of the lungs and in predicting and tracking infant respiratory disease and responses to therapy. However their full potential is still unrealized because of the lack of standardized methods and reference values. Further, some uncertainty remains about the physiologic basis of some of these tests. On the basis of its discussions and the scientific information summarized in this statement, the Committee makes the following recommendations.

Standardization

The measurement procedures for infant pulmonary function testing must be standardized. Equipment standards like those established for pulmonary function testing in adults and children are needed for the instruments used in infants. A committee needs to be established for the express purpose of setting standards for tests of infant pulmonary function in accordance with current knowledge of these measurements. Standards should be revised as new information about these tests is acquired. Patient safety must be assured in all aspects of the development of standards and investigation of respiratory mechanics. This statement does not attempt to address the relative safety of the various sedatives used during infant pulmonary function testing. The risk versus the benefit of any medication given should be assessed on an individual basis.

Physiologic Investigation

It is important to define further the physiologic basis underlying pulmonary function tests in infants in order to clarify what the tests can and cannot measure. For example, the following specific issues need to be addressed: (*1*) The question of whether or not flow limitation is reached during measurements of forced expiration needs to be resolved. (*2*) The effect of active respiratory responses (including the upper airway, chest wall, and other respiratory muscles) on tests performed during assumed passive conditions needs to be investigated. (*3*) The reasons for the consistent discrepancies in measurements of lung volumes in healthy infants by plethysmographic versus gas dilution techniques need to be defined. Although not addressed in this report, the Committee recognizes the need to develop methods for evaluating pulmonary function in preschool children.

Reference Values

Normal reference values for tests of infant pulmonary function need to be obtained from sufficient numbers of subjects. This will require collaborative efforts using equipment and procedures that meet the established standards. Age, gender, race, and other

genetic and environmental factors will need to be considered. The appropriate basis on which to compare the results of the various tests at different stages of growth and development will need to be determined.

Scientific Interaction

The continued development of currently useful tests of infant pulmonary function will be optimized by the exchange of scientific information at regular intervals between investigators working in this area both nationally and internationally. Workshops are recommended both to foster the exchange of scientific information and to educate practitioners of all levels. Constructive interaction must be fostered between scientific investigators in the field and the manufacturers of testing equipment.

Collaborative Investigations

Because of the complexities involved in obtaining reliable pulmonary function data in infants and the relatively small number of subjects available for study in any single center, multicenter collaborative studies and clinical trials should be undertaken to investigate:

(1) The functional development of respiratory mechanics in healthy infants
(2) The impact of prenatal and postnatal factors, including tobacco smoke and drug abuse on respiratory system development
(3) The natural history of the major respiratory disorders of infancy, including CF, asthma, neonatal lung disease, and disease from respiratory syncytial and human immunodeficiency viral infections
(4) The effects of major therapeutic interventions on these disease processes

If tests of pulmonary function in infants are developed in parallel with new diagnostic and therapeutic approaches being derived from the rapid advances occurring in cell and molecular biology, great potential exists to make substantial progress in the diagnosis and treatment of respiratory disorders of early childhood.

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C. Mechanics of Breathing

J J Pérez Fontán

As aquatic animals adapted to life on land, their gas-exchange systems needed to maintain a large contact surface with air without losing large amounts of water to evaporation. Therefore, the lungs of most terrestrial species evolved as invaginated structures. An invaginated lung, however, required a mechanism to force air in and out of the gas-exchanging spaces. In mammals and other higher vertebrates, this mechanism resembles a bellows pump, in which a group of respiratory muscles apply force on the passive elements of the chest wall (rib cage and abdomen) to inflate and deflate the lungs. The function of the pump is regulated by a complex network of sensors, which relay both mechanical information from the pump's components and chemical information from arterial blood to a control center in the brainstem.

Despite the relative simplicity of the pump and the obvious complexity of the regulatory network, the respiratory system is more vulnerable to mechanical than to control dysfunctions. In fact, the increase in energy demand imposed by various types of mechanical breakdown usually causes most of the signs and symptoms of respiratory disease and ultimately leads to respiratory failure.

From a mechanical point of view, the function of the respiratory system is best analyzed in terms of work and energy. Above, we compared the mammalian respiratory system to a bellows pump. Basic physics indicates that the amount of work (ΔW) done by such a pump in order to produce a certain volume change (V_0 to V_1) with a pressure change P can be computed as (equation 1):

$$\Delta W = \int_{V_0}^{V_1} P \, dV$$

amt work : vol/pressure relationship

For the respiratory system, the total amount of work done by the respiratory muscles during a single breath depends on the mechanical characteristics of the lungs and chest wall (which define the magnitude of P) and on the needs for gas exchange (which define the limits of the volume change, $V_1 - V_0$).

Work alone, however, is not a direct measure of the energy that the muscles must extract from the metabolic fuels provided by the circulation. The reason is that the respiratory muscles transform energy (ΔQ) into work with variable efficiency (ε) (equation 2):

energy = amt wk / efficiency

$$\Delta Q = \Delta W / \varepsilon$$

In this regard, energy and work can be envisioned as if on a see-saw on a sliding fulcrum, the position of which is defined by the efficiency of the system. Excluding extreme conditions (e.g. circulatory shock), the circulation provides the respiratory muscles with abundant substrates, and small increases in work or decreases in efficiency caused by mild, or even moderate, mechanical derangements can be compensated by extracting more energy from these substrates and by processing this energy into contractile force. With more severe derangements, however, substrates either may not be available or, more commonly, may not be processed fast enough into work by the muscles' metabolic and contractile apparatus. If so, the balance is tipped beyond the limits of compensation, leading to the gas-exchange abnormalities that characterize *respiratory failure*. We will discuss separately how respiratory work and efficiency are determined in both health and disease, paying particular attention to the unique characteristics of the developing respiratory system.

Determinants of volume–pressure work

As shown by equation 1, the volume–pressure relationships of the respiratory system are the only determinants of how much work the respiratory muscles must do during breathing. These relationships summarize the mechanical behaviors of the lungs and the chest wall. Because lungs and chest wall are linked by a non-compressible boundary (the pleural space), their volumes

cannot change independently of each other or of the respiratory system as a whole, and therefore (equation 3):

$$\Delta V_L = \Delta V_W = \Delta V_{RS}$$

lung chest wall resp system

where ΔV_L, ΔV_W, and ΔV_{RS} represent the volume changes that the lungs, chest wall, and respiratory system, respectively, undergo during breathing.

In contrast, the pressures that the respiratory muscles need to generate in order to inflate the lungs (P_L), chest wall (P_W), and respiratory system (P_{RS}) depend on the pressure difference across each component, and consequently they are all different (equations 4–6):

airway

lungs opening pleura

$$P_L = P_{ao} - P_{pl}$$

chestwall

$$P_W = P_{pl} - P_{B\text{-}atmosphere}$$

$$P_{RS} = P_{ao} - P_B$$

where P_{ao} is the pressure at the airway opening (the nares or the mouth, during normal breathing), P_{pl} is the representative pressure in the pleural space, and P_B is atmospheric pressure. These equations can be easily reworked into the following expression (equation 7):

$$P_{RS} = P_L + P_W$$

which indicates that, at any time during breathing, the total pressure needed to produce a certain volume change in the respiratory system is equal to the sum of the pressures needed to produce the same change individually in the lungs and the chest wall.

Pressures acting on the respiratory system

To move both air and respiratory tissues during breathing, the respiratory muscles must overcome several types of forces, which when applied on tissue surfaces, are translated into pressures. Depending on whether the energy consumed in the effort leaves the system as heat or simply remains stored to be recovered later, the pressures acting on the respiratory system can be classified into non-dissipative and dissipative. **Non-dissipative** pressures include elastic or volume-dependent pressures that arise from the tendency of the lung and chest wall to recover their original shape upon deformation, inertial or acceleration-dependent pressures produced by the changes in velocity experienced by gas and tissues during breathing movements, and gravitational or mass-dependent pressures related to the mere weight of the tissues. **Dissipative** pressures, on the other hand, are commonly grouped together as resistive pressures, and include flow-dependent pressures generated primarily by the friction of the gas against the airway walls, and viscoelastic or time-dependent pressures created by the molecular movements that occur in the tissues and in the gas–liquid interface as the respiratory system changes volume.

Non-dissipative pressures

Inertial and gravitational pressures are small during normal breathing in children and can be neglected. Elastic pressures, in contrast, can be quite large. Their magnitude depends on the volume of the respiratory system, somewhat as the tension developed by a rubber band depends on the extent to which it is stretched. Elastic pressures are best characterized when there are no other pressures operating in the respiratory system. For this to happen, respiratory system volume must be maintained constant for at least a few seconds (e.g. by breath holding at a given level). Under such circumstances, gas ceases to flow in the airways, and pressures at the airway opening and in the alveoli (P_A) become the same. Equations 4–6 can then be rewritten (equations 8–10):

alveoli

$$P_{L.el} = P_A - P_{pl}$$

$$P_{W.el} = P_{pl} - P_B$$

$$P_{RS.el} = P_A - P_B$$

where $P_{L.el}$, $P_{W.el}$, and $P_{RS.el}$ represent the elastic pressures generated by the lungs, the chest wall, and the whole respiratory system, respectively.

The relationships between volume changes and elastic pressures in the respiratory system and its components are quite complex. Graphically, their shape can be described by a sigmoid curve: volume increases much less for a given pressure change at low and high volumes than

at intermediate volumes, when the volume–pressure relationship is steeper (Fig. 11.15). From a mathematical point of view, the description is more difficult. Like any other continuous function, each volume-pressure relationship has a well specified slope at each volume ($\Delta V/\Delta P$). This slope defines the **compliance** of the lungs, chest wall, or respiratory system for that volume depending on whether $\Delta P_{L,el}$, $\Delta P_{W,el}$, or $\Delta P_{RS,el}$ is substituted for ΔP. Unfortunately, no single slope or compliance can accurately describe the totality of the volume–pressure relationship. Only for the intermediate range of volumes is the relationship relatively linear, and $\Delta V/\Delta P$ can be considered constant.

If we rearranged equations 8–10 in a way similar to equation 7, we would find that, just like the total pressure, the elastic pressure developed by the respiratory system is the sum of the elastic pressures developed by the lungs and the chest wall. A graphic analysis demonstrates how this additive interaction of the lungs and the chest wall shapes the volume–pressure behavior of the entire respiratory system (Fig. 11.16). For instance, the points at which the volume–pressure curves intersect the volume axis, the respiratory system and each of its components (lungs and chest wall) are at their respective **relaxation volumes** (i.e. the volumes at which the elastic elements generate no recoil). Lungs and chest wall have different relaxation volumes. The relaxation

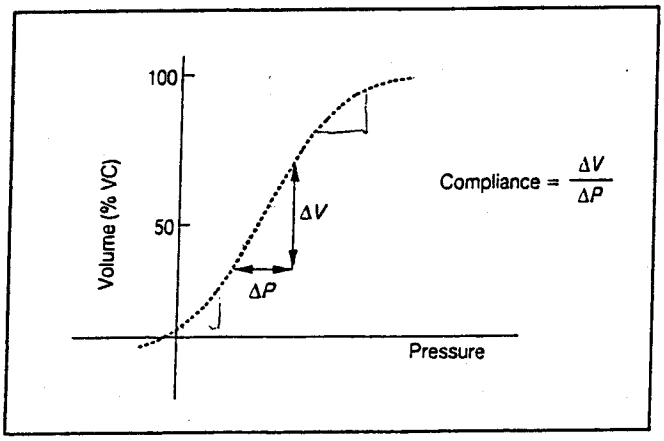


Fig. 11.15. Idealized relationship between volume and elastic pressure in the lungs. Volume is represented as a proportion of the vital capacity of the lungs (VC, the maximal volume that can be [illegible]d after a complete exhalation). The relationship is relatively flat a[illegible]gh and low lung volumes and steeper at intermediate volumes, where breathing normally takes place. At these intermediate volumes, the slope is relatively constant, and the relationship can be described with a single compliance.

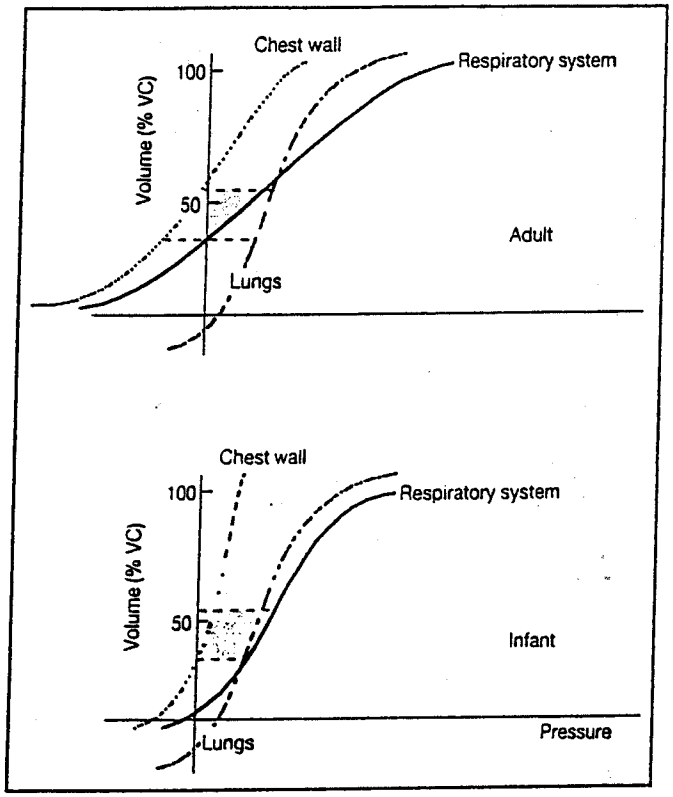


Fig. 11.16. Elastic volume–pressure relationships of the lungs, chest wall, and respiratory system for the range of vital capacity (VC) in an adult and in an infant. These relationships show that the pressure needed to inflate the respiratory system to any given volume is the sum of the pressures that would be needed to inflate the lungs and the chest wall individually to the same volume. The intersection of each relationship with the ordinate represents the relaxation volume of each component. The volume–pressure relationships of the lungs are similar in the adult and in the infant; the volume–pressure relationship of the chest wall, however, is much steeper in the infant, causing both the relaxation volumes of the chest wall and the respiratory system to be lower as well. The stippled area represents the elastic work done by the respiratory muscles for a typical tidal volume. Note that this work tends to be greater in the infant because, at normal breathing volumes, the recoil of the chest wall does not contribute to inflating the lungs as it does in the adult.

volume of the lungs is rather small; if allowed to collapse freely, the lungs would end up containing a gas volume smaller than the normal **residual volume** (the gas volume of the lungs after a forced expiration). The relaxation volume of the chest wall, on the other hand, is considerably larger; in the adult, it exceeds 50 percent of the **vital capacity** (the gas volume of the lungs after a maximal inspiratory effort). The discrepancy between the relaxation volumes of the lungs and the chest wall has three important mechanical consequences. First, it causes the relaxation volume of the respiratory system to occupy

a position intermediate between those of the lungs and the chest wall; beyond the newborn period, the relaxation volume of the respiratory system coincides with the **functional residual capacity** of the lungs (the gas volume of the lungs at the end of a tidal breath). Second, the opposing recoils of the lungs and chest wall create a negative pressure in the pleural space at the end of a normal breath. This negative pressure attaches the lungs to the chest wall and promotes venous return into the heart. Finally, for at least a portion of the volume range, the passive outward recoil of the chest wall contributes to the work of expanding the lungs, thereby reducing the energetic demands on the respiratory muscles (Fig. 11.16).

The elastic recoil generated per unit of lung volume is relatively constant during development. In contrast, the recoil of the chest wall increases substantially after the perinatal period, when a high chest-wall compliance is essential to facilitate passage through the birth canal. As a result of this high chest-wall compliance, the inward recoil of the newborn's lungs is partially unopposed, and the relaxation volume of the respiratory system is proportionally smaller than that of the adult (Fig. 11.16). Because a small lung volume represents a disadvantage in terms of both alveolar stability and oxygenation, newborns of most mammalian species have developed strategies to maintain the functional residual capacity of their lungs above the relaxation volume of their respiratory system. These strategies combine mechanisms directed at prolonging expiratory flow (such as sustaining the tonic activity of the inspiratory muscles during expiration or contracting the adductor muscles of the larynx) with a relatively high breathing rate, which reduces the time available for expiration. The resultant dependence of lung volume on neural control renders the functional residual capacity of newborn and small infants' lungs very vulnerable to changes in muscle coordination and tone. Concurrent decreases in intercostal and upper airway muscle tone during rapid eye movement (REM) sleep, for example, prevent expiratory flow prolongation and may decrease lung volume substantially, particularly in the premature infant. Likewise, muscle weakness, deep sedation, and central nervous system depression all can reduce the functional residual capacity of the lungs, increasing the work of breathing and impairing gas exchange.

Dissipative pressures

A pressure is characterized as dissipative when the energy that is used to overcome it leaves the system (usually as heat) and cannot be used again. In the respiratory system, most dissipative energy losses are produced by the friction of the gas against the internal surface of the airways. A measurable amount of energy, however, is also permanently invested in rearranging molecules in both the tissues and the gas–liquid interface. If this energy is primarily dependent on time then the dissipative pressures are known as viscoelastic. If, on the other hand, the energy used for the molecular rearrangements varies depending on the direction of the breathing movements, then the dissipative pressures are known as plastoelastic (certain materials, like pulmonary surfactant, exhibit high plastoelasticity). Regardless of whether the final pathway is frictional, viscoelastic, or plastoelastic, the energy dissipated during inspiration can no longer contribute to work performed during expiration. Thus, whenever present, dissipative forces cause the volume–pressure behavior of the respiratory system to vary depending on the inspiratory or expiratory direction of the volume changes, a property known as **hysteresis**.

Hysteresis is responsible for the formation of loops when the volume–pressure relationships of the respiratory system are plotted during breathing (Fig. 11.17). In such graphic representation, the dissipative pressures can be identified at any volume as the distance

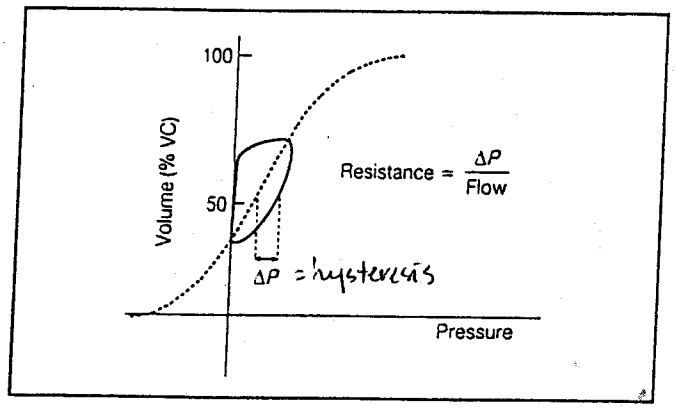


Fig. 11.17. Dynamic volume–pressure relationship showing hysteresis (loop) caused by dissipative energy losses. The magnitude of the dissipative pressure losses can be estimated at any point as the distance between the hysteretic loop and the elastic volume–pressure relationship (ΔP). The resistance of the respiratory system is usually calculated by dividing the dissipative pressure losses calculated in this fashion by the gas flow.

between the point in the loop and the point that the elastic volume–pressure relationship would occupy at a similar volume (ΔP in Fig. 11.17). In the same representation, the area enclosed by the loop provides a measure of the total amount of work done against dissipative pressures (Fig. 11.18). Under normal circumstances, however, only the inspiratory portion of this work is performed by the respiratory muscles. The dissipative work done during expiration is performed at the expense of the energy accumulated in the elastic elements of the lungs and the chest wall during inspiration.

Similar to the elastic pressures, the dissipative pressures in the respiratory system cannot be predicted with a simple mathematical expression. Viscoelastic and plastoelastic pressures, for instance, are complex, nonlinear functions of gas flow, respiratory system volume, and time. In contrast, frictional pressures are generally considered to relate linearly to gas flow in the airways ($\dot{V}$). Based on this consideration and the fact that friction causes the difference between the pressure at the airway opening (P_{ao}) and at the alveoli (P_A), we can write equation 11:

$$P_{ao} - P_A = R_{aw}\dot{V}$$

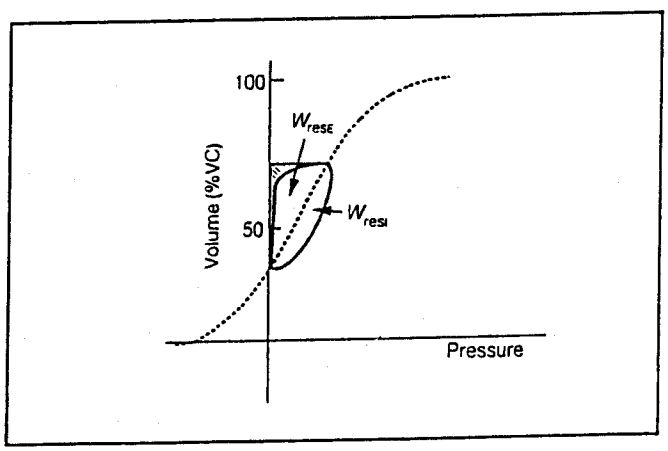


Fig. 11.18. Graphic representation of the work performed during a typical tidal breath. The area enclosed by the loop is a measure of the work done against dissipative forces. Only the inspiratory portion of this work (W_{resi}, stippling), however, needs to be performed by the respiratory muscles; the expiratory portion of the dissipative work (W_{rese}, no stippling) is done by the energy accumulated in the elastic elements of the system during inspiration. A small portion of this elastic energy is used to overcome the tone left in the inspiratory muscles during expiration (cross-hatched area).

where the constant R_{aw} represents the flow resistance of the airways. However, even this formulation is an oversimplification: volume-dependent variations in airway caliber as well as turbulence and other flow perturbations common at points of airway narrowing and bifurcations cause substantial departures from flow–pressure linearity that cannot be accounted for by a constant R_{aw}.

Airway dynamics

An understanding of the relationship between airway caliber and lung volume is essential for the recognition and diagnosis of *airway obstruction*. Central to this understanding is the idea that the airways are elastic tubes, the caliber of which is determined by the coupling of airway wall compliance and airway transmural pressure. Airway wall compliance determines both the distensibility and collapsibility of the airways; it depends on the state of health and maturity of the airway tissue and is modulated by the airway smooth muscle tone. Airway transmural pressure, defined as the difference between the pressures of the gas column inside the airway and the tissue outside the airway, varies during the breathing cycle in a fashion that depends on whether the airway is extra- or intrathoracic.

Extrathoracic airways (nose, pharynx, larynx, and trachea to the thoracic inlet) are exposed to atmospheric pressure on the outside. Because the pressure inside is subatmospheric during inspiration and supra-atmospheric during expiration, the transmural pressure of these airways is always negative (promoting airway collapse) during inspiration and always positive (promoting airway distension) during expiration. The outside surface of the intrathoracic airways (trachea and bronchi) is exposed to a pressure similar to pleural pressure (independent of whether they are embedded in the lung tissue or the mediastinum). Because inspiratory flow requires the pressure inside the airways to be greater than alveolar pressure, and alveolar pressure must in turn be greater than pleural pressure (the difference being equivalent to the elastic recoil of the lungs—$P_{L,el}$ in equation 8), the transmural pressure of the intrathoracic airways becomes increasingly positive (causing the airways to become distended) during inspiration. Expiratory flow, in contrast, requires the pressure inside the airways to be lower than alveolar pressure. Whether the pressure at a specific point inside an airway (P_{aw}) is higher or lower

than the outside pleural pressure (P_{pl}), however, depends on the balance between the frictional pressure losses that occur upstream from the airway ($P_A - P_{aw}$) and the elastic recoil of the lungs ($P_{L,el}$). If, at a certain point, friction causes ($P_A - P_{aw}$) > $P_{L,el}$, then it follows that (equation 12):

$$P_A - P_{L,el} > P_{aw}$$

or, from equation 8 (equation 13):

$$P_{pl} > P_{aw}$$

which means that from this critical point all the way to the thoracic inlet, the transmural pressure is negative and the airway tends to collapse. Obviously, diseases that increase the frictional resistance of the airways (e.g. *asthma*) or decrease the elastic recoil of the lungs (e.g. *emphysema*) will move the critical point closer to the alveoli, causing airway collapse and further increasing airway resistance during expiration.

Depending on the airway wall compliance and caliber, airway collapse during expiration can lead to **flow limitation**, a situation in which expiratory gas flow remains constant even if the subject makes a maximal effort to raise alveolar pressure. Flow limitation can be caused by both the increase in frictional pressure losses (viscous flow limitation) and the formation of areas of critical velocity above which pressure disturbances cannot travel upstream (wave-speed flow limitation) as airway flow increases. Regardless of which of these two mechanisms is operative, the flow rate at which flow limitation occurs at a given lung volume depends only on the caliber and collapsibility of the airways and is highly reproducible. Determinations of maximal expiratory flow during respiratory function testing take advantage of this reproducibility to assess and follow the functional state of the intrathoracic airways over time or in response to therapeutic interventions.

Airway obstruction

Airway obstruction exaggerates the normal changes of the airway caliber during breathing (Fig. 11.19). When

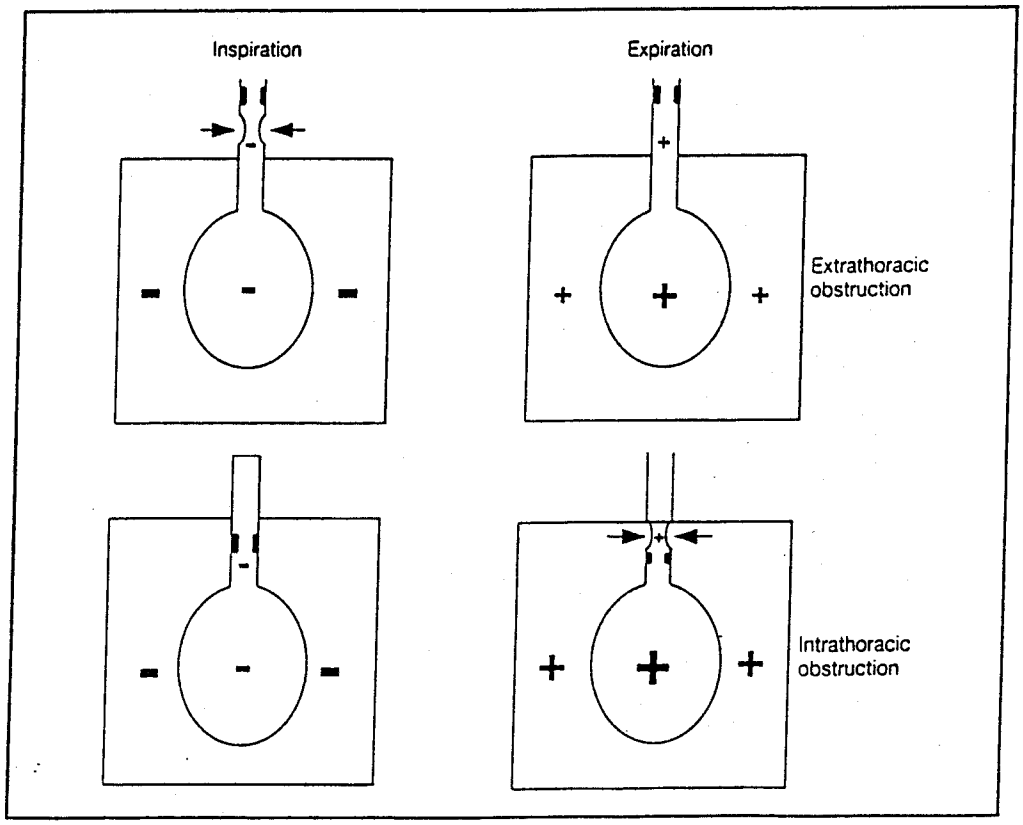


Fig. 11.19. Effects of airway obstruction on airway caliber during inspiration and expiration. Extrathoracic obstruction is exacerbated during inspiration because the highly negative pressure inside the airways is unopposed by the atmospheric pressure outside, causing the airway to collapse (arrows). Intrathoracic obstruction, in contrast, worsens during expiration because, as gas starts to flow towards the mouth, the pressure outside the airways (which is similar to pleural pressure) rapidly exceeds the pressure inside, causing the airways downstream from the obstruction point to collapse (arrows). (From Pérez Fontán JJ, Lister G. In Touloukian RJ, ed. *Pediatric trauma*. 2nd Edition. Saint Louis: Mosby-Year Book Inc., 1990: 46; with permission.)

the obstruction is extrathoracic (e.g. *croup*), the pressure inside the airway segment downstream from the narrow point must become more negative during inspiration in order to overcome the increased frictional resistance of the narrowing. The segment therefore tends to collapse, producing both an inspiratory exacerbation of the obstruction and a characteristic turbulent noise (inspiratory stridor). The obstruction is somewhat relieved during expiration, as the pressure inside the airways must become more positive, again to overcome the narrowing's increased resistance. When the obstruction is intrathoracic (e.g. *asthma* or *tracheobronchomalacia*), very negative pleural pressures tend to dilate the airways during inspiration. During expiration, however, increased frictional pressure losses create a marked pressure gradient from the alveoli toward the airway opening. As a result, the pressure inside the airways is rapidly exceeded by pleural pressure as the lungs deflate, causing an expiratory exacerbation of the obstruction and a distinctive mid- to end-expiratory wheeze on auscultation.

Restrictive and obstructive respiratory disease

The total amount of work that the respiratory muscles must do during breathing is the sum of the work done to overcome the non-dissipative and dissipative pressures. Depending on which of these two work components predominates, the mechanical dysfunctions of the respiratory system can be classified as restrictive or obstructive.

Restrictive disease is caused by processes that increase the elastic recoil of the lungs (e.g. *pulmonary edema, respiratory distress syndrome of the newborn*) or the chest wall (e.g. *abdominal distension, scoliosis*). The increased recoil has two major consequences. First, it increases the amount of work that the respiratory muscles must do during inspiration (expiration continues to be passive). In addition, by lowering the relaxation volume of the respiratory system, the increased recoil also decreases the functional residual capacity of the lungs, promoting alveolar collapse and increased venous admixture. In an attempt to counteract the effects of restrictive disease on lung volume, infants and children often close their glottis toward the end of expiration, generating a grunt, which is a useful diagnostic sign. Positive end-expiratory pressure and continuous airway pressure are therapeutic modalities both directed at preserving alveolar stability.

The small caliber and high compliance of the developing airways renders them particularly vulnerable to obstruction. During normal breathing, small airways represent no particular disadvantage for the child because gas flows are low and dissipative pressure losses also remain small. When obstruction occurs, however, frictional pressure losses increase exponentially with the reduction in airway diameter, an increase that is compounded by the tendency of flow to develop into turbulent patterns in low-caliber tubes. Consequently, the same degree of obstruction has much more dire consequences in the small infant and child than in the adult.

Determinants of breathing efficiency

In a thermodynamic system, efficiency can be defined as the proportion of free energy that is transformed into external work. In the case of the respiratory system (equation 14):

$$\varepsilon = \frac{\text{Work/Time}}{\text{Respiratory Muscle Energy Consumption}}$$

The numerator of this expression represents the amount of volume–pressure work done by the respiratory muscles to inflate the lungs per unit of time (in physical terms, the power of the respiratory system), which depends on the mechanical behavior of the lungs and chest wall, the range of the tidal volume, and the breathing frequency. The denominator includes not only the energy consumed by the muscles to do volume–pressure work, but also the energy applied to perform isometric and postural tasks (which involve no change in volume, and therefore are not proper work) and that wasted in distorting the rib cage (which is proper work, but does not contribute to lung inflation).

Considered in these terms, the respiratory system is an extremely inefficient machine. Efficiency values as low as 8–25 percent occur in adult humans at rest; even lower ones in healthy premature infants (4 percent) and in patients with respiratory disease (1–3 percent). Because of these low starting values, very small changes in efficiency have a large effect on the energy required for breathing. A clear understanding of the factors that influence respiratory system efficiency is important for both the diagnosis and the treatment of most breathing disturbances. Among these factors are breathing pattern,

diaphragmatic configuration, chest wall distortion, and the contractile state of the respiratory muscles.

Breathing pattern

The amount of work that the respiratory muscles must do to generate a given alveolar ventilation (and thus maintain a certain $PaCO_2$) depends on the breathing pattern (Fig. 11.20). Each individual has a well defined optimal breathing frequency, above and below which the work of breathing increases hyperbolically. This theoretical frequency is linked to the volume–pressure relationships of the respiratory system: it increases when the elastic recoil of the lungs or the chest wall increases (e.g. with *pulmonary edema*) and decreases when the dissipative pressures of the respiratory system increase (e.g. with *airway obstruction*). In practice, most subjects, including those with respiratory mechanical disturbances, adopt breathing frequencies that approach their predicted optimal frequency. As a result, one can usually categorize respiratory disease as primarily restrictive or obstructive depending on whether the patient breathes rapidly or slowly. However, the breathing pattern is regulated through neural pathways that respond more to mechanical and irritant stimuli from the respiratory system or to cortical influences than to energetic convenience. Therefore, it is not uncommon for children with respiratory disease to breathe transiently at frequencies that depart substantially from the optimal frequency. In this manner, airway irritation, stretch receptor stimulation, crying, and agitation can reduce the energetic efficiency of the respiratory system and precipitate respiratory failure.

Diaphragmatic length and configuration

Just like any other muscle, the diaphragm develops its maximal contractile force at a certain optimal length (see p. 602), which happens to be attained when the lungs approximate their functional residual capacity. At this volume, the diaphragm is configured as a dome-capped cylinder, an arrangement that has several advantages. First, a cylindrical shape allows a much greater volume displacement for a given fiber shortening than a simple dome shape. Second, as the sides of the cylinder shorten during inspiration, making the dome descend toward the abdomen in a piston-like motion, the area of contact between the internal surface of the rib cage and the lungs increases. This increase provides a way to accommodate

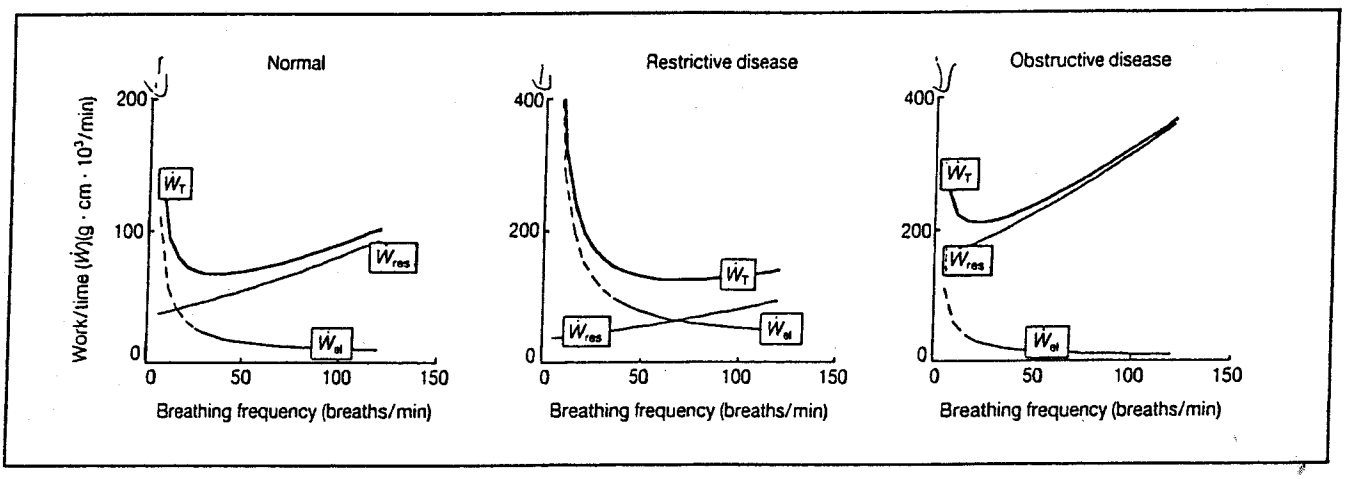


Fig. 11.20. Calculated effect of breathing frequency on the energy expended per unit of time (breathing power, $\dot{W}$) to overcome elastic forces ($\dot{W}_{el}$), resistive forces ($\dot{W}_{res}$), and their sum ($\dot{W}_T$) in a normal infant and in two infants with respiratory disease, one restrictive and the other obstructive. Calculations are based on assumptions that minute alveolar ventilation is constant, breathing pattern is sinusoidal, and volume and flow–pressure relationships are linear. Elastic and resistive power decrease and increase with frequency, respectively. As a result, total power follows a bimodal course, decreasing at low frequencies and increasing at high frequencies. The point at which total power reaches a minimum is the optimal frequency in terms of energy expenditure. The figure shows that the predominance of elastic and resistive power shifts this optimal frequency to higher frequencies in restrictive disease and to lower frequencies in obstructive disease. Note different scales used to accommodate the increase in breathing power caused by restrictive and obstructive disease.

without distortion the inevitable increase in lung surface that occurs as the lungs expand. Finally, for most of the tidal volume range, the sides of the diaphragmatic cylinder are apposed to the internal surface of the rib cage. By transmitting to the ribs and the sternum the increase in intra-abdominal pressure that occurs as the diaphragm descends into the abdomen, this area of apposition establishes a mechanical link between the abdomen and the rib cage, helping to stabilize the chest wall and facilitating inspiration.

The developing diaphragm may lack some of these advantages. Particularly in the newborn and small infant, the lower portion of the rib cage has proportionally wider diameters than in the adult. As a result, the muscle's insertions are spread out, and the sides of the diaphragmatic cylinder are short (Fig. 11.21). Under such conditions, fiber contraction can only increase the radius of the dome: therefore, the volume displaced (and the work done) by a given fiber shortening (or for a certain energy expenditure) is limited. In addition, the shortness of the area of apposition lessens the stabilizing and inspiratory effects of intra-abdominal pressure, further reducing the work/energy ratio and the efficiency of the inspiratory system.

Chest-wall distortion

Until this point, we have assumed that every portion of the chest wall undergoes a similar displacement during breathing, regardless of its location. In reality, not only can different portions of the rib cage and abdomen change volume independently of each other, but they often do it in opposite directions.

Chest-wall distortion is primarily the consequence of regional variations in chest-wall compliance. In the case of the rib cage, areas without bony support (intercostal, suprasternal, and subcostal spaces) are particularly prone to move inward as pleural pressure decreases during inspiration. When pleural pressure becomes very negative to overcome an increased elastic recoil or an airway obstruction, this inward movement of the rib cage becomes more pronounced, causing visible **retractions**.

The chest walls of newborns and infants are very susceptible to distortion. As discussed above, the limited ossification of ribs and sternum increases markedly the passive compliance of the rib cage during early life. In addition, the developing intercostal muscles, the main function of which is to stabilize the chest by contracting simultaneously with the diaphragm, appear to have decreased tone, especially during REM sleep. Finally, the lack of a substantial area of apposition between the

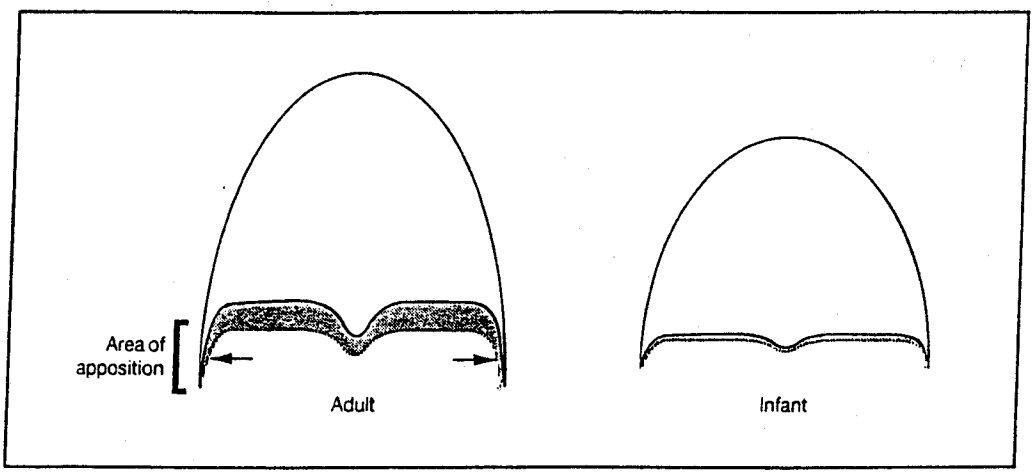


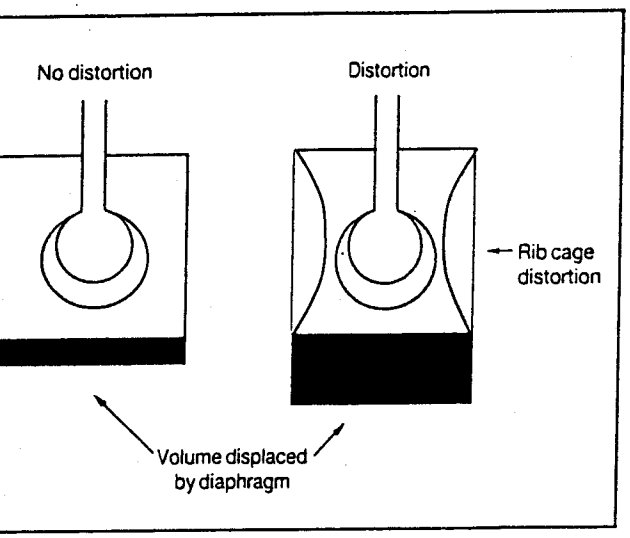
Fig. 11.21. Diagrams of the configuration of the diaphragm in the adult and the infant. In the adult, the diaphragm has the shape of a cylinder with a dome cap. The sides of the cylinder adhere to the internal surface of the rib cage, forming an area of apposition that is used by intra-abdominal pressure to push the ribs and the sternum during inspiration. In the infant, the diaphragmatic insertions are more spread out and both the sides of the cylinder and the area of apposition are smaller. As a result, the volume displaced by the muscle's contraction (stippling) is smaller, and the abdomen and rib cage are linked in a less efficient manner.

iaphragm and the rib cage eliminates the additional tabilizing effect of intra-abdominal pressure on the lower bs and subcostal area at these ages.

Chest-wall distortion can be quantified as a change in olume caused by a change in pressure. Therefore, it epresents a form of work and has a measurable energy ost. Unfortunately, the work done to produce the istortion is not applied to lung inflation, and therefore istortion can be considered a source of inefficiency. This oint of view is well illustrated by a simple analysis of the ork done by the diaphragm in the presence of rib cage tractions (Fig. 11.22). Regardless of whether such tractions are present or not, the tidal volume of the ngs (ΔV_L) has to be equivalent to the sum of the volume anges undergone by the rib cage (ΔV_{rc}) and abdomen V_{ab}) (equation 15):

$$\Delta V_L = \Delta V_{rc} + \Delta V_{ab}$$

onsequently, decreases in ΔV_{rc} caused by rib cage tractions during inspiration must be accompanied by a mmensurate increase in ΔV_{ab}, if ΔV_L is to remain constant. In extreme cases, ΔV_{ab} can in fact be greater than ΔV_L if ΔV_{rc} becomes negative. Because ΔV_{ab} approximates the volume displaced by the diaphragm, the work performed by the muscle is increased markedly by rib cage distortion without a parallel change in the work done on the lungs. The resultant energy waste may contribute to the poor weight gain and easy diaphragmatic fatigability of small infants suffering from respiratory distress.



11.22. Schematic representation of the effects of rib cage actions on the volume displaced by the diaphragm during piration. During a non-distorted inflation, both rib cage and omen expand. During a distorted inflation, however, the phragm must increase its volume displacement (and therefore do e work) to offset the inward movement of the rib cage and ntain the tidal volume of the lungs constant. (From Pérez Fontán Mechanical dysfunction of the respiratory system. In Fuhrman BP, merman JJ, eds. *Pediatric critical care*. Saint Louis: Mosby-Year k Inc., 1992: 399, with permission.)

Contractile state of the respiratory muscles (see p. 603)

Muscle fatigue (the decrease in contractile force that follows excessive muscle activity) appears to increase the energy needed by respiratory muscles to perform a certain amount of work on the lungs, thereby reducing their efficiency. Metabolic disturbances and simple malnutrition may have similar effects.

Summary

As the previous discussion establishes, the developing respiratory system has some mechanical disadvantages. The reader, however, should not be left with the impression that infants and children are constantly on the brink of respiratory failure. On the contrary, they have a remarkable capability to compensate for most mechanical disturbances. This capability is based on the maintenance of a large functional reserve. Recognizing when this reserve becomes threatened is perhaps the most important point in the rational management of children with respiratory disease.

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accp consensus conference

Mechanical Ventilation*

Chairman: Arthur S. Slutsky, M.D., F.C.C.P.

(Chest 1993; 104:1833-59)

A/C = assist-control ventilation; APRV = airway pressure release ventilation; ARDS = adult (or acute) respiratory distress syndrome; auto-PEEP = increase above set PEEP level, in end-exhalation alveolar pressure (also termed dynamic hyperinflation, intrinsic PEEP, also quantified as $\dot{V}_{EE}$); BPF = bronchopleural fistula; CaO_2 = concentration of oxygen in arterial blood; CMV = conventional mechanical ventilation; CPAP = continuous positive airway pressure; DH = dynamic hyperinflation (see auto-PEEP); Do_2 = oxygen delivery; ECMO = extracorporeal membrane oxygenation; $ECCO_2R$ = extracorporeal CO_2 removal; ET = endotracheal; FIO_2 = fractional concentration of inspired oxygen; FRC = functional residual capacity; HFJV = high-frequency jet ventilation; HFV = high-frequency ventilation; ICP = intracranial pressure; I:E = inspiratory:expiratory ratio; ILV = independent lung ventilation; IMV = intermittent mandatory ventilation; IRV = inverse ratio ventilation; IVOX = intravascular blood gas exchanger; LFPPV = low-frequency positive pressure ventilation; LV = left ventricle; MalvP = mean alveolar pressure; MAP = mean airway pressure; MMV = mandatory minute ventilation; OAD = obstructive airways disease; PAP = peak airway pressure; Paw = airway pressure; PCIRV = pressure-controlled inverse ratio ventilation; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Pmus = pressure generated by muscle contraction; Ppl = pleural pressure; PPV = positive pressure ventilation; PS = pressure support; PSV = pressure support ventilation; Ptot = total distending pressure; P-V = pressure-volume; RA = right atrium; RV = right ventricle, residual volume; SaO_2 = oxygen percent saturation (arterial); SIMV = synchronized intermittent mandatory ventilation; T_I = inspiratory time; TLC = total lung capacity; VC = vital capacity; $\dot{V}CO_2$ = CO_2 production (elimination); V_D = dead space; $\dot{V}_E$ = minute ventilation; $\dot{V}_{EE}$ = end-expiratory lung volume; $\dot{V}_{EI}$ = end-inspiratory lung volume; $\dot{V}/Q$ = ventilation/perfusion ratio; V_T = tidal volume; $\dot{V}O_2$ = oxygen consumption (uptake)

"But that life may . . . be restored to the animal, an opening must be attempted in the trunk of the trachea, in which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in air. . . . And as I do this, and take care that the lung is inflated in intervals, the motion of the heart and arteries does not stop . . ."

Andreas Wesele Vesalius, 1543

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Objectives and Specific Recommendations

Section 1: Objectives of Consensus Committee

Although the concept of artificial respiration was recognized in the 16th century by Vesalius, it was not until the 20th century that mechanical ventilation became a widely used therapeutic modality. Over the past 30 years, and especially over the past decade, there has been an explosion of new ventilatory techniques that present a bewildering array of alternatives for the treatment of patients with respiratory failure. Unfortunately, although the number of options available to the clinician has appeared to increase exponentially, well-controlled clinical trials defining the specific role for each of these modes of ventilation and comparing them with other modes of ventilation have not been forthcoming. In addition, over the past few years, our understanding of the detrimental as well as beneficial effects of mechanical ventilation has increased, along with novel strategies for limiting these negative effects.

These issues formed the impetus for the consensus conference described in this document; the conference was held in Chicago on January 28 through 30, 1993. The consensus committee was international in scope (Europe, North America, New Zealand) and consisted of individuals from a broad range of backgrounds (anesthesia, critical care, pulmonary, respiratory therapy). The purpose of the conference was to summarize key concepts related to mechanical ventilation and to present recommendations based on these concepts for clinicians applying mechanical ventilation in the adult ICU setting. Due to the lack of randomized clinical studies on most aspects of ventilatory care, the underlying theme of this document is a physiologic one, the basic tenet being that if the clinician understands the physiologic principles, he or she can apply mechanical ventilation at the bedside in a rational manner. We recognize that rational application of mechanical ventilation does not, in and of itself, guarantee the therapy will be beneficial to the patient. We await randomized clinical trial results for ultimate guidance.

The purpose of the consensus conference was not to deal with every possible aspect of mechanical ventilation. Rather, the focus was on treatment of patients with acute ventilatory failure and the principles of ventilation *after* the decision to initiate mechanical ventilation has been made. The technical needs and medical issues of ventilatory support in non-ICU settings were not dealt with specifically by this conference. These issues include ventilatory support during anesthesia

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and surgery; patient treatment during intrahospital, land, or air transport; and long-term mechanical ventilation in the home. Also not covered were noninvasive (nonintubated) ventilatory support, negative pressure ventilation, and methods and devices for respiratory support not primarily applied to the lungs, such as extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal ($ECCO_2R$), or intravascular blood gas exchanger (IVOX). This conference focused on the clinical application of mechanical ventilators, rather than on their design and operation. Thus, the participants consider these proceedings to be complementary to those of the 1992 AARC Consensus Conference on the Essentials of Mechanical Ventilators.[2]

Despite the multidisciplinary and international composition of the conference, we were able to reach agreement on many difficult clinical issues. Yet even though we engaged in considerable discussion and debate, consensus was not possible on a number of aspects of ventilator care. This is hardly surprising and merely reflects the variety of acceptable approaches that can be used to treat patients with respiratory failure. For example, it was not possible to agree that there was an optimum *mode* of ventilation for any disease state or an optimum method of weaning patients from mechanical ventilation. However, in addition to the specific recommendations discussed in Section 2, there was general agreement on the following principles that should guide the use of mechanical ventilation:

1. The underlying pathophysiology of various disease states varies with time, and thus the mode, settings, and intensity of ventilation should be reassessed repeatedly.
2. Mechanical ventilation is associated with a number of adverse consequences, and as such, measures to minimize such complications should be implemented wherever possible.
3. To minimize side effects, the physiologic targets do not have to be in the normal range. For example, at times it may be beneficial to allow the $PaCO_2$ to increase (controlled hypoventilation, permissive hypercapnia) rather than risk the dangers of lung hyperinflation.
4. Alveolar overdistention can cause alveolar damage or air leaks (barotrauma). Hence, maneuvers to prevent the development of excess alveolar (or transpulmonary) pressure should be instituted if necessary. While recognizing that the causes of ventilator-induced lung injury are multifactorial, the consensus committee generally believed that end-inspiratory occlusion pressure (*ie*, plateau pressure) was the best, clinically applicable estimate of average peak alveolar pressure, and thus, was the most important target pressure when trying to avoid alveolar overdistention. Many individuals on the consensus committee believed that high plateau pressures (>35 cm H_2O) may be more harmful in most patients than high values of FIO_2.
5. Dynamic hyperinflation (DH) (gas trapping, auto-PEEP, intrinsic PEEP) often goes unnoticed and should be measured or estimated, especially in patients with airway obstruction. Management should be directed toward limiting the development of DH and its adverse consequences in these patients.

This consensus document is divided into two major sections: part 1 summarizes the objectives and specific recommendations of the consensus committee; part 2 reviews key principles regarding physiology, complications, and modes of ventilation that form the basis for the recommendations.

Section 2: Objectives of Mechanical Ventilation

Mechanical ventilation and continuous positive airway pressure (CPAP) are methods of supporting intubated patients during illness, and are not, in and of themselves, curative or therapeutic. Indeed, in certain clinical settings, there may be effective alternative therapies that do not require intubation and mechanical ventilation. The fundamental objectives for ventilatory support in acutely ill patients may be viewed physiologically and clinically, as detailed below. The following objectives should be kept in mind, not only when mechanical ventilation is initiated, but also at frequent intervals during the period of support; mechanical ventilation should be withdrawn whenever the underlying pathophysiologic rationale for initiating mechanical ventilation is no longer present.

A. *Physiologic Objectives*

1. *To Support or Otherwise Manipulate Pulmonary Gas Exchange:*

(i) Alveolar Ventilation (eg, *Arterial PCO_2 and pH*).

In most applications of ventilatory support, the objective is to normalize alveolar ventilation. In certain specific clinical circumstances, the objective may be to achieve an alveolar ventilation greater than normal (as in deliberate hyperventilation to reduce intracranial pressure [ICP]), or adequate but less than normal (as in permissive hypercapnia or acute-on-chronic ventilatory failure).

(ii) Arterial Oxygenation (eg, *PaO_2, SaO_2, and CaO_2*).

A critical objective of mechanical ventilation is to achieve and maintain a level of arterial blood oxygenation that is acceptable for the clinical setting, using an inspired oxygen concentration that is also acceptable. In most applications of ventilatory support, this means an SaO_2 >90 percent (roughly equivalent to a PaO_2 >60 mm Hg assuming a normal position of the oxyhemoglobin dissociation curve), although other end points are appropriate in certain settings. There is no clinical evidence that a PaO_2 greater than normal is advantageous. Given other techniques for improving oxygenation, this objective would seldom be the only reason for initiating mechanical ventilation. Because arterial oxygen content is determined by hemoglobin as well as PaO_2, and because systemic oxygen delivery is directly related to cardiac output (Qt), as well as concentration of oxygen in arterial blood (CaO_2), these factors must also be considered in therapy aimed at improving tissue oxygenation.

2. *To Increase Lung Volume:*

(i) End-Inspiratory Lung Inflation.

To achieve sufficient lung expansion, with every breath (or intermittently), to prevent or treat atelectasis and its attendant effects on oxygenation, compliance, and lung defense mechanisms.

(ii) Functional Residual Capacity (FRC).

To achieve and maintain an increased FRC using PEEP in settings in which a reduction in FRC may be detrimental (*eg*, decreased PaO_2, increased lung injury) as in adult respiratory distress syndrome (ARDS) and postoperative pain.

3. *To Reduce or Otherwise Manipulate the Work of Breathing:*

(i) To Unload the Ventilatory Muscles.

To reduce the patient's work of breathing when it is increased by elevated airway resistance or reduced compliance and the patient's spontaneous efforts are ineffective or incapable of being sustained. In these situations, ventilatory support will be used until specific therapies (or other mechanisms) reverse the condition leading to the increased work load.

B. Clinical Objectives

Because, at best, mechanical ventilation serves only to support the failing respiratory system until improvement in its function can occur (either spontaneously or as a result of other interventions), a primary objective should be to avoid iatrogenic lung injury and other complications.

The other primary clinical objectives of mechanical ventilation are as follows:

1. *To Reverse Hypoxemia:* To increase PaO_2 (generally such that $SaO_2 \geq 90$ percent), whether through increasing alveolar ventilation, increasing lung volume, decreasing O_2 consumption, or other measures, to relieve potentially life- or tissue-threatening hypoxia.

2. *To Reverse Acute Respiratory Acidosis:* To correct an immediately "life-threatening" acidemia, rather than necessarily to achieve a normal arterial PCO_2.

3. *To Relieve Respiratory Distress:* To relieve intolerable patient discomfort while the primary disease process reverses or improves.

There are well-defined circumstances in which attempts to improve PaO_2 or pH to their normal ranges would present greater overall risks to the patient, and lower values of these parameters may be appropriate in such circumstances. In addition to the main clinical objectives listed above, other specific goals for mechanical ventilation, in appropriate settings, include the following:

4. *To Prevent or Reverse Atelectasis:* To avoid or correct the adverse clinical effects of incomplete lung inflation, as, for example, in postoperative splinting or neuromuscular disease.

5. *To Reverse Ventilatory Muscle Fatigue:* In most instances, this means unloading the ventilatory muscles in circumstances of acutely increased and intolerable loads.

6. *To Permit Sedation and/or Neuromuscular Blockade:* To allow the patient to be rendered incapable of spontaneous ventilation, as for operative anesthesia and certain ICU procedures and in certain disease states.

7. *To Decrease Systemic or Myocardial Oxygen Consumption:* To lower systemic and/or myocardial oxygen consumption ($\dot{V}O_2$) when the work of breathing or other muscular activity impairs systemic O_2 delivery or produces an overload of the compromised heart. Examples include cardiogenic shock or severe ARDS.

8. *To Reduce Intracranial Pressure (ICP):* In certain circumstances (*eg*, acute closed head injury), to lower elevated ICP through controlled hyperventilation.

9. *To Stabilize the Chest Wall:* In the unusual circumstance of loss of thoracic integrity sufficient to prevent adequate bellows function (*eg*, chest wall resection, massive flail chest), to provide adequate ventilation and lung expansion.

Section 3: Clinical Recommendations

A. Mechanical Ventilation for Specific Entities

Adult Respiratory Distress Syndrome (ARDS): Although it has been argued that patients with ARDS are now more severely ill than those encountered in the past, the failure of ARDS mortality to decrease during the past 15 to 20 years is disappointing, particularly in light of the many technical advances in ICU care. Criteria that selected a severely hypoxemic subset of patients with ARDS were established in the 1974 to 1977 ECMO clinical trial. Recent work indicates that the average survival of such patients with severe ARDS treated with conventional mechanical ventilation only ranges from 0 percent to 15 percent (mean = 12.8 ± 5.2 percent).[3] This is not statistically significantly different from the ECMO clinical trial survival of 9 percent ($p = 0.15$). Recent changes in ventilatory management may have led to increased patient survival, but to our knowledge, this has not been evaluated with controlled clinical trials.[4-6]

There are no convincing data indicating that any ventilatory support mode is superior to others for patients with ARDS. Nevertheless, reported increases in ARDS patient survival have been ascribed to new techniques such as pressure-controlled inverse ratio ventilation (PCIRV) and low-frequency positive pressure ventilation-extracorporeal CO_2 removal (LFPPV-$ECCO_2R$). If they are harbingers of new and effective therapy, their putative benefit may be linked to current concern about iatrogenic lung damage induced by mechanical ventilation. Animal studies have clearly established the damaging effects of overdistention produced by the application of high peak transthoracic pressures to normal and injured lungs. In humans, the nonuniformly injured severe ARDS lung retains only a small fraction of compliant lung still capable of gas exchange. It has been argued that the application of commonly used tidal volumes (0.7 L, 10 ml/kg) to this small fraction of lung may produce similar damage.[3] The best correlate of this injury in animals is the plateau pressure. Conventional mechanical ventilator (CMV) therapy might thus superimpose iatrogenic lung injury. The "lung rest" strategy used in neonatal ECMO therapy,[7] intentional hypoventilation used in patients with ARDS,[4] and reduction of peak pressures permitted by PCIRV or by LFPPV-$ECCO_2R$[8] are consistent with this argument. There is, however, no proof that any of these techniques alter the outcome of patients with ARDS. A recent randomized controlled clinical trial of PCIRV plus LFPPV-$ECCO_2R$ failed to produce evidence of improved survival.[9] Of interest is the fourfold increase in survival of control patients treated with mechanical ventilation only, according to a computerized protocol.[9]

Guidelines:

1. The clinician should choose a ventilator mode that has been shown to be capable of supporting oxygenation and ventilation in patients with ARDS and that the clinician has experience in using.

2. An acceptable SaO_2 (usually ≥90 percent) should be targeted.

3. Based primarily on animal data, a plateau pressure ≥35 cm H_2O is of concern. We, therefore, recommend that when plateau pressure equals or exceeds this pressure that tidal volume (VT) can be decreased (to as low as 5 ml/kg, or lower, if necessary). With clinical conditions that are associated with decreased chest wall compliance, plateau pressures somewhat greater than 35 cm H_2O may be acceptable.

4. To accomplish the goal of limiting plateau pressure, $PaCO_2$ should be permitted to rise (permissive hypercapnia) unless the presence or risk of raised ICP or other contraindications exist that demand a more normal $PaCO_2$ or pH. Rapid rises in $PaCO_2$ should be avoided. In the presence of normal renal function, slow reduction of tidal volume may also allow renal-induced compensatory metabolic alkalosis and the potential for a higher pH at a given tidal volume.

5. Positive end-expiratory pressure (PEEP) is useful in supporting oxygenation. An appropriate level of PEEP may be helpful in preventing lung damage. The level of PEEP, however, should be minimized as PEEP may also be associated with deleterious effects. The level of PEEP required should be established by empirical trial and reevaluated on a regular basis.

6. The current opinion is that FIO_2 should be minimized. The trade-off, however, may be a higher plateau pressure and the relative risks of these two factors are not known. In some clinical situations when significant concerns over both elevated plateau pressure and high FIO_2 exist, consideration for accepting an SaO_2 slightly less than 90 percent is reasonable.

7. When oxygenation is inadequate, sedation, paralysis, and position change are possible therapeutic measures. Other factors in oxygen delivery (*ie*, $\dot{Q}T$ and hemoglobin) should also be considered.

Bronchopleural Fistula: Bronchopleural air leak (bronchopleural fistula [BPF]) occurs during mechanical ventilation in two general circumstances: as a localized lung or airway lesion (*eg*, following trauma or surgery; complicating central line placement) and as a complication of diffuse lung disease (*eg*, ARDS, *Pneumocystis carinii* pneumonia). Although most leaks are physiologically insignificant, BPF can predispose to atelectasis or inadequate inflation of ipsilateral or contralateral lung, interfere with gas exchange, and predispose to pleural spread of infection. It can also prolong mechanical ventilation thus predisposing to additional morbidity. Some BPFs are amenable to direct surgical repair (*eg*, suture of bronchial tear; lobectomy for necrotizing pneumonia), but in most instances, resolution of the BPF depends on resolution of the primary disease process.

Ventilatory support should provide adequate inflation for the uninvolved areas of lung and assure adequate gas exchange.[10] No single ventilatory mode or approach has been shown to be more effective than any other in treating patients with BPF. In the presence of a large air leak and difficulty in maintaining adequate ventilation, a ventilator capable of delivering high inspiratory flow rates and large delivered tidal volumes may be required. Use of independent lung ventilation (ILV) should be considered in the uncommon circumstance of inability to maintain contralateral lung inflation using adjustments of volumes and/or flows. Fortunately, ventilation of patients with BPF is usually adequate. The major problem is usually to facilitate closure of the leak, so that mechanical ventilator support may be withdrawn. In this circumstance, minimizing inflation pressures and tidal volume is the goal. Chest tube suction is necessary to evacuate continued gas leak, but the degree of suction exerts a variable effect on flow through the fistula.[11]

Guidelines:

1. To facilitate closure

a. Use the lowest tidal volume that allows adequate ventilation.

b. Use a ventilatory mode and settings that minimize peak and plateau pressures necessary to maintain adequate ventilation.

c. Consider permissive hypercapnia (discussed under guidelines 3 and 4 under ARDS) to minimize inspiratory pressures and volumes.

d. Minimize PEEP

2. Consider independent lung ventilation (ILV) or high frequency jet ventilation (HFJV) in cases where a large air leak produces inability to inflate lung or failure to adequately oxygenate/ventilate.

Head Trauma: Mechanical hyperventilation to arterial carbon dioxide levels of 25 to 30 mm Hg acutely lowers ICP. Controlled data on the impact of hyperventilation in patients with head trauma are not available. Decreases in ICP do not necessarily reflect increases in cerebral perfusion pressure. Nevertheless, hyperventilation remains a mainstay of emergency therapy for acutely elevated ICP. There is no evidence to support the application of prophylactic hyperventilation in patients with head injury who do not have raised ICP.[12,13] In fact, there is a strong rationale for maintenance of normocarbia in most head-injured patients without elevated ICP because a patient who has prophylactically been hyperventilated to a $PaCO_2$ in the high 20s and who suffers an acute increase in ICP may not be expected to have an effective reduction in ICP following a moderate increase in minute ventilation ($\dot{V}E$). Since the patient is already hyperventilated, a marked increase in $\dot{V}E$ may be required to effect a significant lowering of $PaCO_2$. The increase in mean airway pressure associated with a dramatic increase in $\dot{V}E$ may cause a paradoxic increase in ICP. Therefore, it is likely that stable head-injured patients should receive mechanical ventilatory support at a level sufficient to produce normal arterial blood gas values. Effective monitoring should be instituted to allow a rapid increase in ventilation and oxygenation should signs of increased ICP or hypoxemia occur.

Recommendations:

1. In the presence of increased ICP, maintain $PaCO_2$ 25 to 30 mm Hg or titrate to ICP if monitoring of ICP is available. Monitoring of ICP is desirable.

2. Maintain normocarbia in head-injured patients with normal ICP.

3. When hyperventilation is used to decrease ICP, return to normocarbia should be gradual (over 24 to 48 h).

Myocardial Ischemia and Congestive Heart Failure: In patients with myocardial ischemia, modes of mechanical ventilation that increase work of breathing will increase oxygen demand and may detrimentally affect the myocardial oxygen supply/demand relationship.[14,15] Resultant myocardial ischemia may decrease compliance of the left ventricle (LV). The increasing pulmonary capillary pressure and decreasing lung compliance create a vicious cycle, as resistance and work of breathing increase further. Therefore, in patients with myocardial ischemia and some combination of high lung resistance and/or poor respiratory muscle function, spontaneous ventilation associated with an increase in the work of breathing is likely detrimental.

In severe congestive heart failure, positive pressure ventilation (PPV) would be expected to decrease venous return. Positive pressure ventilation is likely to increase PaO_2 by increasing lung volume and reducing right-to-left shunting (Qs/Qt). Although the effect of PPV on the normal ventricle would be to decrease cardiac output by decreasing LV filling (preload), the effect of PPV on a dilated failing LV operating on the flat (depressed) portion of the cardiac function curve will be different.[16,17] In this circumstance, a reduction in transmural aortic pressure and associated decrease in wall stress and afterload might increase stroke volume.

Guidelines:

1. In the presence of acute myocardial ischemia, choose modes of mechanical ventilation that minimize work of breathing.
2. When life-threatening hypoxemia accompanies severe congestive heart failure, consider the potentially beneficial effect of PPV on decreasing venous return and improving oxygenation.
3. Consideration should be given for assessment of the effect of PPV on hemodynamics.

Neuromuscular Disease: Patients with ventilatory failure due to neuromuscular disease (*eg*, Guillain-Barré syndrome; cervical spinal cord injury) typically have normal ventilatory drive and normal or nearly normal lung function.[18] Because the primary physiologic defect is ventilatory muscle weakness, these patients are predisposed to develop atelectasis (from inadequate lung inflation) and pneumonia (from impaired cough and mucociliary clearance).[19,20] Their main needs during ventilatory management are provision of adequate lung inflation and aggressive airway management.[21] There is no evidence that either PPV or negative pressure ventilation is superior in this situation.

These individuals are at less risk for barotrauma than patients with intrinsic restrictive or obstructive lung disease, and they frequently prefer large tidal volumes (*eg*, 12 to 15 ml/kg). Typically, they are also more comfortable with high inspiratory flow rates. Whether full or partial ventilatory support should be provided depends on the patient's capabilities and the disease process: a patient with a high quadriplegia (*eg*, C1-2) lesion needs full ventilatory support whichever mode is used, whereas partial ventilatory support may be appropriate for individuals with some ventilatory capability, particularly during recovery, as long as patient comfort is maintained.

Guidelines:

1. Large tidal volumes (12 to 15 ml/kg) with or without PEEP (5 to 10 cm H_2O) may be needed to relieve dyspnea. Adjust peak flow rate as needed to satisfy patient inspiration needs (≥60 L/min peak inspiratory flow will typically be required).
2. Use total or partial ventilatory support based on the patient's inherent ventilatory muscle strength.

Obstructive Airways Disease (OAD): Acute respiratory failure in patients with asthma and chronic OAD is associated with significant expiratory obstruction and hyperinflation. Resistance to inspiration is likely to be greater in the patient with asthma because of airway edema and mucus. Both patient groups benefit from mechanical ventilation settings that maximize expiratory time, thus decreasing end-expiratory lung volume (V_{EE}), intrinsic (auto) PEEP, and the risk for hemodynamic compromise.[22] With the same tidal volume, a higher V_{EE} would produce a higher end-inspiratory lung volume (V_{EI}) and a greater risk for barotrauma.[23]

The use of high inspiratory flow rates will maximize expiratory time and minimize V_{EE} and intrinsic PEEP (auto-PEEP, dynamic hyperinflation). This is accomplished, however, at the expense of higher peak airway pressure (PAP) in the central airways. Although PAP generated by increasing flow rate does not correlate closely with barotrauma as well as plateau pressure, the amount of central airway pressure that is actually transmitted to the alveolus (the actual risk factor for barotrauma) is difficult to judge. End-inspiratory plateau pressure with volume-cycled breaths rises as dynamic hyperinflation increases and may be reflective of increasing risk of barotrauma.

Guidelines:

1. No evidence exists that one ventilator mode is better than another for initial management of OAD. The clinician should choose a ventilator mode he or she is familiar with and has used successfully in this setting.
2. Adjust the peak inspiratory flow rate to meet patient demands.[24]
3. Monitor for and minimize dynamic hyperinflation (auto-PEEP). See Section 4, A-6.

a. It is desirable to utilize the least $\dot{V}_E$ that produces acceptable gas exchange and leads to the greatest expiratory time. Maneuvers likely to accomplish this goal are as follows:

i. Decrease in $\dot{V}_E$
ii. Increase in expiratory time
iii Acceptance of hypercapnia

b. When dynamic hyperinflation exists in the presence of patient-initiated mechanical ventilation, application of small amounts of ventilator-applied PEEP may be helpful in reducing the work of breathing (see Section 4, A-6). Application of ventilator PEEP above the level of initial auto-PEEP may lead to further hyperinflation and complications.

4. Based primarily on animal data and as discussed in the ARDS section, end-inspiratory plateau pressure is also a concern in OAD, as it reflects hyperinflation. We believe that attempts to maintain plateau pressure less than 35 cm H_2O are worthwhile even though the impact on patient outcome is unknown. In the acutely ill patient with OAD, measurement of plateau pressure usually requires sedation and paralysis.

5. Use of volume-cycled assist control ventilation in the initial treatment of the awake patient with OAD may be associated with significant risk of increasing hyperinflation and should be avoided.[25]

Asthma: 1. We believe that a high plateau pressure is predictive of hyperinflation of lung units in the patient with asthma. A high PAP may also predict hyperinflation. We recommend that plateau and peak pressures be minimized in patients with asthma. Unfortunately, PAP is significantly influenced by endotracheal (ET) tube size and inspiratory flows.

2. Accept an elevated $PaCO_2$, as long as pH can be maintained at an acceptable level.[26,27]

3. Paralysis and/or sedation may be necessary in some patients if the ventilation mode cannot be matched to the patient's needs (*ie*, patient "fighting" the ventilator). Following paralysis and/or sedation, a decrease in active expiratory effort may be associated with less airway collapse. The associated decrease in CO_2 production (especially of respiratory muscles) may also be advantageous in some circumstances. Paralysis is associated with acute and long-term complications.

COPD: 1. Mechanical ventilation of COPD patients with acute respiratory failure is unlikely to require high PAP or to present problems with CO_2 removal. In the presence of high PAP or difficulty in CO_2 removal in patients with COPD, coexisting abnormalities should be considered (pneumothorax, pulmonary edema, mucus plugging, high degree of bronchospasm).

2. Patients with chronic respiratory acidosis should have alveolar ventilation titrated to pH, not $PaCO_2$.

Postoperative Patients: Few patients require mechanical ventilatory support past the immediate postanesthetic period. However, residual anesthetic effects, usually due to narcotics or muscle relaxants, may require a variable period of mechanical ventilation. An anesthetic-induced decrease in FRC potentially coupled with thoracic or upper abdominal incision predisposes to atelectasis.[28,29] These patients with little or no significant lung disease may be optimally treated with relatively little difficulty. The greatest concern for the clinician is to avoid iatrogenic complications of ventilatory support, including infection, decreased cardiac output, prolonged support requiring unnecessary sedation, hyperventilation, inspissated secretions, and unnecessary exposure to potentially toxic high concentrations of inspired oxygen.[30,31] Often, patients are unnecessarily ventilated in the postoperative period because of the mistaken belief that mechanical ventilation *per se* is beneficial in establishing a more physiologic cardiopulmonary status. Thus, patients who have undergone major operative procedures involving the head, thorax, or abdomen may remain intubated and ventilated unnecessarily. Although prospective analysis has not determined whether such therapy has a significant rate of complication, to our knowledge, no prospective analysis has provided evidence of beneficial effects of such therapy. Future studies should be designed to determine which, if any, patients and/or surgical procedures require ventilatory support past the immediate anesthetic emergence period.

Unilateral Lung Disease: Patients with unilateral lung disease who require mechanical ventilation are infrequently encountered. Therapeutic efforts have included placement of double-lumen tracheal tubes to effect ventilation of each lung separately, positional changes of the patient, bronchial blockers, pneumonectomy, and alteration of inspiratory gas flows in order to improve overall lung function. Usually, such maneuvers ignore the effect of hypoxic pulmonary vasoconstriction on the affected lung and the physiologic principles underlying inflation of the lung during PPV. Were it not for the restricting effect of the rib cage and diaphragm on lung inflation, the unaffected lung would receive the preponderance of the positive pressure breath and/or increase in lung volume secondary to application of CPAP. However, in the presence of an intact thorax, lung inflation depends on increase in transpulmonary pressure, the difference between airway and intrapleural pressure. The individual with unilateral lung disease usually has a marked discrepancy in compliance between the two lungs. A lung with marked decrease in compliance will receive less volume for a given applied airway pressure. Therefore, the noncompliant lung will be ventilated less than will the normal, compliant lung. Should such patients experience significant arterial hypoxemia and/or hypercarbia, more aggressive means of ventilatory support must be considered, as with any type of advanced lung disease. These might include $ECCO_2R$, ECMO, high-frequency ventilation, etc. The ability of these interventions to alter outcome is not known. To date, split-lung ventilation[32,33] with a double-lumen tracheal tube[34] and differential application of positive airway pressure has likewise not been shown to improve morbidity and mortality.

Guidelines:

1. Initially utilize conventional ventilation techniques independent of presence of unilateral lung disease.

2. In the presence of difficulties in oxygenation, a trial of ventilation with the least involved lung in the dependent position is appropriate.

3. If PEEP is applied, initially utilize a single-lumen ET tube.

4. In cases of inability to oxygenate with traditional PEEP application, ILV with a double-lumen ET tube may be tried (synchronization of ventilation is not necessary). This mode of ventilation, however, has not been proved to alter outcome.

B. Discontinuation of Mechanical Ventilation

The consensus committee agreed there were many correct ways to discontinue patients from mechanical ventilation. There are a number of basic principles that are important in discontinuing ventilatory support and these are covered in Part 2 (Section 7). Specific recommendations are given below:

1. Whichever technique is used for discontinuation of ventilatory support, the clinician should know the signs of increasing ventilatory insufficiency and patient distress, and discontinue or modify the process if they appear, persist, or worsen:

(a) Increasing tachypnea: (*eg*, beyond a total rate of 30 to 35 breaths/min) associated with patient distress.

(b) Agitation, panic, diaphoresis, or tachycardia, unrelieved by reassurance and adjustment of the mechanical ventilation system.

(c) Acidemia: acute drop in pH to <7.25 to 7.30, associated with an increasing $PaCO_2$.

2. Excessive imposed work of breathing from demand valves or circuits, as indicated by substantial decreases in airway pressure during patient efforts, should be avoided during attempts at discontinuation of ventilatory support whether using a T tube or the ventilator circuit.

3. If intermittent mandatory ventilation (IMV) is used, the rate and degree of withdrawal of ventilatory support should be guided by pH, P_{CO_2}, total respiratory rate, heart rate, and signs of patient distress.

4. If pressure support ventilation (PSV) is used:

(a) The rate of reduction of the PSV level should be guided by total respiratory rate rather than by tidal volume. As a rule, respiratory rate should not exceed 30 breaths/min.

(b) If a patient can maintain adequate gas exchange and comfort level on a low level of PSV (*eg*, 5 cm H_2O), it is not necessary to reduce this to zero before extubation.

5. In patients in whom ventilatory support cannot be withdrawn successfully over a short period, a systematic approach should be taken to identify and treat contributing factors, such as the following:

(a) *Imposed loads* in the apparatus that increase work of breathing (*eg*, demand valves, small-diameter ET tubes).

(b) *Respiratory factors* (*eg*, bronchospasm, excessive secretions, pharmacologic depression of ventilatory drive, persistence of underlying disease, etc).

(c) *Nonrespiratory factors* (*eg*, cardiovascular dysfunction, increased metabolic rate, acid-base problems, hypophosphatemia, malnutrition, anxiety, etc).

6. In "difficult-to-wean" patients in whom discontinuation of ventilatory support occurs gradually over several days, it may be desirable to increase the level of support at night to enable the patient to rest effectively, as demonstrated by the ability to sleep.

7. Successful extubation requires the ability to protect the upper airway and clear secretions adequately in addition to successful discontinuation of ventilatory support. These factors should be considered and addressed both prior and subsequent to extubation.

Underlying Principles

Section 4: Physiologic Principles Relevant to Mechanical Ventilation

A. *Patient-Related Physiologic Principles*

The response to mechanical ventilation is governed by several physiologic relationships. Two cardinal rules apply:

1. Although the qualitative response of a given physiologic variable to manipulation of ventilator settings may be predictable, the quantitative response is highly variable and patient specific. Thus, an increase in PEEP or level of ventilation usually improves PaO_2 at a given FIO_2. However, the extent of improvement in any given patient may be large or small, and the short-term improvement may produce complications due to the higher pressures (barotrauma). Likewise, an increase in $\dot{V}E$ may be expected to result in a lower $PaCO_2$, but the amount of reduction may be large or small and must be balanced against the potential complications relating to the increase in ventilatory pressures.

2. A ventilator manipulation designed to improve one relation or variable may have undesirable effects on other equally important relations or variables. For example, an increase in PEEP may improve PaO_2 but adversely affect cardiac output, thereby negating the improvement in PaO_2 at the tissue level. Likewise an increase in $\dot{V}E$ to reduce P_{CO_2} may result in greater auto-PEEP or adverse effects on cardiac output. The extent of negative side effects of a given ventilator manipulation is, again, highly variable and patient specific. The physiologic relations that are most important to consider are as follows:

1. *Ventilation Perfusion ($\dot{V}/\dot{Q}$ Relations):* The PaO_2 obtained at a given FIO_2 is a function of the uniformity (homogeneity) of distribution of ventilation and perfusion to different lung units. Units with relatively low ventilation and high perfusion are associated with incomplete oxygenation and, hence, a low P_{O_2} for a given FIO_2. Units with no ventilation at all but which continue to receive perfusion contribute to shunting, which is one extreme of $\dot{V}/\dot{Q}$ inequality.

The distribution of ventilation among different units depends on the following:

(a) Whether the unit is aerated or not at end expiration; units that are air free at end expiration (due to atelectasis or fluid filling) require very high inspiratory pressures if they are to receive any ventilation at all.

(b) For aerated units, the distribution of ventilation is determined principally by regional compliance and resistance. Lung disease is invariably nonuniform, and this is the basic reason for the existence of serious $\dot{V}/\dot{Q}$ mismatching and for difficulty in oxygenation. On theoretical grounds, when the regional differences in mechanics are principally in resistance, distribution of ventilation should become more uniform with long inspiratory times (TIs) and with decelerating flow patterns. Conversely, where the nonhomogeneity involves regional compliances, shorter TIs and square flow pattern should result in more uniformity. Whether equalizing regional ventilation is good or bad for $PaCO_2$ is not entirely predictable, since improving $\dot{V}E$ of a poorly ventilated unit may or may not be beneficial, depending on the state of perfusion of that unit. It is also evident that by rendering the $\dot{V}E$ distribution more uniform, some units (usually the healthy ones) will receive less ventilation as the poorly ventilated units receive more. If perfusion is preferentially distributed to the former, overall $\dot{V}/\dot{Q}$ may worsen as distribution of $\dot{V}E$ is improved.

The regional distribution of perfusion is determined principally by regional resistances in blood vessels supplying and draining different units. Regional resistances are related to gravity (dependent units have lower resistance), vasomotor tone, and mechanical factors (*eg*, lung volume and anatomic narrowing). Regional alveolar pressure (more appropriately, regional transpulmonary pressure) plays a critical role. When transmitted regional alveolar pressure is higher than pulmonary artery pressure (PAP), perfusion is arrested (West zone 1).

For a given degree of $\dot{V}/\dot{Q}$ mismatching and FIO_2, PaO_2 is critically affected by mixed venous O_2 saturation (SvO_2); lower venous O_2 saturation is associated with lower PaO_2; SvO_2 is, in turn, dependent on cardiac output, metabolic rate, and hemoglobin.

From the standpoint of oxygenation, the primary beneficial effect of increased distending pressure (PEEP or greater tidal volume V_T) is the recruitment of nonfunctional or very poorly ventilated units. The benefit can be enhanced or mitigated through secondary and unpredictable effects on the following: (1) the distribution of ventilation to other units (by upward displacement of these units to more favorable or less favorable segments of pressure volume curve); (2) the distribution of perfusion (through effects on the relation between Palv and PAP and on lung volume [and hence vascular dimensions]); and (3) on mixed venous P_{O_2} (through effects on metabolic rate [less or more fighting, less or more work of breathing] or cardiac output).

2. *Relation Between Ventilation and $PaCO_2$:* The relation between minute ventilation ($\dot{V}_E$) and $PaCO_2$ is:

$$PaCO_2 = 0.863\ \dot{V}_{CO_2}/[\dot{V}_E\ (1 - V_D/V_T)]$$

where $\dot{V}_{CO_2}$ is CO_2 production in milliliters per minute STPD, a reflection of the metabolic activity of tissues, and V_D/V_T is equal to the tidal volume dead space ratio.

This equation emphasizes the fact that $PaCO_2$ is determined by the relationship between metabolic rate and ventilation, and not solely by the absolute level of $\dot{V}_E$. The bracketed term reflects the fact that not all breathed gas ($\dot{V}_E$) is useful for CO_2 exchange; only the fraction ($1 - V_D/V_T$) is effective.

In normal subjects, much of the dead space (V_D) is due to the volume of the conducting airways (anatomic V_D). Since this volume changes little with V_T, V_D/V_T tends to decrease as V_T increases and V_D/V_T rarely exceeds 0.3 (*ie*, 30 percent of V_T). In ventilated patients, particularly those with intrinsic lung disease, V_D/V_T can reach extremely high values (*eg*, 0.7 to 0.8) and V_D is principally related to ventilated but poorly perfused lung regions (alveolar V_D). In such cases V_D/V_T need not decrease with an increase in V_T since the higher alveolar pressure required to generate the larger V_T may increase alveolar V_D (increasing the amount of zone 1, see above). Thus, quantitatively, the change in $PaCO_2$ as V_T is increased may not be predictable. The response of P_{CO_2} to changes in $\dot{V}_E$ is further confounded by possible effects of changes in ventilator settings on metabolic rate (see above equation). Thus, a patient may become more relaxed (and hence lower $\dot{V}_{CO_2}$) or more agitated as ventilator settings are adjusted. Increases in V_D/V_T and $\dot{V}_{CO_2}$ should be considered whenever a change in $\dot{V}_E$ does not result in the expected change in $PaCO_2$ or whenever a large $\dot{V}_E$ is required to maintain a reasonable $PaCO_2$.

The above equation also emphasizes the effectiveness of accepting a higher $PaCO_2$ (permissive hypercapnia) or of lowering metabolic rate (*eg*, by sedation, paralysis) in reducing the required level of ventilation. A lower ventilation is usually associated with lower distending pressures. To the extent that high distending pressures contribute to barotrauma and negative hemodynamic consequences, permissive hypercapnia and reductions in metabolic rate may help reduce the complications of ventilatory support.

3. *Thoracic Pressures and Cardiovascular Function:* Blood returns to the thorax along a pressure gradient from peripheral vessels to the right atrium (RA). To the extent that intrathoracic pressure affects RA pressure, it may alter the gradient for venous return. Since cardiac output cannot be different from venous return, an increase in intrathoracic pressure will, all else being equal, tend to reduce cardiac output. This effect is enhanced in the presence of hypovolemia.

Right ventricular (RV) output can also be affected by changes in RV afterload. The latter is affected in a complex way by lung volume; an increase in lung volume tends to increase the resistance of alveolar vessels while decreasing the resistance of extra-alveolar vessels. The net effect on total resistance is unpredictable. Changes in RV afterload can aggravate or minimize the effect of changes in intrathoracic pressure on RA pressure.

Changes in intrathoracic pressure also affect LV function; a higher intrathoracic pressure acts to reduce LV afterload. Where poor LV function is limiting cardiac output, an increase in intrathoracic pressure may result in better LV emptying, with secondary consequences on RV afterload (decrease) and venous return (increase). Changes in lung volume may also reflexly affect peripheral vascular tone.

It is clear that effects of changes in ventilator settings on hemodynamics are complex. However, in general, cardiac output is adversely affected by increases in intrathoracic pressure; the actual response varies.

4. *Tissue Oxygenation:* One of the main objectives of ventilatory support is to ensure that tissues are provided with their O_2 requirements. The rate at which O_2 is delivered to the tissues (O_2 delivery [$\dot{D}_{O_2}$]) is a function of cardiac output ($\dot{Q}_T$), hemoglobin (Hgb), and O_2 saturation (SaO_2). Thus:

$$\dot{D}_{O_2} = 1.39\ Hgb \times SaO_2 \times Qt + 0.003 \times PaO_2$$

D_{O_2} represents the theoretical maximum for O_2 consumption by the tissues. In practice, tissues cannot extract all the delivered oxygen. As D_{O_2} is reduced, the tissues are capable of increasing the fraction extracted such that their O_2 needs are met. A point is reached, however, where the fraction of O_2 that can be extracted reaches a maximum level. As O_2 delivery decreases below this critical level, the O_2 needs of the tissues cannot be met. This state (O_2 extracted < amount warranted by metabolic activity) may ultimately result in tissue damage and can, theoretically, account for multisystem failure in critically ill patients.

This critical level of O_2 delivery is related to the metabolic activity of tissues (the higher the activity, the higher the critical $\dot{D}_{O_2}$) and to the maximum fraction that tissues can extract from delivered O_2. In disease, metabolic rate (*ie*, $\dot{V}_{O_2}$) is often high. There is also evidence that in some clinical states (notably sepsis), the maximum fraction that can be extracted is reduced. Both factors tend to raise critical $\dot{D}_{O_2}$.

Mechanical ventilation affects two of the main determinants of $\dot{D}_{O_2}$, namely SaO_2 and $\dot{Q}_T$. Often, ventilator measures that are aimed at increasing one variable cause an opposite change in the other (*eg*, PEEP may improve SaO_2 but concomitantly may reduce $\dot{Q}_T$). Where maintaining a reasonable PaO_2 (*eg*, >60 mm Hg) requires PEEP in excess of 10 cm H_2O, it is important to consider whether the net effect (after allowing for possible adverse effects on $\dot{Q}_T$) is beneficial (*ie*, increase in $\dot{D}_{O_2}$), whether the remaining benefit, if any, warrants the extra risk of high PEEP or FIO_2, and whether the same improvements in $\dot{D}_{O_2}/\dot{V}_{O_2}$ relation may not be accomplished less dangerously through reduction

in metabolic rate or by increasing hemoglobin.

5. *Respiratory Mechanics:* The pressure required to produce a given tidal volume (V_T) in a given time (T_I = inspiratory time) is a function of the elastic and resistive properties of the respiratory system. The elastic properties are defined by the static pressure-volume (P-V) relation. This relation is sigmoidal with the system being most compliant (lowest elastance) in the midvolume range and becoming substantially stiffer near the upper (total lung capacity [TLC]) and lower volume extremes. Normally, end-expiratory volume is at about 40 percent of vital capacity (VC), and tidal changes in volume occur in the middle, most compliant, range. In ventilated patients, the V_T may be located near the upper or lower extremes of the P-V curve where the system is naturally stiff. The former situation—V_T encroaching on TLC—occurs under two conditions: (1) when VC is extremely small as a result of severe intrinsic lung disease; here, the flat portion of the P-V curve might lie within the target V_T; and (2) in the presence of high PEEP (external or intrinsic) which increases FRC.

Tidal volume occurs in the stiff range near residual volume (RV) under two conditions: (1) with obesity and abdominal distention which force end-expiratory volume (the starting position for the next breath) to be in the low range of VC. In this case, the increased stiffness is partially related to chest wall stiffness and partially to alveolar collapse. A variable portion of the applied pressure is, therefore, dissipated across the chest wall and not the lung (*ie*, less likelihood of barotrauma for the same distending pressure); and (2) when airway or alveolar closure occurs at higher than normal volumes. In this situation, airway closure may occur within the V_T range, and this derecruitment causes the lung to appear stiffer.

When measured compliance (V_T/[plateau pressure minus end-expiratory pressure (total PEEP)]) is too low, it is important to ascertain whether this is in part due to the V_T cycling near one of the volume extremes and, if so, whether cycling is occurring near TLC or RV. This has important implications both in terms of identifying the underlying pathophysiology (is the increased stiffness due to structural changes [true stiffness or not?]) and in defining the ventilator strategy to be used to minimize barotrauma. This distinction can be made with simple manipulations of ventilator output while monitoring airway pressure. One simple approach is to decrease V_T for one to two breaths and then assess compliance with the smaller V_T. An increase in compliance as V_T decreases suggests that lung volume is near the stiff upper part of the P-V curve. An unchanged compliance indicates that V_T is cycling in the linear midrange. Conversely, if compliance decreases as V_T is lowered, volume is likely cycling near the stiff lower range of the P-V curve. In this case, addition of PEEP should improve the operating compliance (by raising end-expiratory volume toward the more compliant range). This should be helpful, particularly during weaning.

The conventionally measured compliance reflects the elastic properties of both chest wall and lung. A low measured compliance may be due to stiff lungs and/or a stiff chest wall or to as small fraction of the lung being ventilated (*eg*, ARDS). Increased lung stiffness is the predominant mechanism with intrinsic lung disease, with auto-PEEP, and where there is airway or alveolar closure in the V_T range (see above). Increased chest wall stiffness may be the predominant cause of decreased compliance with primary chest wall disease (*eg*, kyphoscoliosis) or where obesity or abdominal distention causes V_T to cycle near RV where the chest wall is naturally stiff (see above). Determination of the contribution of lung and chest wall to decreased compliance is possible only by concurrently (with airway pressure [Paw]) estimating pleural pressure using an esophageal catheter. Thus, if Paw during an inspiratory hold is 40 cm H_2O higher than end-expiratory pressure (PEEP) while the corresponding value from pleural pressures (Ppl) (*ie*, Ppl during plateau minus Ppl at end expiration) is 30 cm H_2O, then the lung contributes a quarter of the stiffness while the chest wall contributes three quarters, and so on. Where increased lung stiffness is the major reason for decreased compliance, the lung receives the brunt of the distending pressure and, all else being the same, the risk of barotrauma will theoretically be greater.

The other component to the distending pressure is that related to resistance. In ventilated patients, total resistance is made up of two components, ET tube resistance and resistance of the patient's airways. In many cases, ET tube resistance is the major component of total resistance. The resistance of the ET tube is not constant, but increases with flow rate. With the exception of obstructive diseases, the patient's resistance normalized for lung volume (specific resistance) is normally very small. In obstructive diseases, resistance is high and is often volume dependent, being higher at low lung volume. It should be remembered that the measured resistance value is determined by the size of the aerated compartment; thus, in ARDS (a condition in which the aerated capacity may be only one third of normal), the measured resistance value may be high, while the specific resistance is normal or low.

Whereas total elastance and total resistance determine the total distending pressure required to attain a given V_T in a given T_I, regional differences in respiratory mechanics can importantly influence the distribution of inhaled volume within the lungs. This may result in some lung regions becoming relatively overdistended even though total V_T may be reasonable. The regional distribution of V_T is affected in a complex way by the underlying reason for nonhomogeneity (*ie*, regional differences in resistance or compliance), T_I, and flow pattern.

The total distending pressure applied at any instant (Ptot) is the sum of pressure applied to overcome elastic recoil (Pel, a function of volume above passive FRC and the P-V curve), and the pressure applied to overcome resistive elements (Pres, a function of flow rate and resistance):

$$Ptot = Pel + Pres$$

In paralyzed or apneic patients Ptot is entirely supplied by the ventilator and Paw = Ptot. When the elastic and resistive properties are known, Ptot can be estimated. Any difference between Paw and Ptot is a reflection of the pressure generated by the patient. This approach can thus be utilized to assess the extent of patient effort and, hence, adequacy of ventilatory support.

6. *Dynamic Hyperinflation and Auto-PEEP:* Dynamic hyperinflation (DH) is defined as failure of lung

volume to return to passive FRC (volume at which elastic recoil equals external PEEP) prior to the onset of the next inspiration. Whenever this happens, alveolar pressure remains higher than external PEEP throughout expiration, and unless airways completely collapse, expiratory flow continues until the onset of the next inspiration.

Auto-PEEP is the difference between alveolar pressure and external airway pressure at end expiration. A difference (*ie*, auto-PEEP) will always exist whenever expiratory flow continues until the end of expiration (this is the gradient for flow). In the passive patient, such a gradient can only result from dynamic hyperinflation since alveolar pressure in this case reflects only passive elastic recoil; a gradient thus means lung volume did not return to passive FRC. In the patient with active expiratory muscles, alveolar pressure is also affected by the pressure generated by expiratory muscles. A gradient (auto-PEEP) can therefore exist even though volume is at, or even below, passive FRC. Auto-PEEP in the active patient does not necessarily signify the presence of DH and its magnitude is not an index of the magnitude of DH. This is important to recognize, since the physiologic consequences and management of auto-PEEP due to dynamic hyperinflation and to expiratory activity differ (see below). Expiratory muscle activity frequently exists in the presence of high respiratory drive and/or high expiratory resistance.

Dynamic hyperinflation develops in the setting of high expiratory resistance or expiratory flow limitation and is influenced by the compliance of the respiratory system, the volume from which exhalation begins, and the expiratory time. In ventilated patients, the delay in emptying may be patient related (obstructive diseases) or, very commonly, may be due to "plumbing" problems (narrow ET tube, kinking or water clogging of exhalation tube, poor exhalation valve, etc). Measurement of Paw during expiration helps to distinguish between problems intrinsic in the patient and ET tube, from problems within the external circuit (high Paw during exhalation points to the latter causes).

Auto-PEEP (DH, air trapping, intrinsic PEEP) has been described in many conditions (*eg*, COPD, asthma, ARDS) and can occur whenever $\dot{V}_E$ is relatively high. Dynamic hyperinflation most commonly occurs, however, in the setting of severe airflow obstruction. Here, the ventilation requirements may be modest, but expiratory resistance is often severalfold greater than its inspiratory counterpart.

The consequences of DH are related to the associated changes in lung volume and pleural pressure. (1) It causes V_T to cycle closer to TLC where compliance is low (see above). More distending pressure is required to attain the same V_T. (2) It interferes with triggering in the assisted mechanical ventilation or pressure support modes; the patient has to generate enough pressure to offset auto-PEEP plus trigger sensitivity before triggering occurs. (3) Because of 1 and 2, it increases the work of breathing during weaning attempts. (4) It affects hemodynamics in a manner similar to external PEEP. (5) It can cause overestimation of the pressure difference required for tidal ventilation and subsequent underestimation of the true compliance of the respiratory system.

Auto-PEEP in the absence of DH (*ie*, end-expiratory lung volume at or below passive FRC) does not cause V_T to cycle near TLC (in fact, it may have an opposite effect by reducing end-expiratory lung volume below passive FRC), has little effect on triggering, does not increase work of inspiratory muscles (in fact, it may spare inspiratory muscle work through sharing of total work between inspiratory and expiratory muscles), and does not result in underestimation of true compliance. In fact, where volume begins below passive FRC due to expiratory muscle activity, the opposite (overestimation of compliance) may occur. Administration of external PEEP under these circumstances serves no purpose and may make it more difficult for expiratory muscles to reduce lung volume.

In the passive state, and for a given degree of expiratory obstruction, the two variables that are most critical in determining extent of DH are total $\dot{V}_E$ and the inspiratory/expiratory (I:E) ratio. A higher $\dot{V}_E$ will cause more DH whether the high $\dot{V}_E$ is the result of a large V_T or high f. In the former case (larger V_T), more time is required to return lung volume to the passive FRC, whereas in the latter case (high f), less time is available to empty the same V_T. It is for this reason that reduction in $\dot{V}_E$ (through permissive hypercapnia or reduction in ventilatory demand) is one of the most effective ways of reducing DH. At a given f, the I:E ratio determines the time for delivery of the V_T. Higher values tend to increase auto-PEEP.

Measurement: Auto-PEEP should be suspected in all patients with airways obstruction or whenever the flow tracing demonstrates persistent flow at end exhalation. During *passive* ventilation (patient is not making respiratory efforts), auto-PEEP can be measured by comparing the end-expiratory airway occlusion pressure (easily measured in only a few currently available ventilators) with the set level of PEEP or by observing the amount of positive airway pressure required to initiate inspiratory flow. A helpful method for executing end-expiratory port occlusion in the passive patient uses the ventilator's inflation onset as the timing mechanism with a Braschi valve. Auto-PEEP can also be measured using plateau pressures. Operationally, plateau pressure is first recorded during a single cycle of volume-controlled ventilation at the usual ventilating frequency. (To avoid further hyperinflation, the end-inspiratory pause should not be applied for more than a single cycle.) Inflation is then prevented for approximately 20 s by a marked reduction in frequency, after which a single end-inspiratory plateau pressure is remeasured. The difference in plateau pressures is auto-PEEP.

Another similar method is first to measure the additional (dynamically trapped) volume released when a single routine tidal inflation is delayed by 20 to 30 s, and then to divide the measured trapped volume by respiratory system compliance. Under passive conditions, compliance is perhaps best judged by dividing the difference in static end-inspiratory ("plateau") pressures observed at two distinctly different V_T into that volume difference. This, however, is valid only if compliance is constant throughout V_T (*ie*, V_T is fully within the linear segment of the P-V curve).

In a passively ventilated patient, the effect of PEEP on lung and chest volumes can be accurately assessed by observing the peak dynamic or static airway pressures. Failure of these pressures to rise in response to adding PEEP indicates dynamic airway compression, flow limita-

tion, and potential benefit to the addition of PEEP.

Finally, when auto-PEEP results from dynamic airway compression, the least PEEP increment required to evoke a detectable increase in lung volume or peak cycling pressure is sometimes considered to be the pressure required to counterbalance the original level of auto-PEEP. This technique is invalid, however, when expiration is not flow limited (*ie*, when DH is due to a simple increase in resistance and not to flow limitation). Moreover, the applied pressure needed to counterbalance the "critical" pressure approximates only 75 percent to 85 percent of the auto-PEEP determined by expiratory port occlusion.

In patients with active respiratory efforts (*ie*, assist mode, PSV, etc) auto-PEEP can not easily be approximated by the end-expiratory occlusion, since expiratory muscle activity can influence the measured value. It can also be estimated as the esophageal pressure deflection required to initiate inspiration or to terminate expiratory flow. Interestingly, auto-PEEP estimated by this method is usually less than that measured by end-expiratory port occlusion. Although the reason for this disparity remains unclear, it has been argued that gas begins to flow into the lung when auto-PEEP in the least affected units has been overcome.

As indicated above, the auto-PEEP measured in patients with active respiratory efforts need not reflect dynamic hyperinflation. To our knowledge, there are currently no accepted methods of assessing the extent of DH in patients with active respiratory efforts. The use of external PEEP in these cases should be based more on clinical response to graded external PEEP (*ie*, more or less distress) than on the measured value of auto-PEEP.

7. *Respiratory Muscle Output and Endurance:* Laboratory studies have shown that inspiratory muscles fatigue when forced to generate pressures in excess of critical levels.[35] The critical pressure output above which fatigue occurs is a function of inspiratory muscle strength (*eg*, maximum inspiratory pressure). It is not clear whether fatigue occurs outside the laboratory setting, where inspiratory muscle output is spontaneously selected by the patient and not imposed (as in the laboratory). Nevertheless, the laboratory results point out the limited capacity of inspiratory muscles to sustain relatively high pressure outputs.

It is very difficult to assess the potential for fatigue in the ventilated patient. Whereas actual muscle output can be estimated through measurement of work of breathing, the pressure generated by muscle contraction or Pmus (see above), the denominator (maximum possible output) is difficult to determine. Furthermore, the critical fractions developed in the laboratory (*eg*, tension-time index >0.15) need not apply in the critically ill patient. So far, the best indication of whether the patient's muscles are overstressed remains the clinical impression of respiratory distress.

8. *Control of Breathing:* There is tremendous interindividual variability in the level of ventilation desired by patients (*ie*, ventilatory demand). The range extends from a few liters per minute (as in patients with chronic CO_2 retention) to >30 L/min (*eg*, in sepsis). High levels of ventilatory demand are related to high metabolic rate (muscle activity, fever), excessive V_D/V_T, or to a lower CO_2 set point where the patient targets a subnormal P_{CO_2} (metabolic acidosis, neural reflexes, central problems). In the presence of high $\dot{V}_E$ demand, high $\dot{V}_E$ output by the ventilator is required in order for the patient to feel comfortable. In turn, high $\dot{V}_E$ output by the ventilator translates into greater distending pressure (more volume and flow) and greater tendency for auto-PEEP. In patients with high ventilatory demands, every effort should be made to identify the mechanism and, if possible, correct it. Should the distending pressures required to maintain comfort remain excessive, forced reduction in ventilatory drive through sedation and, if necessary, paralysis (to reduce metabolic rate) may be appropriate. At present, there are insufficient data to indicate the precise pressures (or volumes) that must be avoided (see complications, Section 5-B).

B. *Ventilator-Related Physiologic Principles*

During spontaneous unassisted breathing, contraction of the diaphragm and other accessory muscles of inspiration results in a decrease in intrathoracic pressure, followed by a corresponding decrease in alveolar and airway pressures. These decreased pressures cause an increase in thoracic volume and the movement of a V_T into the lungs. Relaxation of ventilatory muscles returns these pressures and volumes to their resting levels. That is, the elastic recoil of the thoracic cage and of the lung increases intrathoracic pressure, causing an increase in alveolar and airway pressure, allowing exhalation of the V_T. During mechanical ventilatory assistance, the magnitude and the direction of these pressures may be grossly altered with potential adverse effects as outlined elsewhere in this text. As a result, the appropriate selection of gas delivery settings and monitoring of system pressures is likely important.

1. *Ventilator Settings:*

(a) *Volume*. In volume-targeted (*ie*, volume-cycled) ventilation, a machine-delivered V_T is set to be consistent with adequate gas exchange and patient comfort. The V_T selected in adults normally varies from about 5 to 15 ml/kg of body weight.[36,37] Numerous factors, such as lung/thorax compliance, system resistance, compressible volume loss, oxygenation, ventilation, and barotrauma, are considered when volumes are selected.[36] Of critical importance is the avoidance of localized overdistention.[38] This can generally be accomplished by selecting V_T that remain on the steep aspect of the P-V curve of the patient-ventilator system and by ensuring that peak airway and alveolar pressures do not exceed a maximum target.[37,39] Although controversy exists regarding specific target levels, many would agree that a peak alveolar pressure greater than 35 cm H_2O raises concern regarding the development of barotrauma and ventilator-induced lung injury increases.[37,40] With pressure-targeted (in pressure-limited) ventilation, delivered V_T varies depending on target pressure selected, system impedance, and the patient's spontaneous ventilatory pattern.

(ii) *Respiratory Rate*. Setting of mandatory ventilator gas delivery rate is dependent on the mode of ventilation selected, the delivered V_T, dead space to tidal volume ratio, metabolic rate, target $PaCO_2$ level, and level of spontaneous ventilation.[36] With adults, set mandatory rate normally varies between 4 and 20/min, with most clinically stable patients

requiring mandatory rates in the 8 to 12/min range;[36] in patients with either acute or chronic restrictive lung disease, mandatory rates exceeding 20/min may be necessary, depending on desired $\dot{V}_E$ and the targeted $PaCO_2$. Along with $PaCO_2$, pH, and comfort, the primary variable controlling the selection of mandatory rate is the development of air trapping and auto-PEEP.[22] As with the selection of most ventilator settings, development of air trapping should be avoided because of its effect on $\dot{V}/\dot{Q}$ matching, work of breathing, and barotrauma.[22,41]

(iii) *Flow Rate*. The selection of peak inspiratory flow rate during volume-targeted ventilation is primarily determined by the level of spontaneous inspiratory effort. In patients triggering volume-targeted breaths, patient effort, work of breathing, and patient ventilator synchrony depends on the selection of peak inspiratory flow.[42] Peak inspiratory flows should ideally match patient peak inspiratory demands. This normally requires peak flows to be set at 40 to 100 L/min, depending on $\dot{V}_E$ and drive to breathe. During controlled ventilation, peak flows may be set lower than 40 L/min in order to establish a specific T_I. With pressure-targeted ventilation, the peak inspiratory flow is determined by the interaction of the set pressure, respiratory resistance, and patient effort. The specifics of how *quickly* the pressure target is reached is defined by the manufacturer.

(iv) *Inspiratory Time/I:E Ratio*. The selection of a specific T_I and I:E ratio is generally based on hemodynamic response to ventilation, oxygenation status, and level of spontaneous breathing. In spontaneously breathing patients, gas delivery should be coordinated with patient inspiratory effort to ensure synchrony. This normally requires about 0.8 to 1.2 s and an I:E of about 1:2 to 1:1.5.[43] During controlled mechanical ventilation, T_I or I:E ratios may be lengthened in order to elevate mean airway pressure (MAP) and enhance oxygenation.[44] When lengthening T_I and I:E ratios, the impact of these alterations on the cardiovascular system must be carefully monitored. The primary factors limiting increases in both T_I and I:E ratios are patient discomfort, the need for sedation, the development of auto-PEEP, and hemodynamic compromise.[44]

(v) *Flow Profile*. Few data identifying differing physiologic responses to inspiratory flow profiles are available when adjusted for the same V_T and T_I/T_{TOT}.[45,46] Essentially no differences exist among square, decelerating, and sine wave delivery profiles in terms of gas exchange or work of breathing, and these approaches appear to be equally acceptable in the majority of patients requiring ventilatory support, provided that the mean flow rate is adequate. To our knowledge, no data supporting the use of an accelerating flow pattern are currently available. Selection of flow profile is available only in volume-targeted approaches to ventilation. With all pressure-targeted modes, an exponentially decelerating pattern is normally established as the ventilator attempts to rapidly achieve the pressure target set and to maintain the target constant throughout the inspiratory phase.

(vi) *Sensitivity*. Since mechanical ventilators and artificial airways impose a resistive load on the spontaneously breathing ventilator-assisted patient, ventilator-trigger sensitivity should be set at the most sensitive level that prevents self-cycling. Generally, this is -0.5 to -1.5 cm H_2O. Recently introduced flow cycling systems are generally more efficient than pressure cycling approaches, but the clinical significance of this is unclear.[2,47] These systems should also be set at maximum sensitivity (1 to 3 L/min).

(vii) *FIO_2*. The selection of the FIO_2 is dependent on the target PaO_2, PEEP level, MAP, and hemodynamic status. In general, as a result of concerns regarding the effect of high FIO_2s on lung injury, the lowest acceptable FIO_2 should be selected. However, the effect of FIO_2 on lung injury must be balanced by the effect of airway and alveolar pressures on lung injury. In those patients who are most difficult to oxygenate, FIO_2 can be minimized by optimizing PEEP and MAP, by deep sedation with or without pharmacologic paralysis, and by lowering the minimally acceptable SaO_2 to <90 percent while ensuring adequate cardiac output.[48]

(viii) *PEEP*. Positive end-expiratory pressure is applied to recruit lung volume, elevate MAP, and improve oxygenation.[49] PEEP may decrease venous return and preload of the LV,[50] as well as decreasing the triggering work of breathing caused by auto-PEEP.[41] The optimal level of PEEP depends on the desired physiologic response. In ARDS, PEEP level is established in conjunction with FIO_2 and T_I settings to establish a target PaO_2 (SaO_2) or O_2 delivery. Although it is difficult to identify an upper limit for PEEP in this setting, most would agree that the lower limit should be at or above the lower inflection point on the P-V curve in the early phase of acute lung injury.[51] This is generally a PEEP level of about 8 to 12 cm H_2O. As with any pressure, avoidance of high PEEP levels is desirable.

2. *Pressure Measurements:* During the delivery of a positive pressure breath, system pressure can be measured in a number of locations (internal to the ventilator, at the airway opening, and at the carina). The farther away the measurement is from the alveoli, the greater the possible difference from actual alveolar pressure. During patient triggering, alveolar pressure is more negative than carinal pressure, which is more negative than airway opening pressures, which are more negative than internal ventilator pressures.[52] Because of resistance to gas flow during a positive pressure breath, pressure measured internal to the ventilator is greater than airway opening pressure, which is greater than carinal pressure, which is greater than alveolar pressure.[52] Pressure measured at all of these locations is only equal during periods of zero flow.

(i) *Peak*. Peak pressure is the maximum pressure obtainable during active gas delivery. In volume-targeted ventilation, peak pressure is dependent on both compliance and airways resistance, as well as V_T, peak flow, and flow pattern. For a given compliance and airway resistance, higher peak flow results in higher PAP. Generally, with all other variables equal, an accelerating flow profile results in a higher PAP than any other profile, since the highest flows are delivered with this pattern at end inspiration. With pressure-targeted ventilation, the peak inspiratory pressure is approximately equal to the target pressure. However, because of the high initial flow and the decelerating flow pattern in pressure-targeted ventilation, the initial system pressure may exceed the pressure target by about 1 to 3 cm H_2O.

(ii) *Plateau*. This is normally defined as the end-inspiratory pressure during a period of at least 0.5 s of zero gas

flow.[43] It should be measured on the first breath after the setting of an inflation hold and requires passive ventilation. The plateau pressure is the pressure required to counterbalance end inspiratory forces and roughly approximates the average peak alveolar pressure. With pressure-targeted ventilation, the pressure target approximates to the plateau (alveolar) pressure if a period (0.5 s) of zero delivered gas flow is observable.

(iii) *Mean.* The system pressure averaged over the entire ventilatory period is defined as the MAP. Because expiratory resistance usually exceeds inspiratory resistance,[53] MAP as displayed on monitoring devices almost always underestimates mean alveolar pressure (MalvP) to some extent.[44] The MalvP can be estimated from the MAP by the following formula:

$$MalvP = (\dot{V}_E/60)(R_E - R_I) + MAP$$

where R_I and R_E are inspiratory and expiratory resistances, respectively. Provided sufficient PEEP is applied to seek out recruitable lung units, oxygenation and MAP demonstrate a predictable and quantifiable direct relationship.[44]

(iv) *End-Expiratory.* This is the airway pressure at the termination of the expiratory phase, normally equal to atmospheric or the applied PEEP level. However, in patients with prolonged expiration or short expiratory times, end-expiratory alveolar pressure may be further elevated as a result of the development of auto-PEEP. Alveolar and airway pressures are not the same unless periods of no-flow are established. That is, end-inspiratory airway pressure normally exceeds alveolar pressure because of resistance to gas flow, whereas end-expiratory alveolar pressure may exceed airway pressure because of the development of auto-PEEP and MalvP always exceeds MAP.

3. *Machine Problems:*

(i) *Demand Valves.* In all assisted modes of ventilation, the patient must activate gas delivery. This requires a pressure differential sufficient to trigger the ventilator. Once triggering occurs, sufficient gas flow must be provided to meet inspiratory demand. Both of these processes impose work on the patient. The amount of effort required to activate any given ventilator varies greatly and is generally greater with pressure triggering than flow triggering.[54] The addition of PEEP or CPAP may increase imposed work because of the adjustments the ventilator must make to maintain PEEP/CPAP during spontaneous breathing.[55] Although the work imposed by these systems is generally minimal, total imposed work of breathing can be significant when demand valves are considered in series with the work imposed by ET tubes and humidifier systems.

(ii) *Humidifiers.* Three different types of humidifiers are used during mechanical ventilation: bubble-through, passover, and artificial noses. Of these, the passover humidifier is the only one that does not have the potential to impose added work of breathing. Bubble-through humidifiers have minimal effect on imposed work of breathing if the machine sensing of patient effort is on the expiratory side of the circuit or at the circuit "Y." However, if patient effort is sensed on the inspiratory side, imposed work of breathing may be markedly increased because of the need to create a pressure gradient across the humidifier.[55] Artificial noses represent a resistance load placed in series with the ET tube and demand valve.[24] Their effect on work of breathing is dependent on length of use, patient ventilatory drive, and design of the valve.[56] In general, artificial noses should not be used in patients with marked ventilatory muscle dysfunction, particularly if small-sized ET tubes are used and if the development of auto-PEEP is an ongoing issue. Regardless of humidifier used, it should be able to establish at the carina a temperature of 30° to 32°C with an absolute humidity of 30 mg.[57]

(iii) *Apnea Ventilation.* Many ventilators do not incorporate backup apnea ventilation during pressure support or CPAP breathing. As a result, careful setting of low respiratory rate, low V_T, and low minute volume alarms are critical for the safe application of these modes of ventilation. In ventilators where apnea ventilation is available, apnea of definable time periods results in the provision of a backup control mode volume-targeted approach to ventilation. Resumption of spontaneous breathing or practitioner intervention reestablishes the original ventilatory mode.

C. *Patient-Ventilator Interactions*

The use of a mechanical ventilator often superimposes a clinician-selected pattern of ventilation on the patient's natural breathing rhythm. Under these circumstances, certain interactions between patient and ventilator will occur. These fall into two categories: (1) the response of the mechanical breath delivery system to patient efforts; and (2) the response of patient efforts to ventilator settings.

1. *Response of the Breath Delivery System to Patient Efforts:* If the ventilatory demands of the patient do not coincide with the quantity (or quality) of ventilation provided by the ventilator, patient-ventilator dyssynchrony can impose an inspiratory muscle load. This, in turn, leads to increased oxygen consumption of the respiratory muscles and patient discomfort, which is diagnosed as the patient "fighting" the ventilator. This detrimental patient-ventilator interaction may be due to the patient's "inappropriately" high ventilatory drive or to inappropriate ventilator settings or circuits. If the clinician determines that this problem is due to "inappropriate" patient demands, it may be appropriate to use sedation or paralysis to eliminate patient respiratory effort. Conversely, the problem may relate to the ventilatory mode or ventilator setup being used. These detrimental interactions between patient and ventilator can occur during any of the following phases of breath delivery.

(i) *Triggering.* Triggering is the initiation of gas delivery. Significant imposed ventilatory muscle loads can be imposed by insensitive or unresponsive triggering[54,58] systems. In addition, the presence of auto-PEEP,[41,59] narrow ET tubes,[60] obstructed airways, and stiff parenchyma[61] will serve to magnify the insensitivity or unresponsiveness of the triggering system. Attempts to maximize trigger sensitivity and responsiveness through demand valve adjustments or through the counterbalancing of auto-PEEP with applied PEEP are appropriate. Unfortunately, oversensitive valves can result in spontaneous ventilator cycling independent of patient effort.

(ii) *Gas Delivery.* Gas flow from the ventilator is governed (or limited) by a set flow (flow limited) or set pressure (pressure limited) on most ventilators.[62] Any patient effort during flow-limited breaths will only result in a decrease in airway pressure since additional flow above what is set is not

available.[63,64] This can produce a significant imposed load on the ventilatory muscles. In contrast, any patient effort during a pressure-limited breath will result in an increase in flow but no change in airway pressure.[65,66] A patient's flow demands are thus theoretically more readily met by a pressure-limited breath strategy.[61,65] The capability of adjusting the rate of rise of airway pressure during pressure-limited breaths further enhances control of this variable.[67,68]

(iii) *Cycling*. On current systems, gas delivery can be terminated by set volume, set time, or set flow.[68] With volume or time cycling, continued patient effort is ignored by the machine and this can lead to the patients pulling against a closed inspiratory flow valve. Conversely, active expiratory efforts by the patient with volume or time cycling result in elevation in airway pressure that can result in automatic breath termination in association with a high pressure alarm limit. Flow cycling gives the patient more control than breath cycling.[62,65,66] Usually flow cycling is set to occur at 25 percent of peak flow. Increasing patient effort can thus delay cycling such that more gas is delivered. Conversely, decreasing efforts (or even initiation of expiratory efforts) cause these flow criteria to be met earlier and thus a smaller volume of gas is delivered over a shorter period. Synchrony between end of patient effort and end of pressure limiting is, however, not assured even with flow cycling.[68] Depending on the strength of patient efforts vs set pressure on respiratory mechanics and on the flow level at which cycling occurs, pressure may continue beyond the patient's inspiratory effort (thereby interfering with expiration) or may terminate prematurely before end of patient effort.

2. *Response of Patient Efforts to Ventilator Settings:* Ventilator settings, such as V_T, flow rate, and pattern with flow-limited volume-cycled breaths, or the pressure level and rate of pressure rise with pressure-limited breaths are capable of the following: (1) altering the activity of mechanoreceptors in the airways, lungs, and chest wall; (2) altering blood gas tensions; and (3) eliciting respiratory sensations in conscious or semiconscious patients.[65,69] In turn, these can alter the rate, depth, and timing (T_I,T_E) of respiratory efforts through neural reflexes, chemical control (chemoreceptors), and behavioral responses. These changes in patient effort may modify expected responses to changes in ventilator settings. These modifications may take several forms, including the following: (1) failure of $\dot{V}_E$ or V_T to change in the expected direction or to the expected magnitude as ventilator settings are changed to increase or decrease these variables; (2) periodic breathing, with periods of apnea, as P_{CO_2} cycles around the CO_2 set point; (3) loss of synchrony between patient and ventilator; and (4) changes in ventilatory demand (increase or decrease) as a result of altered level of consciousness (following a change in ventilator settings) or of changes in mechanoreceptor output (acting via reflex or behavioral mechanisms). There are very few systematic studies on the effect of various changes in ventilator settings on pattern of patient effort. This information is needed particularly with the current shift in emphasis from controlled ventilation methods to patient-interactive methods (*eg*, PSV).

Section 5: Complications of Mechanical Ventilation

Although mechanical ventilation offers vital life support, its use can result in untoward or life-threatening side effects.[70] Many such hazards can be modified or avoided by appropriate attention to the technique of implementation. Interventions associated with mechanical ventilation include airway intubation, application of positive pressure to the respiratory system, provision of supplemental oxygen, imposition of unnatural breathing patterns, and the administration of sedative or paralytic agents.

A. *Complications of Airway Intubation*

Endotracheal intubation is usually performed transnasally or transorally. The nasal route provides a more stable artificial airway and allows mouth closure, improving comfort in some patients. However, a bleeding diathesis is a contraindication to nasal intubation. Moreover, because a nasal tube is generally smaller than its oral counterpart, it presents greater flow resistance and may impede extraction of retained secretions from the central airways.[71] Sinusitis is a potential complication of ostial occlusion and impeded drainage by the nasal tube.

The artificial airway allows potential pathogens to enter the trachea from the external environment, dramatically increasing the risk of nosocomial pneumonia.[70,71] Moreover, disruption of the coughing mechanism and mucociliary escalator encourages retention of airway secretions. Endotracheal tubes prevent aspiration of gross particulates, but permit pharyngeal secretions to enter the trachea via the interstices of the balloon cuff, frequently resulting in tracheal colonization and increasing the risk of nosocomial pneumonia.

Tube misplacement and dislocation occur frequently. Although intubation of the right or (less frequently) left main bronchus most commonly occurs at the time of intubation, head movement may cause the tube orifice to migrate 2 cm in either direction from its neutral position along the tube axis. Overdistention of the ventilated lung and hypoventilation or atelectasis of the nonintubated lung are especially likely to occur in the heavily sedated patient receiving PPV. Hypoxemia, barotrauma, and cardiovascular compromise may result. Inadvertent extubation is among the most dangerous complications associated with mechanically ventilating a physiologically unstable patient; consequently, disoriented and uncooperative patients should be made as comfortable as possible, but they should be securely restrained.

Glottic injury often occurs during unusually difficult or emergency intubation. Glottic edema and minor erosive lesions of the vocal cords occur commonly during prolonged intubation. Postextubation glottic dysfunction and lasting damage to the vocal cords may occur, especially among women and among those patients in whom large tubes are placed. Risk factors for tracheal erosion, glottic stenosis, tracheal dilatation, and tracheomalacia are not precisely defined; however, cuff pressures that exceed capillary perfusion pressure (≅25 cm H_2O) are likely to cause ischemic ulceration and more advanced forms of mucosal damage.[71] In the absence of reliable guidelines to indicate optim

timing, most practitioners reserve tracheostomy for those patients who are not making clear and steady progress after 2 to 3 weeks of therapy or for those with suspected abnormality of the upper airway. Tracheostomy affords reduced V_D, partially restores glottic function, improves secretion clearance, enhances comfort, and holds the potential to allow both oral feeding and verbal communication. It may be associated, however, with life-threatening complications such as tracheal erosion, tracheo-innominate artery fistula (hemorrhage), and extraluminal migration of the tube orifice in the early postoperative period. Stomal granulation or stenosis are frequent problems after decannulation.

B. *Complications of PPV*

During PPV, the lungs and chest wall distend, intrathoracic pressure rises, and the lungs are often exposed to high inspired fractions of oxygen. In the setting of ARDS, for example, PaO_2 is improved by providing high fractional concentrations of inspired O_2 and by raising mean and end-expiratory alveolar pressures. Each of these interventions has an associated risk-benefit ratio. Although considerable experimental data have been accumulated, detailed clinical information is not yet available regarding which oxygen concentrations, pressures, and ventilation patterns are safe to apply for extended periods.

1. *Barotrauma:* For adult patients, flow-limited, volume-cycled ventilation using large V_Ts (10 to 15 ml/kg), rapid inspiratory flow rates, and PEEP when needed to adjust lung volume has previously been the standard of practice in managing most problems of ventilatory support.[72] Widely held objectives of ventilation have given priority to "normalizing" arterial blood gas values and ensuring adequate oxygen delivery. Until recently, respiratory system pressures have been monitored, but not tightly constrained.

There is little doubt that high ventilating pressures and excessive *regional* lung volumes are damaging. All forms of barotrauma that have been described previously in the pediatric literature, including interstitial and subcutaneous emphysema, pneumomediastinum, pneumoperitoneum, pneumopericardium, pneumothorax, tension cysts, systemic gas embolism, and damage similar to bronchopulmonary dysplasia, have now been recognized in adult patients, as well. Susceptibility to barotrauma may vary with the stage of the disease process; pressures well tolerated during the earliest stage of illness may prove excessive later on.[73] Many forms of barotrauma occur with increased frequency after ventilation for extended periods, especially in patients with ARDS.

It has been shown in a variety of animal models that ventilation with high V_Ts or high PAP can induce or extend acute lung injury.[74-80] In previously normal lungs, such damage is characterized by granulocyte infiltration, hyaline membranes, and increased vascular permeability. Fibroblast proliferation follows over a period of days.[79] Such lung injury occurs with peak inspiratory pressure (PIP) as low as 30 cm H_2O in normal sheep,[81] and with PIP as low as 20 cm H_2O in rabbits whose lungs have been lavaged with saline solution.[79] There are also suggestions from the experimental literature that ventilatory pattern influences the incidence and severity of injury, but further evidence is needed, and an optimal pattern has not been defined.[79]

Although ARDS has previously been considered a problem of *diffuse* lung injury and a generalized increase of tissue recoil, it now appears that the radiographic, densitometric, and mechanical consequences of ARDS are heterogeneous.[36,82] In severe cases, the inflation capacity of the lungs may be less than one third of normal.[36] The compliance and fragility of tissues comprising the aerated compartment in patients with ARDS may be closer to normal than previously envisioned, especially in the earliest phase of this disease. It is currently believed that ventilatory patterns that apply high transalveolar stretching forces cause or perpetuate tissue edema and damage.[74-76,79] Some experimental data suggest that large V_Ts, themselves, may also extend tissue edema, independent of the maximal pressure to which the alveolus is exposed.[75,80] It is not clear, however, that large V_Ts are injurious when peak alveolar pressures are kept below 35 cm H_2O and sufficient PEEP is used to prevent widespread alveolar collapse and thereby maximize respiratory system compliance. Use of small V_Ts that avoid tissue overdistention and the acceptance of any consequent elevation of $PaCO_2$ (permissive hypercapnia) have been suggested to minimize the risk of barotrauma in patients with asthma and ARDS.[37,83,84] Although it remains unproved, some data suggest that periodic inflations with a relatively large volume may be needed to avert collapse of unstable lung units when very small V_Ts and low levels of PEEP are used.[77,79,85] In animal models, recruitment of lung volume by adequate amounts of PEEP can substantially reduce the ventilator-associated lung injury resulting from high PIP.[77,80] As yet, such application has not been shown to have a similar benefit in patients.

Strategies that prevent the exposure of the lung to high pressures (limiting overdistention) and those that lower the $\dot{V}_E$ requirement may be associated with less ventilator-induced tissue injury and improved outcome. Such approaches include permissive hypercapnia,[37,84] pressure-controlled ventilation,[86] and pressure-limited, volume-cycled ventilation.[87] Based on the experimental literature, maximal transalveolar pressure should not exceed 30 to 35 cm H_2O during each tidal cycle.[74,75,79] (This usually corresponds to 35 to 45 cm H_2O end-inspiratory static [plateau] pressure, depending on chest wall compliance.) In certain experimental settings, even pressures lower than this have been associated with tissue injury, especially when applied for extended periods. It may be desirable to allow spontaneous ventilatory efforts whenever it is possible to do so without incurring an excessive breathing workload or unbalancing the $\dot{V}O_2/\dot{D}O_2$ relationship. These modes, which include intermittent mandatory ventilation (IMV), pressure support, airway pressure release ventilation (APRV),[88] bi-level airway pressure, intermittent mandatory pressure release ventilation (IMPRV),[89] CPAP,[90] and various modes applied without airway intubation (noninvasive ventilation), tend to reduce maximal transalveolar pressure but do not guarantee a reduced incidence of barotrauma.

Adjunctive measures to conventional ventilation aimed at enhancing tissue oxygen delivery or increasing CO_2 removal (extracorporeal [$ECCO_2R$] or intracaval [IVOX] gas exchange[91] tracheal gas insufflation,[92] high-frequency ventilation [HFV]) decrease the exposure of the lung to high pressures (and volumes) and may, at times, allow better gas

exchange than is otherwise possible. The success of these hazardous methods depends heavily on the skill with which they are applied. At the present time, their utility for general medical practice must be considered unproved.

2. *Oxygen Toxicity:* High fractions of inspired O_2 (FIO_2) are potentially injurious when applied over extended periods.[88] In the laboratory setting, tissue injury depends on the FIO_2 and the duration of exposure. Because alveolar injury is an exponential function of inspired oxygen concentration (FIO_2), even modest reductions in FIO_2 over the range of 0.6 to 1.0 may attenuate tissue damage. There is no convincing evidence that sustained exposure to $FIO_2 \leq 0.5$ causes tissue injury, and for practical purposes, most clinicians do not attempt aggressive measures to reduce FIO_2 (*eg*, vigorous diuresis, inotropic pharmacotherapy, high levels of PEEP, experimental modes of ventilation, or adjunctive support) until the inspired O_2 concentration exceeds approximately 0.60. The combinations of O_2 concentration and duration of exposure that produce significant damage have not been firmly established in the setting of critical illness, and may well vary with disease type, severity, and individual susceptibility.

3. *Cardiovascular Complications:* Ventilatory support can help restore the balance between DO_2 and O_2 consumption when it alleviates an intolerable breathing workload. Conversely, PPV often impairs cardiac output by disturbing the loading conditions of the heart, as described earlier in Section 4, A-3.[93]

Mean lung volume or MalvP correlates best with the tendency of a given ventilatory pattern to cause hemodynamic compromise. *Under conditions of passive inflation,* MAP (as a clinically measurable reflection of MalvP) relates fundamentally to oxygen exchange, cardiovascular performance, and fluid retention.[44,94] The importance of each effect varies greatly in different patients. Mean airway pressure can be raised by adding PEEP, by extending the inspiratory time fraction (increasing I:E ratio), or by increasing $\dot{V}_E$. The tendency for an elevation of MAP to compromise hemodynamic performance is heightened by impaired cardiovascular reflexes and depletion of intravascular volume. The proportion of the alveolar pressure transmitted to the pleural space is determined by the relative compliances of the lung and chest wall:

$$\Delta Ppl = \Delta Palv \times (Cl/[Cl + Cw]).$$

Therefore, the hemodynamic effect of a given increment in MalvP will be accentuated when the lungs are relatively compliant and/or the chest wall is stiff. Hemodynamic consequences are predictably less when the patient makes spontaneous breathing efforts. For these reasons, dynamic hyperinflation occurring in a passively ventilated patient with severe airflow obstruction produces auto-PEEP that is particularly likely to cause hemodynamic compromise.[22,95] Auto-PEEP can be attenuated by reducing $\dot{V}_E$ or by reducing I:E ratio, thus increasing expiratory time.

Limiting tissue demand for oxygen and maintaining effective cardiovascular function are essential to an effective ventilation strategy. Recent studies suggest that survival in overt sepsis and sepsis syndrome correlates with oxygen delivery.[96,97] At the time of this writing, however, it is not clear whether therapeutic interventions that attempt to maximize O_2 delivery (when it is already in the normal range and there are no overt signs of tissue hypoxia) or avoid depression of cardiac output improve outcome. Maximizing O_2 delivery may require expansion of intravascular volume, an intervention that has been associated with adverse outcomes in patients with acute lung injury.

4. *Breathing Effort and Patient-Ventilator Asynchrony:* The use of mechanical ventilation superimposes a clinician-selected pattern of ventilation on the patient's natural breathing rhythm. Circuits that impose substantial resistance and machines that respond poorly to the flow demands or cycling cadence of the patient may result in dyspnea and an unnecessary breathing workload. Factors that have been shown to increase the breathing workload during partial ventilatory support include ET tube resistance, excessive triggering threshold or response delay, insufficient flow capacity of the ventilator to meet peak patient demands, and the development of dynamic hyperinflation. The latter gives rise to auto-PEEP, which depresses the *effective* functional triggering sensitivity and may contribute to intermittent failure of the machine to respond to patient effort.[98] Inappropriately slow inspiratory flow rates may cause the patient to enter the expiratory phase of the tidal cycle before the volume-cycled breath from the machine has been completed, often resulting in conflict between the natural and the imposed breathing rhythms. The magnitude and importance of these effects is a direct function of $\dot{V}_E$.

Pressure-limited modes of ventilation (*eg*, pressure support) are theoretically unlimited with respect to meeting maximal flow demands; however, this ideal is seldom accomplished in practice. Such modes often present important problems of their own for the vigorously breathing patient. Pressure support, for example, although invaluable for overcoming ET tube resistance and for assisting the patient with moderate ventilatory requirements, is not well suited to the needs of a patient breathing at a rapid cycling frequency, one with variable ventilatory requirements, or one who has a very high airway resistance (especially from a very small ET tube). Tidal volume can fall dramatically as frequency increases, especially in patients with airflow obstruction. Moreover, a fixed level of pressure support cannot compensate for a change in ventilatory impedance or the development of auto-PEEP. A patient who requires a high level of pressure support when breathing at a rapid rate may find the applied level of pressure excessive when the ventilatory requirement abates.

C. *Adverse Effects of Sedation and Paralysis*

Sedation and paralysis are often required to allow patient comfort and to facilitate the imposition of ventilatory patterns (*eg*, inverse ratio ventilation [IRV]) which would otherwise conflict with the patient's own ventilatory pattern. Sedation may result in vasodilation that contributes to hypotension and reduced cardiac output. Paralytic agents immobilize the patient, encouraging secretion retention, atelectasis, and muscle wasting. With breathing efforts prevented, such patients are totally dependent on the ventilation set by the clinician and provided by the machine. Inadvertent disconnection of the ventilator circuit can prove

rapidly catastrophic in this setting. Certain neuromuscular-blocking agents have been recently associated with neuromuscular weakness that persists long after withdrawal of drug treatment.[99] At present, it is not certain whether such effects relate primarily to the nature, dose, or duration of the drug, to synergism with corticosteroids, or to the depth of paralysis itself.

D. *Other Complications*

Among the wide variety of noncardiopulmonary complications that have been described for mechanical ventilation, perhaps the most important involve mental distress and dysfunction of the renal, gastrointestinal, and central nervous systems. Psychological distress during mechanical ventilation is exceedingly common, for reasons that include (but are not limited to) sleep deprivation and impaired sleep quality, pain, fear, inability to communicate, and the use of drugs (*eg*, benzodiazepines) with dissociative properties.

Renal dysfunction during PPV is believed to be a consequence of reduced circulating blood volume. This tends to alter perfusion of the renal parenchyma, redistribute intrarenal blood flow, release antidiuretic hormone, or inhibit atrial natriuretic peptides. In any event, reduced free water clearance and generalized fluid retention are commonplace during ventilation with high pressures.

Gastrointestinal consequences of mechanical ventilation include gut distention (due to air swallowing), hypomotility, and obstipation (due to pharmacologic agents and immobility), vomiting (due to pharyngeal stimulation and motility disturbances), and mucosal ulceration and bleeding. Serious dysfunction of the liver that occurs as a direct consequence of mechanical ventilation is rare. However, PEEP has been associated with hyperbilirubinemia and mild elevations of liver enzyme levels in the serum, possibly related to altered hepatic perfusion and impeded venous and biliary drainage.

Increased intrathoracic pressure can elevate jugular venous and intracranial pressures, and thereby reduce cerebral perfusion pressure. Such effects assume particular importance in the setting of reduced mean arterial pressure and reduced intracranial compliance resulting from head injury or surgical intervention. The risk of intracranial hypertension in patients ventilated with high MAPs is attenuated by conditions that limit transmission of alveolar pressure to the pleural space (low ratio of lung to chest wall compliance).

Section 6: Specific Modes of Ventilation

A. *Standard Modes*

1. *Introduction:* Assisted modes of ventilation are those in which part of the breathing pattern is contributed or initiated by the patient. The work of breathing performed by the patient is never abolished, and one of the difficulties for the physician is to determine the appropriate settings to match the patient's demand, both in terms of gas exchange and work of breathing. The main reasons for using assisted modes in the ICU are the following: (1) to synchronize patient and ventilator activity: (2) to reduce the need for sedation: (3) to prevent disuse atrophy of the respiratory muscles; (4) to improve hemodynamic tolerance of ventilatory support; and (5) to facilitate the weaning process.

Significant differences exist among ventilators concerning demand-valve sensitivity and opening delay, the algorithm for pressure support (PS) (rise in pressure, mechanism, and criteria for cycling from inspiration to exhalation, plateau pressure), flow-impedance characteristics of the expiratory circuit, and equipment. A great deal of data obtained experimentally and in patients suggest that these differences may alter the work of breathing.[55,58,100] Many of the proposals listed below may be modified by the quality of the equipment used.

2. *Assist-Control (A/C):* This is a mode of ventilation in which every breath is supported by the ventilator. A back-up control ventilatory rate is set; however, the patient may choose any rate above the set rate. Until recently, most ventilators using this mode delivered breaths that were volume cycled or volume targeted. Using volume-targeted, A/C ventilation, the V_T, inspiratory flow rate, flow waveform, sensitivity, and control rate are set. Most of the data in the literature concerning A/C were obtained with this mode.[25,42,63,101] Pressure-limited or pressure-targeted A/C in which pressure level, T_I, control rate, and sensitivity are set is now available on several ventilators.

Advantages. Assist-control ventilation combines the security of controlled ventilation with the possibility of synchronizing the breathing rhythm of patient and ventilator, and it ensures ventilatory support during every breath.

Risks or Disadvantages. (1) Excessive patient work occurs in cases of inadequate peak flow or sensitivity setting, especially if ventilatory drive of the patient is increased (volume-targeted A/C);[25,42,101] (2) it may be poorly tolerated in awake, nonsedated subjects and can require sedation to ensure synchrony of patient and machine cycle lengths; (3) it may be associated with respiratory alkalosis; (4) it may potentially worsen air trapping in patients with COPD; and (5) if pressure-targeted A/C is used, there is risk of variable (and potentially markedly decreased) V_T during changes in lung impedances, patient ventilatory drive, or patient-ventilator dyssynchrony.

Patient work of breathing or effort during volume-targeted A/C is dependent on sensitivity, flow rates (flow rate lower than 40 L/min should probably be avoided), and respiratory drive of the patient. This is dependent on many stimuli, including fever, anemia, hypoxia, pain, hypovolemia, level of consciousness, etc. Since patient work is dependent on the ability of the ventilator to rapidly recognize patient effort and provide sufficient flow to meet inspiratory demand, the set-up of the ventilator may play an important role in the patient's tolerance of this mode.[63,101] With pressure-targeted A/C, the ventilator, once triggered, provides sufficient flow to allow the set pressure plateau level to be achieved rapidly. As a result, concern with excessive patient work is potentially minimized in pressure-targeted A/C.

3. *Synchronized Intermittent Mandatory Ventilation (SIMV):* Synchronized IMV is a mode of ventilation and a mode of weaning that combines a preset number of ventilator-delivered mandatory breaths of predetermined V_T with the facility for intermittent patient-generated spontaneous breaths.[102,103] Similar to A/C, several ventilators offer the possibility of delivering pressure-targeted breaths instead of volume-targeted breaths during mandatory cycles. Mandatory breaths can be patient triggered with SIMV; however, if patient effort is not sensed within a specific

period, the ventilator delivers a mandatory breath. Pressure support (see below) may be applied during nonmandatory breaths.

Set-up Parameters. These include V_T, flow rate and/or T_I, frequency of controlled breaths, and sensitivity. When pressure-targeted breaths are used, pressure level and T_I must be set.

Advantages. (1) The patient is able to perform a variable amount of respiratory work and yet there is the security of a preset mandatory level of ventilation; (2) SIMV allows for a variation in level of partial ventilatory support from near-total ventilatory support to spontaneous breathing; and (3) it can be used as a weaning tool.[102]

Risks. With IMV, there are risks of dyssynchrony between the patient effort and machine-delivered volume.

With SIMV the risks are as follows: (1) hyperventilation and respiratory alkalosis are possible, similar to A/C. (2) Excessive work of breathing due to the presence of a poorly responsive demand valve, suboptimal ventilator circuit (its impedance will vary with the particular ventilator used), or inappropriate flow delivery could occur. In each case, extra work is imposed on the patient during spontaneous breaths. This work can be minimized or abolished with the addition of pressure support. (3) Worsening dynamic hyperinflation has been described in patients with COPD.

The total work (or power) performed by the patient is dependent on the number of mandatory breaths. It was initially thought that the effort performed by the patient was virtually zero during mechanical breaths. However, recent data suggest that the muscular effort of the dyspneic patient during machine-assisted breaths does not vary substantially from the unassisted cycles on a breath-to-breath basis, *ie*, at the same overall level of ventilator support, effort is more or less independent of whether or not the breath is assisted.[64] The work of breathing may also vary with the addition of pressure support during spontaneous cycles and with the use of pressure-targeted mandatory breaths. There has been no demonstrated advantage of using IMV over T-piece trials in terms of reducing weaning duration.[104,105]

4. *Pressure Support Ventilation (PSV):* Pressure support ventilation is a pressure-targeted, flow cycled, mode of ventilation in which each breath must be patient triggered. It is used both as a mode of ventilation during stable ventilatory support periods and as a method of weaning patients.[55,65,106-111] It is primarily designed to assist spontaneous breathing and therefore the patient should have an intact respiratory drive.

With PSV, at the onset of inspiration, the pressure rises rapidly to a plateau that is maintained for the remainder of inspiration. The patient and ventilator work in synchrony to achieve the total work of each breath. On most ventilators, termination of inspiration occurs when a flow threshold is reached during the decelerating phase of inspiratory flow. That is, the breath is flow cycled to exhalation (this has been made possible by incorporating pneumotachographs in the ventilators). To avoid confusion, it should be stressed that the difference with pressure-targeted A/C, described above, is that termination of inspiration is different: it is time cycled for pressure-targeted A/C (*ie*, the T_I is fixed), whereas it is flow cycled for pressure support, *ie*, airway pressurization always stops before reaching the zero flow, and inspirato duration is dependent on patient's effort.

Set-up Parameters. These include pressure level a sensitivity. No mandatory PS rate is set; however, ma ventilators incorporate volume-targeted back-up modes the event of apnea. In some ventilators, it is possible adjust the rate of rise in pressure at the beginning inspiration or to adjust the flow threshold for cycling fr inspiration to expiration.

Advantages. (1) As a result of the patient having sign cant control over gas delivery, overt dyssynchrony is l likely than with A/C or SIMV. When the PS level is chos appropriately, this mode is generally regarded as comfortal for most (but not all) spontaneously breathing patients.[65] (2) Pressure support ventilation reduces the work of brea ing roughly in proportion to the pressure delivered and associated with a decrease in respiratory frequency a increase in V_T with increasing levels of PS.[65,105,106] The breathing pattern characteristics may be useful in selecti the appropriate PS level. (3) Pressure support ventilati can be used to compensate for the extra work produced the ET tube and the demand valve.[107,108] (4) It allows fo wide variation in the level of partial ventilatory supp from nearly total ventilatory support (high pressure leve to essentially spontaneous breathing. (5) Pressure supp ventilation may be useful in patients who are "difficult wean." Preliminary data suggest either no difference wh compared with other modes or a shorter weaning durati and a higher success rate in selected patients using pressu support.

Disadvantages. Tidal volume is not controlled and dependent on respiratory mechanics, cycling frequency, a synchrony between patient and ventilator. Therefore, care monitoring is recommended in unstable patients; a back- $\dot{V}_E$ seems necessary for safety; hypoventilation may devel during continuous-flow nebulizer therapy. Pressure supp ventilation may be poorly tolerated in some patients w high airway resistances because of the preset high init flow and terminal inspiratory flow algorithms. This may improved, however, with adjustment of initial flow ra which is possible on new systems.[67,68]

Work of Breathing. Increasing PS levels decrease r piratory effort as indicated by a number of changes breathing pattern. This mode can be combined wi SIMV[111,112] and has been used to compensate for the ad tional work of breathing due to the ET tube and the dema valve, adding PS (5 to 10 cm H_2O) during the nonmandato breaths.[107,108] Higher levels of PS can also be used, combini mandatory and supported breaths. At the present tim clinical studies are lacking to demonstrate the superiority one mode of partial ventilatory assistance over othe Pressure support has been widely accepted in many IC and for some physicians, it seems to be the most use modality for delivering assisted ventilation either as f ventilatory support or as a mode for gradually withdrawi mechanical ventilation. For others, it is a useful adjunct existing modes.

5. *Continuous Positive Airway Pressure (CPA* Continuous positive airway pressure is a mode designed elevate end-expiratory pressure to levels above atmosphe pressure to increase lung volume and oxygenation.[1

constant positive airway pressure is supplied by the ventilator throughout the ventilatory cycle; all breaths are spontaneous. It is also proposed as a means of reducing the pressure gradient between the mouth and the alveoli in patients with air trapping.[41,58] It is designed to assist spontaneously breathing patients and therefore requires an intact respiratory drive.

Until recently, two main types of CPAP systems were used. Those offered by most mechanical ventilators work via a demand valve that needs to be opened to deliver the gas to the patient. This demand valve is pressure triggered or flow triggered. Other specially designed systems work on the principle of a continuous high flow of pressurized gas in the external circuit from which the patient can breathe spontaneously. The advantage of the first system is that ventilator monitoring is still available but the major drawback is that work of breathing is increased by the presence of a demand valve. A continuous-flow system is incorporated in some mechanical ventilators in an attempt to combine the advantages of the two previous systems.[47,114] In this mode, an adjustable, constant flow of gas is continuously delivered in the external circuit during the expiratory phase. Both the inspiratory flow and the expiratory flow are measured and compared by the machine. A difference between these two flow rates indicates to the ventilator that inspiration or expiration is occurring, leading to an adjustment in the delivered flow rate.

Set-up Parameters. These include pressure level and sensitivity: level of negative pressure (demand valve system) or flow threshold and basal flow rate (continuous-flow systems and/or flow-triggered systems).

Advantages. CPAP offers the benefits of PEEP to spontaneously breathing patients. It will improve oxygenation if hypoxemia is in part secondary to decreased lung volume; it may recruit collapsed lung units, minimizing the work of breathing and improving oxygenation. It may help to reduce the work of breathing in patients with dynamic hyperinflation and auto-PEEP.

Recent data suggest that the work of breathing is reduced with systems incorporating a continuous-flow system in comparison to demand valve systems.[47,114]

Risks. Hyperinflation and excessive expiratory work may result if excessive CPAP levels are used. Poor clinical tolerance may increase inspiratory work of breathing, if hyperinflation is produced or if nonthreshold PEEP devices are used. There will be increased expiratory work if hyperinflation is produced or if PEEP devices with large flow resistances are used. The use of demand valves with intubated patients receiving CPAP may lead to patient ventilator dyssynchrony.

This mode can be used in intubated patients as well as nonintubated patients (*eg*, patients with sleep apnea). Although inspiration is not really assisted, modern ventilators deliver a small level of pressurization, *ie*, a 1 to 3 cm H_2O level of pressure support, to avoid negative airway pressure relative to the end-expiratory level during inspiration. It is not clear, however, whether this has a significant clinical effect.[58]

6. *Servo-Controlled Modes:* Servo-controlled modes are used both for ventilation and for weaning patients. The basic principle is the use of a feedback system to control a specific variable within a given narrow range.[115-117] The ventilatory mode is either SIMV or PSV. The targeted parameter is set by the physician and can be either $\dot{V}_E$ or a component of the breathing pattern (respiratory rate, V_T).

Examples of servo-controlled modes include the following:

(i) *Mandatory Minute Ventilation (MMV).* MMV relies on a patient's spontaneous breathing to meet a predetermined $\dot{V}_E$. If this goal is not met, mechanical breaths at predetermined volume are delivered with a rate sufficient to supply the required $\dot{V}_E$. Here the targeted parameter is $\dot{V}_E$. In some ventilators used to implement MMV, the basic mode is SIMV; in others, it can be PSV.

(ii) *Servo-Controlled PSV (With the Exception of MMV).* The underlying mode is PSV and the targeted parameter is respiratory rate or V_T. If the targeted value is not met, the ventilator can either modify the pressure target level or the way the breath is cycled. The regulation of the targeted variable varies among ventilators. It can take different forms: volume-assured PS, pressure augmentation, volume support, pressure-supported breaths, and volume-assisted breaths.

(iii) *Knowledge-Based Systems.* More complex systems have been implemented in microcomputer-driven ventilators and are being studied or are already used for the routine treatment of patients in specialized centers.[9,118-120] These systems have been proposed to help in the treatment of patients with ARDS or to automatically wean patients from mechanical ventilation. At the present time, none of these systems is commercially available.

Advantages include adaptation of the ventilator to the needs of the patient. These systems try to combine the advantages of a partial ventilatory support with the variability in the needs of the patient.

Disadvantages include the following: (1) The algorithm may induce nonphysiologic breathing patterns. (2) The adequate target value can be difficult to adjust (*eg*, adequate level of $\dot{V}_E$ for MMV). (3) Measurement of $\dot{V}_E$ may give false information if breathing pattern is not considered (rapid shallow breathing may go unrecognized). The published data and clinical experience with these modes are minimal.

B. Alternate Modes of Ventilation

1. *Introduction:* During the last decade, a new concept has emerged regarding acute lung injury. In severe cases of ARDS, only a small part of the lung parenchyma remains accessible to gas delivered by the mechanical ventilator. This is widely known as the *"baby lung"* concept. As a consequence, V_T of 10 ml/kg or more may overexpand and injure the remaining normally aerated lung parenchyma (See Section 5, B-1) and could worsen the prognosis of severe acute respiratory failure by extending nonspecific alveolar damage.[121] Because lung volumes and airway pressures relationships are determined by the respiratory P-V curve, and because the apparent "stiffness" of ARDS lung appears related to the fraction of aerated lung, rather than to a generalized increase in elastic recoil, *the specific compliance of the remaining aerated lung parenchyma may be nearly normal.* High airway pressures may result in overdistention and local hyperventilation of more compliant parts of the ARDS lung.[30] Overdistention of lungs in animals has produced diffuse alveolar damage.[75,122] There are also

data in the literature suggesting that ventilation using relatively low end-expiratory pressures (less than the inflection point [opening pressure] of the pressure-volume curve) causes progression of lung injury in animal models of ARDS.[123] This is the reason why alternative modes of mechanical ventilation—all based on a reduction of end-inspiratory airway pressures and/or V_T delivered to the patient and some based on ventilation between the lower and upper inflection points of the P-V curve—have been developed and are clinically used by many physicians caring for patients with severe forms of acute respiratory failure. Three of them, HFV, IRV, and airway pressure release ventilation (APRV), will be described in this section. Since, to our knowledge, there are no data demonstrating the superiority of these nonconventional ventilatory modes in terms of morbidity and mortality, only their physiologic rationale and their putative advantages and disadvantages will be presented.

2. *High-Frequency Ventilation (HFV):* High frequency ventilation is the administration of small V_T—1 to 3 ml/kg—at high frequencies—100 to 3,000/min.[124] Because it is a mode of mechanical ventilation based on a marked reduction in V_T and airway pressures, it has the greatest potential for reducing pulmonary barotrauma. Mechanisms of gas transport change from conventional bulk flow ($V_A = f_x(V_T - V_D)$ to other types when $V_T < V_D$. Proposed mechanisms include coaxial flow, Taylor dispersion, pendelluft, and augmented molecular diffusion. Under these conditions, the f_xV_T product is usually much higher than during conventional mechanical ventilation and V_A appears to be more influenced by V_T than f. There are a number of different types of HFV. The three most common are high-frequency oscillation, high frequency PPV, which is used in anesthesia, and high-frequency jet ventilation (HFJV), which is used both in anesthesia and in critically ill patients with acute respiratory failure. HFJV is the only high-frequency mode routinely used to ventilate patients with ARDS, mainly in Europe. Convincing comparative data concerning the advantages of HFJV over conventional mechanical ventilation (CMV) have been presented in the following limited number of clinical studies. There is no agreement, however, that HFJV is better than CMV in these situations: in ARDS patients with circulatory shock,[125] in cardiac patients with low cardiac output state,[126] and in patients with tracheomalacia, BPF, and tracheoesophageal fistula.[127]

In one well-controlled multicentered clinical trial (the HIFI trial), high-frequency oscillation was found not to be superior to CMV in ventilation of neonates with infant respiratory distress syndrome, but this study has been criticized because of the lack of a volume recruitment protocol.[84] In a number of animal studies, ventilation above the inflection point is required for the beneficial effects of HFV;[128,129] HFV may need to be implemented early in the course of the disease to be effective.

Because of the risk of gas trapping related to expiratory flow limitation, HFV is generally contraindicated for asthma and COPD. Although some European groups routinely use HFJV in combination with low V_T conventional ventilation to treat patients with severe forms of ARDS (8 to 10 tidal volumes per minute of 3 to 4 ml/kg superimposed on HFJV), there are no convincing data demonstrating the superiority of this method of mechanical ventilation in terms of pulmonary barotrauma and mortality. It must be pointed out that the only prospective randomized study comparing HFJV with conventional ventilation which was performed in nonhomogeneous population of cancer patients with ARDS did not demonstrate any significant advantage for one or the other method.[130] HFJV can be safely administered in the clinical setting of the ICU according to the following guidelines:

(i) Clinicians must be very familiar with the technique (ventilatory settings, types of injection, humidification).

(ii) Like all other forms of HFV, HFJV, when administered for periods longer than 8 h, requires adequate humidification of delivered gases or severe necrotizing tracheobronchitis can occur.[131] Because the pressure drop across the injection system is very large *(the operating pressures are between 1 and 3 atmospheres whereas MAP is between 1 and 30 cm H_2O)*, gas expansion occurs within the trachea causing cooling. Therefore, specially designed devices for providing adequate humidification during HFJV are required. One such device is a specially constructed high-temperature vaporizer.[127] Many detrimental effects of HFJV are, in fact, due to inadequate humidification.

(iii) The effects of ventilator parameters related to airway pressures and V_T are reasonably well understood. Respiratory effects of changing ventilatory settings are markedly influenced by the patient's respiratory mechanics. Increasing I:E ratio and driving pressure increase FRC and V_T. Increasing respiratory frequency markedly decreases V_T volume and increases $PaCO_2$ and has minimum effect on FRC in patients with stiff lungs.[132] The more compliant the respiratory system, the larger the increase in FRC induced by increasing I:E ratio, driving pressure, and respiratory frequency.

(iv) Mean airway pressure should be continuously monitored using an intratracheal catheter located at least 5 cm below the injection site. It has been demonstrated in experimental[133] and clinical conditions[134] that MAP measured during HFJV is a reasonably good reflection of MalvP in patients *without* significant obstruction.

(v) There is a large body of evidence in various animal models that HFV is most effective in diseases with stiff lungs when applied following a volume recruitment maneuver. The aim is to ventilate the lung at a pressure above the inflection point, yet at pressures sufficiently low not to cause high pressure (or volume) damage to the lung.[135] This approach has been used in neonates with success, but to date, these clinical trials have been relatively small.

Potential Risks. Due to the large flow rates used and the fact that gas transport is less well understood, HFV is inherently more dangerous than CMV. Outflow obstruction can rapidly lead to increases in lung volume and attendant hemodynamic compromise and barotrauma. Air trapping due to the high flow rates is always of concern, especially in patients with compliant lungs and airways obstruction. Air trapping can be assessed by measuring airway opening pressure under static conditions after airway occlusion, by monitoring esophageal pressure, or by measurements of lung volume obtained at the chest wall (*eg*, inductive plethysmography). Inadequate humidification can indu

severe necrotizing tracheobronchitis as described above.

3. *Inverse Ratio Ventilation (IRV):* Inverse ratio ventilation is the use of I:E ratio >1:1 during CMV.[87] There are two different types of IRV: pressure-controlled (pressure-limited) IRV, where the ventilator generates a servo-controlled square wave of pressure to the airways via a decelerating inspiratory flow, and volume-cycled IRV, where the ventilator generates a predetermined V_T via a constant or a decelerating inspiratory flow. Flow profiles of appropriate length of inspiratory "holds" or "pauses" are applied as necessary for the desired I:E ratio. Pressure-controlled IRV is more widely used than volume-cycled IRV in patients with ARDS. Since MAP is a major determinant of PaO_2, a major part of the rationale for using IRV in ARDS is to maintain MAP relatively high, but to hold peak alveolar pressure within a safe range. The second theoretic concept underlying IRV is the prolongation of inspiration to allow for recruitment of lung units with long time constants. If air trapping does not develop, MAP will increase without a change in PAP or V_T. On the other hand, if T_I is so prolonged that air trapping does develop, the resulting auto-PEEP will either raise PAP (volume-cycled IRV) or decrease V_T (pressure limited or pressure-controlled IRV). Indeed, it appears that many of the reported advantages of IRV in improving PaO_2 are related to air trapping (auto-PEEP), and that similar beneficial effects on oxygenation or O_2 transport may be obtained by using conventional I:E ratios with sufficient PEEP to obtain the same increase in mean lung volume.[136,137] Deep sedation and/or paralysis are nearly always required. At present, there is a lack of convincing data to support the advantage of IRV over conventional ventilation. To our knowledge, no study has evaluated the outcome or the comparative incidence of pulmonary barotrauma in ARDS patients treated with IRV as opposed to conventional ventilation. Nevertheless, if IRV is used, it can be safely implemented in the critically ill with ARDS, according to the following guidelines:

(i) Volume-controlled IRV may be more easy to implement than pressure-controlled IRV since volume-cycled modes are often more familiar to many clinicians. This ventilatory mode guarantees a preset V_T and is available on all ICU ventilators.

(ii) Deep sedation is required in most patients under IRV to avoid dyssynchrony with the ventilator.

(iii) Careful monitoring of PAP and end-inspiratory plateau pressure is required during volume-controlled IRV. The high pressure alarm should be set at 10 cm H_2O above the intended PAP.

(iv) Careful monitoring of $\dot{V}_E$ is required during pressure-controlled IRV because V_T is markedly dependent on the patient's respiratory mechanics.

(v) The auto-PEEP level, which may develop as the I:E ratio increases, should be regularly measured (see Section 4, A-6).

(vi) Hemodynamic status should be assessed using a Swan-Ganz catheter when IRV is implemented.

These guidelines should help minimize the two major complications associated with the use of IRV: pulmonary barotrauma and hemodynamic deterioration.

4. *Airway Pressure Release Ventilation (APRV):* Airway pressure release ventilation increases alveolar ventilation by intermittently releasing continuous positive pressure generated by the ventilator. In passive patients, APRV is identical to pressure-controlled IRV; however, the patient's ability to breathe spontaneously during APRV creates a markedly different intrapleural pressure waveform.[90,138] The rationale for APRV is to limit PAPs, thereby limiting barotrauma. APRV is not intended for patients with severe airflow obstruction.

There are two types of pressure release ventilation: APRV during which pressure release time is preset,[139] and IMPRV. Both are specifically designed for assisting spontaneously breathing patients.[90] In these modes, ventilatory assistance is provided by intermittent changes in FRC related to changes in PEEP. Comparative experimental and clinical studies have shown that APRV and IMPRV can improve alveolar ventilation of animals and humans breathing with CPAP, without a deterioration in arterial oxygenation or an increase in PAP.[90,139] When compared with CMV, APRV was shown to produce similar hemodynamic effects at similar MAP in patients with acute respiratory failure.[140] Whether this type of ventilatory support has any advantage over CMV with PEEP in terms of pulmonary barotrauma is not known. APRV can be provided by a CPAP breathing circuit in which the CPAP level can be modified by opening or closing a release valve connected to a timer.

IMPRV, which has been integrated in an ICU ventilator,[90] provides end-expiratory pressure changes according to the patient's spontaneous breathing activity. Respiratory monitoring and alarms are available and each spontaneous inspiration can be assisted by PS. If the patient's respiratory frequency increases above 30/min, auto-PEEP becomes a limiting factor and IMPRV is no longer an efficient method of ventilatory support.

During APRV, the following respiratory parameters are preset: upper and lower airway pressure levels, frequency of pressure release, and pressure release time. During IMPRV, the following respiratory parameters are preset: upper and lower PEEP levels, frequency of PEEP changes and sensitivity of the trigger. Ventilatory assistance is maximum when PEEP is changed in each of two spontaneous respiratory cycles and can be progressively decreased by spacing PEEP changes (PEEP release every 2,3,4,5,6 cycles, *etc.* . . . spontaneous expiration). Whether this type of ventilatory assistance can facilitate weaning of patients with acute respiratory failure is not known.

Section 7: Discontinuation of Mechanical Ventilation

A. *What Is It, and When Does It Begin?*

Weaning has been defined as the process whereby mechanical ventilation is *gradually* withdrawn and the patient resumes spontaneous breathing.[141] Within the daily vernacular of the ICU, most clinicians do not employ the term weaning in the strict sense, but rather they use it to include the overall process of discontinuing ventilator support. To enhance communication between investigators and clinicians, it may be wise to drop the term *weaning*, and replace it by a term such as discontinuation of mechanical ventilation. This, in turn, could be subdivided into different categories depending on the pace of the discontinuation

process—these terms could replace older, less precise terminology such as the "fast wean" and "slow wean." Alternatively, the term *discontinuation* could be used to describe disconnecting the patient from the ventilator over a short, predefined time limit, while *weaning* refers to the more gradual process; unfortunately, the dividing line between these two processes is arbitrary with no obvious basis.

It has become increasingly difficult to define the precise time at which the discontinuation process commences. It was relatively easy to define this time in the past when volume-cycled A/C ventilation and T-tube trials were the sole or predominant method of treating patients. With the widespread use of IMV and PSV in modern ICUs, it has become increasingly difficult to define the precise time at which these modes are no longer being used as the primary mode of ventilator support and are being adjusted to assist with the discontinuation process. In an ICU setting, ventilator support is typically initiated because of an episode of acute respiratory failure. In general, most clinicians would consider it imprudent to start a discontinuation process until there is evidence of significant resolution of the initial precipitating illness. Unfortunately, rigorous physiologic or clinical indices have never been proposed to help to define this time. This largely relates to the lack of data characterizing the changes in respiratory function from the time that ventilator support is instituted until the time that it can be safely withdrawn. Until this time can be defined in clear-cut objective terms, it is going to be extremely difficult to conduct trials comparing the efficacy of different techniques of discontinuing mechanical ventilation.

B. *Relative Importance of Pathophysiologic Determinants of the Discontinuation Process*

There are four major factors that determine the ability to discontinue ventilator support: (1) respiratory load and the capacity of the respiratory neuromuscular system to cope with this load; (2) oxygenation; (3) cardiovascular performance; and (4) psychological factors.

To our knowledge, systematic studies have never been conducted to determine the relative importance of these pathophysiologic mechanisms. However, many clinicians and investigators suspect that respiratory muscle dysfunction resulting from an imbalance between respiratory neuromuscular capacity and load is the most important determinant. Unfortunately, measurements of each of the components included in this balance have not been systematically obtained in patients at the time that ventilator support is being discontinued. Measurements of respiratory center output indicate that a depressed respiratory drive is rarely responsible for the inability to discontinue ventilator support.[142,143] Phrenic nerve function is usually satisfactory, except for a small proportion of patients who develop problems following coronary artery bypass surgery. Respiratory muscle strength is reflected by measurements of maximal inspiratory pressure.[144] Available evidence suggests that this, *on its own*, is not an important determinant of the ability to resume and sustain spontaneous ventilation after a period of mechanical ventilation.[145] A number of techniques can be used to assess respiratory muscle endurance or fatigue in a research laboratory. None of these has ever been reliably applied in ventilator-supported patients. Thus, we do not know if respiratory muscle fatigue ever occurs in patients who are unable to resume spontaneous ventilation and, if it occurs, how important it is in determining clinical outcome or patient treatment. Respiratory muscle fatigue has been defined in dichotomous terms (present or absen but the impairment in contractility is more likely to exist in the form of a continuum. Thus, it is quite conceivable that "mild fatigue" *per se* may not seriously interfere with the process of discontinuing ventilator support. This is an area where additional research is sorely needed.

The load on the respiratory system is primarily determined by an increase in respiratory resistance, a decrease in respiratory compliance, and the presence of auto-PEEP, which poses an additional threshold load. Each of these factors could produce a marked increase in respiratory work and interfere with the process of discontinuing the ventilator. Although measurements of respiratory work have been obtained in patients at the time of discontinuing mechanical ventilation, most studies contain significant methodologic flaws.[141] Even allowing for these limitations, it is doubtful that a single threshold value of respiratory work can reasonably discriminate between patients who are able to successfully sustain spontaneous ventilation and those requiring continued ventilator support. In particular, there is a tremendous need for research defining the precise interplay between respiratory load and respiratory muscle performance in such patients. Such knowledge would be important not only in elucidating the mechanisms responsible for the inability to resume spontaneous ventilation, but it would also help in guiding optimal ventilator support prior to the discontinuation attempts.

Although mechanical ventilation is commonly instituted because of problems with oxygenation, this is rarely a cau of difficultly at the time that mechanical ventilation is being stopped, largely because ventilator discontinuation is not contemplated in patients who display significant problems with oxygenation.

Research into the discontinuation of ventilator support has primarily focused on factors affecting the respiratory system. Although impaired cardiovascular performance has significant impact on the respiratory system (decreasing O_2 supply to the respiratory muscles, increasing respiratory work secondary to pulmonary edema, and hypoxemia as a result of a low mixed venous O_2 tension), remarkably few studies have examined the role of cardiovascular performance as a determinant of the ability to resume successful spontaneous ventilation.[146] In patients with known coronary artery disease, significant cardiovascular impairment reflected by a marked increase in pulmonary artery occlusion pressure has been documented at the time of resuming spontaneous ventilation. This is another area where much research is required, both in patients who require ventilator support primarily because of cardiovascular problems, and in patients without obvious underlying cardiovascular disease. In particular, it is important to document the time course of significant decompensation in such patients and to determine if this differs significantly from the pattern occurring in patients with a primary pulmonary disorder.

Psychologic factors are a major determinant of outcome in some patients, especially in those patients who requ prolonged ventilator support.[147] Minimal research has be

conducted into this important issue, and, thus, it is difficult to state its relative importance in determining the ability to resume spontaneous ventilation.

C. *Predictive Indices*

A wide variety of physiologic indices have been proposed to guide the process of discontinuing ventilator support. Traditional indices include the PaO_2/FIO_2 ratio, the alveolar-arterial P_{O_2} gradient, maximal inspiratory pressure, VC, $\dot{V}_E$, and maximum voluntary ventilation.[144,145] Newer indices include pressure measured 0.1s after occlusion of the airway, the f/V_T ratio, and integrative indices such as CROP (an integrative index which includes compliance, rate, oxygenation and pressure[146]), the pressure-time index, and V_E40.[143,146,148] In general, these indices evaluate a patient's ability to sustain spontaneous ventilation. They do not assess a patient's ability to protect his/her upper airway. Indices of upper airway function have been developed for treating postoperative patients, but similar indices have not been evaluated in critically ill patients.

There are enormous discrepancies in the literature on the accuracy of indices in predicting successful discontinuation of mechanical ventilation. Discordance is due, at least in part, to methodologic problems and differences among studies. These include the following: (1) characteristics of the patient population; (2) the method of making the measurements; (3) reproducibility of the measurement; (4) the method of selecting the threshold value of an index; (5) the method of testing the accuracy of an index; and (6) definition of end points in the evaluation study.

As currently employed, predictive indices are most commonly used in evaluating a patient for extubation. Measurement of these physiologic indices may suggest to a physician that ventilator support can be discontinued at an earlier time than he/she might otherwise have thought possible. This may help in decreasing the risk of complications associated with mechanical ventilation. When an index suggests that resumption of sustained spontaneous ventilation is unlikely to be successful, it can provide important information regarding the patient's underlying pathophysiologic state. However, there is no evidence to suggest that a particular set of physiologic indices is helpful in guiding the selection of a particular technique to hasten the process of discontinuing ventilator support. Accordingly, at this time, it is impossible to say precisely if, and how, such physiologic indices should be used in clinical decision making or in the treatment of a patient who is still requiring ventilator support.

It is important to remember that the condition of ventilator-dependent patients can vary considerably from day to day. Thus, a patient's ability to successfully resume and sustain spontaneous ventilation should be evaluated on a recurrent basis.

D. *Techniques of Discontinuing Ventilator Support*

The major techniques of discontinuing ventilator support include T-tube trials, IMV, and PSV.

There is considerable variation among clinicians in the manner of applying T-tube trials.[141,150] Some clinicians continue maximal ventilator support (*eg*, CMV with neuromuscular blockade, or A/C) up until the point at which they believe that a patient has a reasonable chance of extubation. This decision is usually based on clinical examination and measurement of physiologic indices. At this point, the ventilator is stopped and the patient breathes through a T-tube system. The duration of such a T-tube trial has never been standardized, and it varies from about 30 min to several hours. During the trial, a decision is made to extubate the patient (provided that problems with upper airway protection are considered unlikely) or to reinstate ventilator support. Some clinicians do not attempt another T-tube trial for ≥24 h after an unsuccessful attempt. Other clinicians employ intermittent T-tube trials of gradually increasing duration (from 5 to 60 min) intermittently (*eg*, 3 to 4 h apart); this is conducted on an empirical basis.

Intermittent mandatory ventilation was the first alternative approach to T-tube trials.[150,151] IMV involves a gradual reduction in the amount of support being provided by the ventilator and a progressive increase in the amount of respiratory work being performed by the patient. The pace of decreasing the IMV rate is generally based on clinical assessment and measurement of arterial blood gas values, but precise guidelines do not exist. As discussed elsewhere in this consensus conference, breathing through the demand valve of an IMV circuit can produce a marked increase in the work of breathing (see Section 4, B-3).

Pressure support ventilation can also be used to gradually decrease the level of ventilator support.[152-154] The level of PSV is gradually decreased so that a patient becomes increasingly responsible for a larger proportion of overall ventilation. It is commonly assumed that the level of PSV can be decreased to a low level that will compensate for the resistance of the ET tube and circuit, and that the patient can then be extubated at that level of PSV.[108,155,156] Unfortunately, there are no simple parameters than can predict the level of PSV that compensates for this resistance in an individual patient.

A gradual approach to the discontinuation of mechanical ventilation (*ie*, IMV or PSV vs abrupt T-tube trials) has two theoretical advantages: (1) the use of less positive pressure (since these are modes of partial rather than full assistance), and, thus, a potential for fewer pressure-related complications, and (2) performance of some level of respiratory work should prevent the development of respiratory muscle atrophy—this is mainly an advantage when contrasted with a patient receiving CMV with neuromuscular blockade, since patients being treated with A/C (with or without intermittent T-tube trials) probably perform sufficient work to prevent significant deconditioning.

In addition to the independent use of T-tube trials, IMV, or PSV as approaches to discontinuing ventilator support, these techniques are frequently integrated and specific protocols defined for a given patient in an attempt to establish the most optimal approach. That is, PSV and IMV have been combined, with both gradually decreased, or the level of one technique kept constant while the other is gradually decreased. T-tube trials have also been integrated with PSV and IMV.

At the present time and to our knowledge, no study has been published that has compared the optimal use of the three major techniques of discontinuing mechanical ventilation.

E. *Treatment of the Difficult Patient*

Discontinuation of mechanical ventilation poses considerable difficulty in a significant proportion of patients. These patients account for a disproportionate amount of healthcare costs, and they pose enormous clinical, economic, and ethical problems. In addition to the factors already discussed, several other issues need to be considered in these patients. Increasing ventilator support at night to ensure maximal rest is recommended. In a recent study, the institution of a ventilator-management team was shown to decrease the number of ventilator and ICU days.[157] Nutritional support needs to be considered since these patients are dependent on a ventilator for a relatively long time. Uncontrolled, retrospective studies suggest that nutritional supplementation can expedite the discontinuation of mechanical ventilation, but this has yet to be examined prospectively.[141] Likewise, respiratory muscle training appeared promising in an uncontrolled study,[158] but its benefit has yet to be evaluated prospectively. Finally, a prospective study of biofeedback was shown to be particularly beneficial.[147] However, skilled practitioners are not widely available, and the initial beneficial findings in this study need to be confirmed.

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PREDICTED VALUES

FLOW AT FRC	1.1-1.9
SPECIFIC FLOW	1.1-1.4
FRC/KG	10-20 ML/KG
COMPLIANCE	0.8-4.0 ML/CM H2O/L
SPECIFIC COMPLIANCE	50-60 ML/CM H2O/L
RESISTANCE	0.03-0.07 CM H2O/ML/SEC
TIME CONSTANT	0.2/SEC

$$C = \Delta V / \Delta P = \frac{ml}{cmH_2O/L}$$

$$R = \frac{\Delta P}{\dot{V}} \quad \frac{cm\,H_2O}{cc/sec}$$

pediatric annals

Clinical Disorders of Water Metabolism: Hyponatremia and Hypernatremia

ELLIS D. AVNER, MD

Hyponatremia and hypernatremia are the two most common electrolyte disorders. This article reviews the basic pathophysiology of these two major disorders of water metabolism and provides a pathophysiologically based, stepwise approach to the diagnosis and treatment of hypernatremia and hyponatremia in pediatric patients. Other articles can provide the interested reader with a more comprehensive review of the physiology and clinical pathophysiology of water metabolism.[1-11]

Cerebral overhydration produces abnormalities that range from apathy, anorexia, nausea, vomiting, agitation, and headache to altered consciousness, seizures, and coma.

PATHOPHYSIOLOGY OF CLINICAL DISORDERS OF WATER METABOLISM: OSMOLALITY AND THE REGULATION OF TONICITY

The overall concentration of solutes in the extracellular fluid (ECF) is tightly regulated to maintain a stable internal milieu. Sodium is the major osmotically active solute in the ECF, so in general, disorders of osmolality present clinically with an abnormal serum sodium concentration.[1-3,6,12,13]

It is important to recognize that osmolality and tonicity are not identical. Osmolality is a measure of the number of solute particles per weight of solvent. Measured osmolality of a solution includes all particles whether they are osmotically active or inactive. Sodium chloride or other impermeable solutes such as mannitol or glucose do not readily cross cell mem-

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In patients with nephrotic syndrome, a clinical rule of thumb is that an increase of triglycerides of 1 g/dL will decrease serum sodium concentrations by 2 mEq/L.

branes to enter cells. They remain restricted to the ECF space and are thus "effective osmols" by obligating water to remain extracellularly. Cell membranes are freely permeable to solutes such as urea, methanol, or ethanol. While contributing to measured osmolality, these "ineffective osmols" do not obligate water to remain in the ECF space. Tonicity takes into account only osmotically active impermeable solutes and is the important physiological parameter.

Osmolality can be measured or estimated by the following formula:

calculated osmolality (mOsm/kg = $2 \times ([Na] + [K]) + BUN/2.8 + glucose/18$.

Measured osmolality is ordinarily about 10 mOsm/kg higher than calculated osmolality because the formula ignores calcium, magnesium, protein, amino acids, and other minor solutes.

Regulation of tonicity of the ECF is maintained by osmoreceptors in the supraoptic and paraventricular nuclei of the hypothalamus. Body water content is altered by changing intake or excretion of water. Axons project from the hypothalamic thirst center to the cerebral cortex and lead to a perception of thirst and subsequently to increased water ingestion as tonicity rises. Hypotonicity suppresses thirst. In addition, axons from neurons in the hypothalamic thirst center project into the posterior pituitary. As tonicity of the ECF rises, release of vasopressin or antidiuretic hormone (ADH) from the neurohypophysis occurs. In the kidney, ADH reduces excretion of solute free water and increases water reabsorption leading to urinary concentration. When ADH is absent, urinary dilution occurs.

The normal value of serum osmolality is 287 ± 4 mOsm/kg with a normal range (mean ± 2 standard deviations) of 280 to 295 mOsm/kg. In any given individual, regulation of osmolality is quite precise. An increase in osmolality of 1% leads to stimulation of thirst and ADH release. Antidiuretic hormone release rises in linear fashion as further increases in plasma osmolality occur. Conversely, suppression of thirst and ADH release occur with comparable falls in ECF tonicity.

There are also a number of clinically important nonosmotic stimuli for ADH release such as physical pain, emotional stress, hypoxia, liver disease, adrenal insufficiency, cardiac failure, and most importantly, volume depletion. Afferent vagal and glossopharyngeal pathways from the left atrial and carotid sinus baroreceptors appear to modulate nonosmotic regulation of ADH. In clinical settings, it is important to recognize that nonosmotic stimuli may predominate over osmotic stimuli to produce ADH release. For example, a volume-depleted patient may become profoundly hyponatremic. In this setting, hypoosmolality does not suppress ADH release; rather, ADH release is driven by the more potent nonosmotic hypovolemic stimulus. The rationale for such a hierarchy of control is clear. Protection of ECF volume is fundamental to the maintenance of all organ systems.

CLINICAL DISORDERS OF WATER METABOLISM: HYPONATREMIA

Symptoms and Signs of Hyponatremia

The clinical manifestations of hyponatremia are quite variable, but tend to be more obvious when the serum sodium concentration falls rapidly <120 mEq/L. As serum osmolality decreases, water moves across the osmotic gradient from the extracellular to the intracellular space. Cellular overhydration is manifest predominantly through central nervous system and musculoskeletal dysfunction. Cerebral overhydration produces abnormalities that range from apathy, anorexia, nausea, vomiting, agitation, and headache to altered consciousness, seizures, and coma. Musculoskeletal signs of hyponatremia include muscle cramps and weakness. In general, the severity of symptoms depends on the magnitude and rapidity of the decrease in serum sodium concentration. Patients with chronic hyponatremia, which develops over days or weeks, may be largely asymptomatic or manifest only subtle neurological abnormalities such as focal weakness, ataxia, or a positive Babinski's sign.

Clinical Evaluation and Therapy

The evaluation of the hyponatremic child is outlined in Figure 1. Initially, one must determine whether hyponatremia reflects true hypotonicity. There are two clinical circumstances in which hyponatremia may be present without hypotonicity. High levels of plasma lipids or proteins increase plasma volume, which decreases the percentage of plasma volume that is water. Because many clinical laboratories measure and report sodium concentrations in mEq/L of plasma (not in mEq/L of plasma water), the reported sodium concentration will be artificially low. Newer methods of sodium measurement that use ion selective electrodes measure serum sodium activity directly in plasma water and are not affected by the proportion of serum occupied by lipids and proteins. A clinical clue to such "pseudohyponatremia" is the presence of lipemic serum and a normal measured serum osmola-

continued on page 26

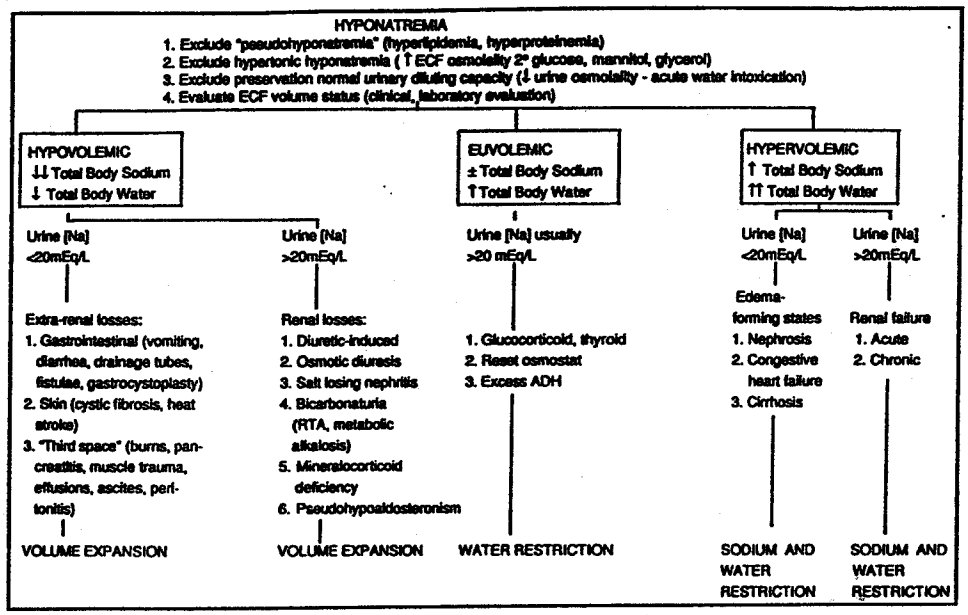

Figure 1. Clinical evaluation and therapy of the patient with hyponatremia. See text for details. Adapted from references 1-3, 7, and 8.

continued from page 24

lity (because lipids or proteins have large molecular weights and therefore are minor components of overall plasma osmolality). In patients with nephrotic syndrome, a clinical rule of thumb is that an increase of triglycerides of 1 g/dL will decrease serum sodium concentrations by 2 mEq/L.

The second situation in which a patient may be hyponatremic, but not hypotonic, occurs when an osmotically active solute (eg, glucose or mannitol) has been added to the extracellular space. Water drawn out of cells by such an osmotically active particle will dilute the serum sodium concentration despite isotonicity or even hypertonicity. A clinical rule of thumb is that serum sodium concentration is lowered by 1.6 mEq/L for each 100 mg/dL increase in glucose concentration. The presence of an osmotically active nonglucose solute in the extracellular space is readily identified by comparing the calculated osmolality with measured osmolality. If they differ by >10 mOsm/kg, it can be inferred that some other solute (mannitol or glycerol) may be present. Such an osmolal gap might be the first clue to ingestion of a foreign substance such as methanol or ethanol.

Following the exclusion of nonhypotonic states, the clinician must next determine whether hyponatremia has occurred with maintenance of the normal capacity for urinary dilution by measuring urine osmolality, which should be <120 mOsm/kg (specific gravity <1.003) if maximal urinary dilution is present. Hyponatremia hypotonicity with normal urinary dilution occurs in acute water intoxication. In this setting, water intake exceeds maximal urinary free water excretion, which is 26 L per 1.73 m^2 per day. This may occur through errors in intravenous fluid administration, ingestion of inappropriately mixed low-solute formula, extensive use of tap water enemas, swallowing of excessive quantities of water while swimming or bathing, or abnormal drinking behavior in psychiatric patients. These conditions generally are identified by history and physical examination, and are treated with water restriction.

The next step is the clinical evaluation of the ECF volume. Extracellular fluid volume contraction is manifest by lethargy, tachycardia, orthostatic hypotension, decreased skin turgor, dry mucus membranes, decreased tears and sweating, oliguria, azotemia, and often a history of luid loss. Euvolemic patients lack overt signs of water imbalance. Hypervolemic patients have edema, cardiopulmonary manifestations of excess ECF volume, and often a history of excessive fluid intake or retention. Basic laboratory tests should be obtained: serum electrolytes, BUN, creatinine, glucose, and osmolality along with urine sodium and osmolality. With these data, hyponatremic patients can be classified into one of three categories on the basis of their ECF volume status (Figure 1). Such classification guides appropriate diagnosis and therapy.

Hypovolemic patients with hyponatremia have sodium depletion in excess of water depletion. Volume depletion may occur due to the loss of sodium-containing fluids via an extrarenal route (urine [Na]<20 mEq/L) or via the kidney due to primary renal disease or diuretics (urine [Na]>20 mEq/L) (Figure 1). In these settings, patients generally will be drinking fluids more dilute than fluids being lost. In addition, volume depletion leads to ADH release, which will augment distal nephron free water reabsorption. Finally, patients treated with diuretics may have abnor-

mal function of distal diluting sites. Treatment of hypovolemic hyponatremic patients consists of volume expansion and discontinuation of any diuretics. Patients with acute symptomatic hypovolemic hyponatremia and serum [Na]<120 mEq/L initially should receive hypertonic saline sufficient to restore the serum [Na] to 120 mEq/L.

Acute increases in serum [Na] may be accomplished by using a 3% saline solution (513 mEq of sodium per liter) with the number of mEq of sodium necessary to achieve a serum level of 120 mEq calculated by the following formula:

$$\text{mEq sodium required} = 120 - \text{present sodium (mEq/L)} \times 0.6 \times \text{weight (kg)}.$$

Correction can be achieved over 4 to 6 hours. Rapid correction of hyponatremia has been associated with central pontine demyelination and neurological deterioration, particularly in adults with chronic hyponatremia.[14] Although rarely reported in pediatric patients, it is recommended that once [Na] has been corrected to 120 mEq/L, further correction be accomplished over 24 to 48 hours.

Euvolemic patients with hyponatremia have normal or near-normal total body sodium and a slight excess of total body water. They lack overt signs of water imbalance. All patients in this group have impaired water excretion by the kidney. The most common cause of euvolemic hyponatremia is inappropriate secretion of ADH (SIADH).[7,15] This syndrome has many causes (Table 1). The diagnostic criteria for SIADH include: hypotonic hypernatremia; urinary osmolality usually greater than serum osmolality; normal renal, adrenal, pituitary, and thyroid function; and absence of hypovolemia, dehydration, and edema. In general, urine [Na] in SIADH is high.

Treatment in all of these euvolemic conditions consists of water restriction. In rare situations (serum sodium <120 mEq/L and acute central nervous system symptoms), serum sodium concentration may be increased acutely by giving intravenous hypertonic saline along with intravenous furosemide.[16] This therapy mandates close monitoring of serum electrolytes, as well as sodium and potassium losses into the urine that must be replaced while minimizing water replacement. Patients with chronic SIADH who are unresponsive to chronic water restriction may respond to chronic therapy with lithium or demeclocycline, which inhibit ADH action.[17]

The third group of patients with hypotonic hyponatremia demonstrate an increase in ECF volume and are hypervolemic. Total body water is increased to a greater degree than total body sodium. These patients generally fall into two groups: those with edema-forming states (urine [Na] <2 mEq/L) and those with renal failure (urine [Na] >20 mEq/L) (Figure 1).

The edema-forming states include low cardiac output (congestive heart failure), loss of fluid from the intravascular space into the interstitium (nephrotic syndrome and cirrhosis), or A-V shunting and splanchnic pooling (cirrhosis). Patients with oliguric renal failure may develop water overload through ingestion. Treatment of all of these disorders consists of water restriction to correct hyponatremia, sodium restriction to correct edema, and correction of the underlying disorder when possible.

TABLE 1

Causes of the Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)*

Central Nervous System Disorders
Infection (meningitis, encephalitis, and abscess)
Hypoxia-ischemia
Trauma
Cerebrovascular accident
Tumor
Psychosis
Miscellaneous (Guillain-Barré syndrome, vasculitis, anatomic abnormalities, V-A shunt obstruction, cavernous sinus thrombosis, and stress)

Pulmonary Disorders
Infection (bacterial, tubercular, viral, mycoplasma, and fungal)
Decreased left atrial pressure (pneumothorax, atelectasis, asthma/bronchiolitis, patient ductus arteriosus, ligation, and cystic fibrosis)

Tumors
Bronchogenic carcinoma
Adenocarcinoma of the pancreas and duodenum
Carcinoma of the ureter and prostate
Thymoma
Acute leukemia (ALL)
Lymphoma
Lymphosarcoma
Mesothelioma

Drugs
Increase water permeability of nephron (vasopressin, desmopressin, and oxytocin)
Promote antidiuretic hormone release (nicotine, barbiturates, narcotics, carbamazepine, colchicine, isoproterenol, vincristine, vinblastine, and amitriptyline)
Inhibit prostaglandin synthesis (salicylates, acetaminophen, and nonsteroidal anti-inflammatory drugs)
Potentiate antidiuretic hormone action (chlorpropamide and cyclophosphamide)

*Adapted from references 3, 5, 7, and 8.

CLINICAL DISORDERS OF WATER METABOLISM: HYPERNATREMIA

Signs and Symptoms of Hypernatremia

Thirst is a prominent symptom of ECF hyperosmolicity unless the thirst center has been destroyed. The

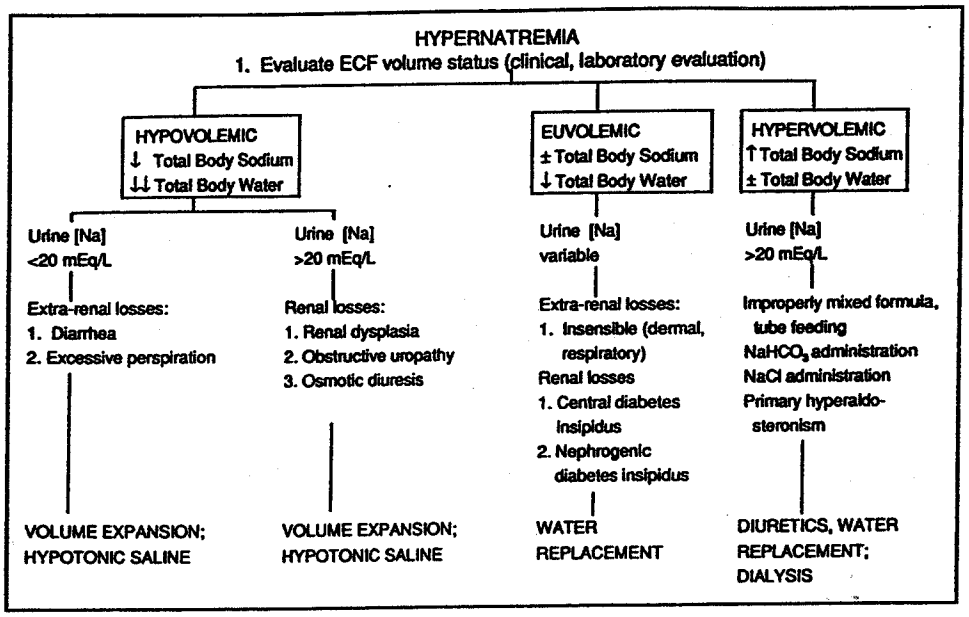

Figure 2. Clinical evaluation and therapy of the patient with hypernatremia. Adapted from references 2, 3, 10, and 11.

other symptoms and signs of hypertonicity are relatively nonspecific and consist of lethargy or confusion, neuromuscular irritability, seizures, or coma. Extracellular fluid hypertonicity leads to decreases in intracellular water and cell size. In the central nervous system, shrinkage of brain cells can lead to tearing of the arachnoid with subarachnoid hemorrhages and subsequent neurological damage. When ECF hypertonicity develops slowly, brain intracellular osmolar content increases in a protective fashion to minimize cell shrinkage. Generation of "idiogenic osmols" (believed to be largely electrolytes and amino acids) tends to decrease the extracellular-intracellular osmolar gradient and minimize disruption of brain cells. This protective mechanism must be considered during treatment of hypertonic states. Because idiogenic osmols are not dissipated rapidly, aggressive correction of hypertonicity with hypotonic fluids can lead to rapid uptake of water by brain cells, resulting in cerebral edema and CNS dysfunction.

Evaluation and Therapy

Although hypernatremia is diagnostic of ECF hypertonicity, not every hypertonic patient is hypernatremic. If hypertonicity has developed from a solute other than sodium (such as glucose or mannitol), serum sodium may be normal or reduced despite hypertonicity. In such settings, hypertonicity can be recognized by an increase in calculated or measured osmolality. The clinical approach to hypernatremia, like that to hyponatremia, follows a clinical paradigm based on the bedside and laboratory evaluation of volume status (Figure 2).

Hypertonic patients who are clinically hypovolemic have total body water losses in excess of sodium losses. This situation may occur from extrarenal (urine [Na] <20 mEq/L) or renal (urine [Na] >20 mEq/L) losses. Diarrhea is the most common cause of hypotonic fluid losses in children, particularly if complicated by decreased fluid intake or vomiting. Infants, with their relatively large surface area to volume, are particularly susceptible to hypernatremic dehydration with fever. Patients with cystic fibrosis or heat stroke and excessive hypotonic losses through perspiration are additional high-risk groups. Infants with congenital renal disease, such as obstructive uropathy or renal dysplasia, often have tubular dysfunction and urinary concentrating abnormalities even with normal glomerular filtration rates. Such children are at particular risk of hypernatremic dehydration when challenged with diarrhea, vomiting, or lack of access to free water. The osmotic diuresis of diabetes mellitus, or administered mannitol or glycerol, can lead to excessive hypotonic urine losses and result in hypernatremia.

The treatment of hypernatremic dehydration involves the initial restoration of effective circulating plasma volume followed by the administration of hypotonic fluids such as ¼ to ½ normal saline containing 2.5% dextrose and 20 to 40 mEq/L KCl.[18] Recognition that generated intracerebral idiogenic osmols may lead to brain cell swelling with rapid rehydration mandates that ECF hypertonicity be corrected slowly. Deficits and ongoing losses should be replaced over a 48-hour period, and serum sodium should be monitored closely. With such a regimen, if serum sodium is falling <0.5 mEq/L/hour, the rate of fluid administration should be increased temporarily by 30% to 50%. Conversely, if serum sodium is falling >0.5 mEq/L/hour, the rate of fluid administration should be decreased temporarily by 30% to 50%.[18]

Because of the risk of hypocalcemia with hypernatremic dysfunction, serum calcium should be monitored. Hyperglycemia, an additional complication of hypernatremic dehydration, may be minimized by the administration of low dextrose-containing solutions.

A second group of patients demonstrate hypernatremia secondary to solute-free water losses. Therefore, their total body sodium is essentially normal while their total body water is decreased. These patients appear to be euvolemic or mildly hypovolemic due to their mild reduction in ECF. Free water losses may be excessive from extrarenal losses such as increased respiratory and dermal insensible losses (ie, a newborn with respiratory distress on a radiant warmer) or inadequate access to water. In this setting, urine is hypertonic, and urinary sodium is variable. The more common clinical setting for hypertonicity due to pure water loss is excessive hypotonic renal losses in diabetes insipidus. As noted in Table 2, diabetes insipidus may be classified as central (failure of ADH production) or nephrogenic (failure of the renal tubule to respond to adequate amounts of ADH).

The etiology of central diabetes insipidus is usually central nervous system disease. Nephrogenic diabetes insipidus may be congenital (x-linked defect in the ADH receptor or autosomal recessive defect in the aquaporin water channel[19]), secondary to any renal disease that destroys tubular integrity or the ability to generate a hypertonic medullary interstitium (such as obstructive uropathy or renal dysplasia), or secondary to drug administration.

In diabetes insipidus, polyuria is present with essentially a free-water diuresis with urine specific gravity ranging <1.005 and urine osmolality <200 mOsm/kg. After all fluid and electrolyte abnormalities have been corrected, the diagnosis is confirmed with a water deprivation test done under close observation. This test also separates central from nephrogenic diabetes insipidus.[2,9-11,18,19] When ADH is administered exogenously after water deprivation, patients with a normal ADH axis have no change in their urinary osmolality, patients with central diabetes insipidus will show an increase in urinary osmolality, and patients with nephrogenic diabetes insipidus will show no response.

The straightforward treatment of hypertonicity due to pure water loss is to restore existing water deficit while replacing water loss. In hypernatremic dehydration, water deficit cannot be calculated using clinical signs of 5%, 10%, or 15% (as described in Dr Watkins' article, "The Basics of Fluid and Electrolyte Therapy," pages 16-22). This is because the dehydration is primarily intracellular, and it is the interstitial dehydration and hypovolemia that produce these signs. The water deficit can be calculated using the assumption that the dehydration is due to the loss of free water and total body sodium remains unchanged Thus, current body water (the unknown) × curren [Na] = prior body water or 60% of the patient estimated prior body weight × the patient's n [Na] or 140 mEq/L. So, current body wa

TABLE 2

Causes of Diabetes Insipidus*

Central
Primary
- Nonfamilial
- Congenital and familial

Secondary
- Head trauma (skull and orbit)
- Suprasellar/intrasellar tumors (craniopharyngioma and metastatic)
- Granuloma (sarcoid, tubercular, Wegener's, and syphilis)
- Infections (encephalitis and meningitis)
- Histiocytosis
- Vascular (aneurysm, thrombosis, hemorrhage sickle-cell disease, and vasculitis)

Nephrogenic
Primary
- X-linked
- Autosomal recessive

Secondary
- Renal disease (dysplasia, obstructive uropathy, reflux, medullary cystic, polycystic, tubulo-interstitial nephritis, and renal tubular acidosis)
- Electrolyte imbalance (hypokalemia and hypercalcemia)
- Systemic disease with renal involvement (sickle-cell disease, amyloidosis, sarcoidosis, and cystinosis)

Drugs Inhibiting Antidiuretic Hormone Rel
Systemic α-adrenergic agonists
Ethanol
Opiate antagonists
Diphenylhydantoin
Clonidine
Carbon monoxide poisoning

Drugs Inhibiting Peripheral Action of Antidiuretic Hormone
Lithium
Demeclocycline
Methoxyflurane
Amphotericin B
Cisplatin
Cyclophosphamide
Propoxyphene
Angiographic dyes
Osmotic diuretics

Other
Septic-optic dysplasia
Cleft lip/palate
Familial cerebellar ataxia

*Adapted from references 2-4 and 9-11.

0.6 × prior body weight × 140/current [Na]. Subtracting current body water from prior body water gives the deficit. This deficit, in addition to maintenance fluids and ongoing fluid losses, should be administered over a 24- to 48-hour period using the previously noted guidelines for correction of hypertonicity in hypernatremic dehydration. Antidiuretic hormone should be administered to patients with central diabetes insipidus.

A final group of patients are hypernatremic on the basis of pure sodium addition to the ECF. They demonstrate hypervolemia with an increased total body sodium and essentially normal total body water. Such patients have urine [Na] >20 mEq/L (unless severe congestive heart failure has developed). In the pediatric population, pure sodium excess, or salt poisoning, is unusual but has been reported as a consequence of giving improperly mixed high-sodium formulas or rehydration solutions, or as the consequence of excessive $NaHCO_3$ administration during resuscitation. A rare cause is ingestion of sea water, which may contain up to 480 mEq of sodium/L. Treatment for hypernatremic, hypervolemic patients includes augmentation of sodium excretion with diuretics, as well as concomitant water administration. Cardiovascular compromise with pulmonary edema may require extracorporeal sodium and fluid removal through dialysis or hemofiltration.

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Table 85.1 Laboratory findings in SIADH, diabetes insipidus (DI), and cerebral salt wasting (CSW)

	[Na]*	[UNa]†	Serum osmolality (mOsm/kg of serum water)	Urine osmolality (mOsm/kg of urine water)	Urine specific gravity	Urine output (ml/kg/hr)	Central venous pressure (mm Hg)
SIADH	≤130	≥60	≤275	≥500	≥1.020	<1	≥8
DI	≥150	≤40	≥305	≤250	≤1.005	>3	≤4
CSW	≤130	≥120	≤275	≥300	≥1.010	≥1	≤4

*[Na] is serum sodium concentration in mEq/liter.
†[UNa] is urine sodium concentration in mEq/liter.

Treatment of SIADH

TREATMENT OF THE ASYMPTOMATIC PATIENT

1. Transfer and treat the patient in the PICU.
2. Place cardiorespiratory monitor and begin hourly checks of neurologic status until serum sodium stabilizes in the normal range.
3. Place Foley catheter and strictly record fluid intake and output.
4. Volume-restrict fluids to 50% to 75% of maintenance.
5. Use 5% dextrose in ½ normal saline or 5% dextrose in lactated Ringer's solution as intravenous fluid.
6. Measure serum sodium every hour until serum sodium becomes ≥135 mEq/L and then measure serum sodium every 2 to 6 hours.
7. Place central venous pressure monitor if any serious question of volume status exists.
8. Reassess physical examination and laboratory data every hour and readjust therapy as indicated.
9. Liberalize fluids when serum sodium reaches 135 to 140 mEq/L.

TREATMENT OF THE SYMPTOMATIC PATIENT

1. If the patient is seizing or showing other signs of increased intracranial pressure, treat emergently with 0.5 to 2 g of mannitol per kilogram intravenously.
2. Begin oxygen by mask if respiratory distress is present.
3. Place on cardiorespiratory monitor and pulse oximeter (particularly in the presence of respiratory distress).
4. Once stabilized, transfer and treat the patient in the PICU.
5. Begin checks of neurologic status every 30 minutes until serum sodium stabilizes in the normal range.
6. If respiratory distress or pulmonary edema or anasarca is present, give 1 to 2 mg of furosemide intravenously and consider urine replacement with normal or hypertonic saline.
7. If neurologic symptoms are present, begin phenytoin therapy as seizure prophylaxis.
8. Place Foley catheter and strictly record fluid intake and output.
9. Volume-restrict fluids to 50% of maintenance.
10. Measure serum sodium every hour until serum sodium becomes ≥135 mEq/L and then measure serum sodium every 2 to 6 hours.
11. Place central venous pressure monitor to help guide fluid therapy.
12. Reassess physical examination and laboratory data every hour and readjust therapy as indicated.
13. Liberalize fluids when serum sodium reaches 135 to 140 mEq/L.

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Diabetic Ketoacidosis

Biochemistry, Physiology, Treatment, and Prevention

*Elliot J. Krane, MD**

In spite of many recent advances in the outpatient management of juvenile diabetes and the proliferation of social programs for young diabetics and their families, the incidence of diabetic ketoacidosis (DKA) is not declining.[40] Furthermore, several epidemiologic surveys in this country and abroad have documented that the prevalance of insulin-dependent diabetes is steadily increasing,[14, 23, 26, 66, 73, 78, 94] and that the number of patients with diabetes is approximately doubling every decade. DKA therefore will be seen more commonly on pediatric wards and in intensive care units.

Before the introduction of insulin into clinical practice 50 years ago, patients rarely survived DKA. The mortality of DKA is presently 5 to 17 per cent,[10] essentially unchanged in the past 25 years.[21, 22] Ketoacidosis is a common illness among children, accounting for 14 per cent of all diabetic hospital admissions in this country and 16 per cent of overall diabetic mortality.[22] DKA accounts for over half of all deaths of diabetic patients under the age of 24 years, and is thus the single most common cause of death in diabetic children. Prevention and optimal treatment of DKA are therefore important in reducing diabetes-related morbidity and mortality. This review begins with a discussion of the biochemistry of glucose-regulating hormones and DKA, followed by a prioritized treatment plan based on an understanding of the physiologic consequences of these derangements.

ENDOCRINOLOGY OF GLUCOSE-REGULATING HORMONES AND DKA

Glucose and lipid homeostases are regulated by an intricate interplay of the pancreatic hormone insulin, which lowers blood glucose and lipid

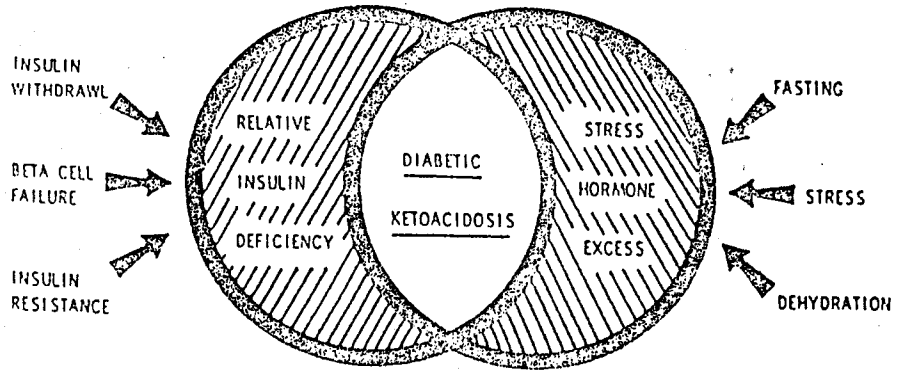

Figure 1. The hormonal basis for the development of diabetic ketoacidosis. (*From* Dahlquist G, Gustavsson KH, Holmgren G et al: Acta Paediatr Scand 71:7, 1982; with permission.)

concentrations, and a group of hormones broadly classified together as the counterregulatory hormones, the actions of which largely oppose those of insulin. When relative insulin deficiency occurs in the setting of elevated counterregulatory hormone activity, DKA results (Fig. 1).

Insulin

Insulin is secreted by the beta cells of pancreatic islets and is the body's primary anabolic hormone, stimulating the synthesis of energy storage molecules in the nonfasted state. During a fast, when blood glucose concentration falls, insulin secretion decreases to basal levels, which allows mobilization of stored energy substrates. Glycogen is broken down to form glucose (glycogenolysis), protein is catabolized and the amino acids are converted to glucose (gluconeogenesis), and fats are broken down to free fatty acids, which are converted in the liver by acetyl-CoA to glucose or ketoacids (ketogenesis). The resulting increase in blood glucose leads to the release of insulin, which attenuates the magnitude of increase of blood sugar. Insulin acts throughout the body, but its effects on three target organs are most important in DKA. In the liver, insulin increases the rate of glucose uptake from portal blood, stimulates glycogen synthesis, and inhibits gluconeogenesis and glycogenolysis. In skeletal muscle, insulin also increases glucose uptake from blood, stimulates protein synthesis, and inhibits proteolysis. In fat cells, insulin is required for glucose and lipoprotein uptake from blood, stimulates lipogenesis, and inhibits lipolysis.[21] Only the brain, the renal medulla, and the formed blood elements do not require the presence of insulin to transport extracellular glucose within the cell. Insulin deficiency is the major endocrine abnormality responsible for the metabolic changes of DKA. Although counterregulatory hormone activity is important in amplifying the consequences of insulin deficiency, this activity alone is not sufficient to cause DKA.[51]

is stimulated by stress, and in their presence insulin requirements are increased. Their actions in turn are modulated by insulin; therefore in the diabetic patient their unopposed effects may be fully expressed. From a temporal standpoint, glucagon, cortisol, and catecholamines are important for acute changes in the metabolic process, whereas growth hormone's effect is delayed.

Glucagon is a counterregulatory hormone secreted from pancreatic alpha cells, the effects of which are effectively modulated by the secretion and action of insulin in the normal subject. These effects are an increased hepatic glucose production via activation of glycogenolysis and gluconeogenesis (without the compensatory increase in glucose utilization that would be seen in the normal subject with intact insulin secretion), which results in sustained hyperglycemia.[63] In the diabetic patient with DKA, however, both glucagon levels are increased by 400 to 500 per cent and the glycemic effects of glucagon are not subject to inhibition by insulin.[63, 74] Glucagon enhances hepatic ketone production by 300 per cent independently of the serum free fatty acid concentration[47, 84, 85] and also stimulates lipolysis. The importance of glucagon in the genesis of DKA is seen in animal experiments in which inhibition of glucagon secretion retards the rate of DKA development and decreases the severity of DKA.[12]

Epinephrine and norepinephrine release is stimulated by activation of the sympathetic nervous system by stress, acidosis, or fever. These hormones stimulate two important processes: they increase blood glucose and free fatty acid concentrations. Elevated epinephrine levels increase hepatic glucose output by activating gluconeogenesis and stimulating glycogenolysis,[84] an effect that dissipates after 60 to 90 minutes. Peripheral glucose clearance from the blood is reduced; an effect that is sustained for the duration of the elevated blood levels of epinephrine.[79] Adipose tissue lipases are activated, resulting in fatty acid mobilization and secondary ketogenesis by the liver.[84] These actions differ in insulin-dependent diabetic patients. In the absence of elevated insulin levels, a sustained (rather than a transient) increase in hepatic glucose production is seen. In the insulin-deficient patient, elevated serum catecholamine levels result in a five- to sevenfold greater increase in serum glucose concentrations than in the normal patient.[84]

Cortisol depresses peripheral glucose utilization while exerting little effect on glucose or ketone production,[80] although there is some evidence to suggest that cortisol may increase hepatic glucose production in diabetic patients.[80] Insulin-deficient children will experience a greater increase in blood glucose in the presence of hypercortisolemia than will normal subjects.[84]

Growth hormone has no acute effects on metabolism; however, a sustained increase in growth hormone levels, such as may occur during prolonged periods of stress, accelerates hepatic glucose production and leads to increased lipolysis and free fatty acid levels, which feed hepatic

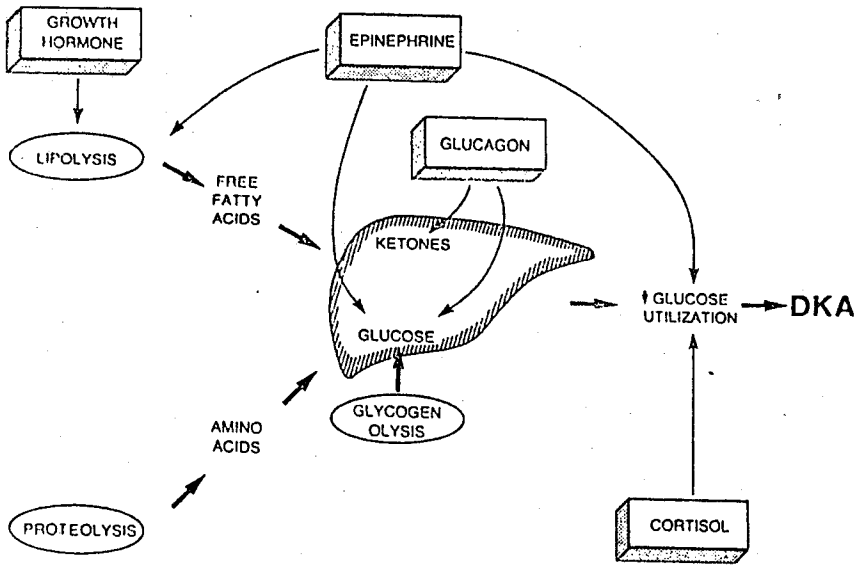

Figure 2. The major sites of action of the counterregulatory hormones.

indiscretion alone in the diabetic will not lead to DKA, only hyperglycemia. To develop DKA there must be both a relative lack of insulin and a relative overactivity of the counterregulatory hormones.[35] Serum glucose levels rise owing to increased glucose production by the liver and decreased glucose utilization by the body, increased levels of amino acids and free fatty acids occur, and ketone levels increase dramatically because of both augmented ketone production and inhibited utilization. Glycogen is broken down in the liver, and glycogen depletion occurs during the first several hours of ketoacidosis. Muscle protein is actively catabolized to amino acids. Increased levels of ketone bodies result in metabolic acidosis. Thus, we have accounted for the triad of DKA: hyperglycemia, ketosis, and metabolic acidosis. Diabetic ketoacidosis is a superfasted state robbed of normal homeostatic mechanisms, with the body's tissues deprived of their normal energy substrate, glucose. This complicated cycle is most often triggered by a stress in a person with insulin deficiency, who is unable to increase endogenous insulin levels to counteract the effects of increased activity of stress-induced counterregulatory hormones. The precipitating stress may be of diverse causes, or may be physiologic (e.g., surgery, strenuous sustained exertion, pregnancy, dehydration, hyperthermia), infectious, or even, perhaps, psychological in nature.[35]

PHYSIOLOGY OF DKA

Hyperglycemia and ketoacidosis induce important alterations in organ physiology. Hyperglycemia causes an osmotic diuresis and eventually leads to dehydration, electrolyte depletion, [illegible]

in turn cause changes in renal function, the function of the central nervous and cardiovascular systems, oxygen transport by red blood cells, and bowel motility. Understanding this chain of events is helpful to the development of a treatment strategy.

Consequences of Hyperglycemia

Renal Function. Normally, all the glucose filtered by the glomeruli is reabsorbed by the proximal tubules. When the plasma glucose concentration exceeds the renal threshold for glucose reabsorption, glucose appears in the urine. Hyperglycemia induces an osmotic diuresis and loss of water, which may lead to dehydration. Because glucose is freely distributed throughout the extracellular water, and because in the absence of insulin, glucose is not transported into cells, an osmotic gradient between the extracellular and intracellular fluids results in movement of water from the intracellular to extracellular space, masking the clinical severity of the patient's dehydration by minimizing its hemodynamic consequences.

The patient with intact thirst mechanisms and normal renal function will become only moderately hyperglycemic during episodes of ketoacidosis because the kidneys can normally excrete excess glucose at rates equal to the accelerated glucose production rates of DKA. The patient with DKA who is vomiting or who is obtunded, however, cannot take in enough fluid to match the ongoing osmotic diuresis. The small child with DKA may have his or her fluid intake regulated less by physiologic thirst mechanisms than by parents, and will also be unable to meet the demands of diuresis. Dehydration, volume contraction, and consequently reduced glomerular filtration rates (GFR) occur. Reduction of GFR limits glucose excretion, which augments hyperglycemia and exacerbates hypertonicity and cellular dehydration. Severe hyperglycemia in excess of 600 mg per dl not only denotes severe DKA, but implies marked dehydration (over 10 per cent) with significant reduction of renal function,[1, 44, 47, 71] and accounts for the observation that the blood glucose concentration of patients with severe DKA may be reduced to about 300 mg per dl by treatment with rehydrating fluids alone and no insulin.[44, 71] Figure 3 illustrates this concept. During early DKA, blood glucose becomes elevated, but glycosuria does not occur until the renal threshold for glucose reabsorption is exceeded (nephrons 2 and 3). A steady state is reached at which glucose excretion is equaled by excess glucose production (nephron 4), and blood sugar will remain stable if dehydration does not occur. If dehydration supervenes, however, GFR and the quantity of filtered glucose will decline (nephron 5), resulting in a higher blood sugar at the new steady state at which glucose excretion will again equal excess glucose production (nephrons 6–8). It is clear then that severe hyperglycemia by necessity is accompanied by significant reductions in renal function, and that restoration of a normal GFR will promote return of the blood glucose to about 300 mg per dl.

The osmotic diuresis of DKA causes passive loss of electrolytes as well as free water. Typical sodium losses are generally between [illegible] and 13 mEq per kg, potassium losses between 4 and 10 mEq per kg, [illegible] phosphate

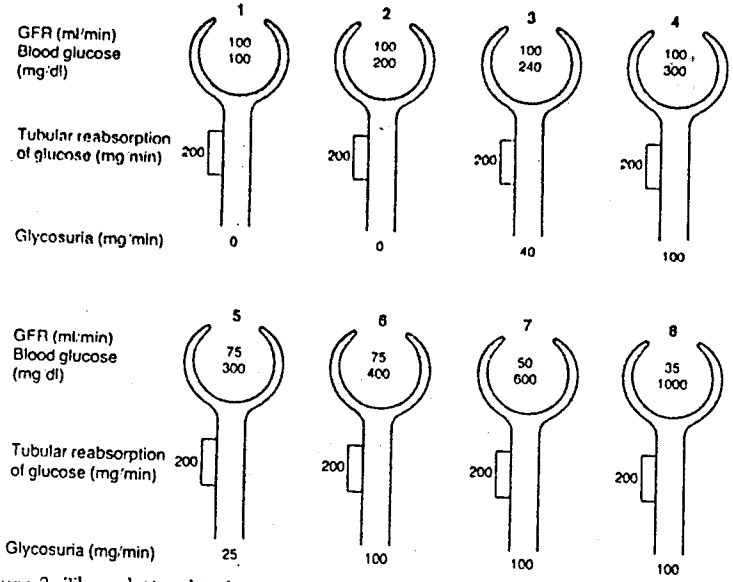

Figure 3. The relationship between glomerular filtration rate and maximal possible blood glucose concentration, assuming a constant excess glucose production rate. The first nephron illustrates the euglycemic subject. The subsequent nephrons illustrate the diabetic patient with an excess production rate for glucose of 100 mg per min or 1400 μmol per min (the difference between glucose production and utilization rates).[41] Maximal tubular reabsorption for glucose is estimated to be 200 mg per min.[46, 71] Urinary glucose excretion is determined by the amount of glucose filtered (GFR × blood glucose concentration × 100) less the amount reabsorbed. See text for further discussion.

of electrolyte wasting are seen on cardiovascular function and on oxygen transport by red blood cells.

Dehydration. Free water losses of patients hospitalized with DKA are usually between 100 and 150 ml per kg, depending on the severity of and length of illness. The magnitude of elevation of blood glucose affords an estimate of the degree of dehydration and volume contraction.[44] Hypovolemia exacerbates the metabolic acidosis of DKA by two mechanisms. Volume contraction leads to decreased tissue perfusion and lactic acidosis, which may account for up to 25 per cent of the acidemia of DKA.[103] Hypovolemia also reduces renal function and the excretion of organic acids. As DKA is treated and blood glucose concentration falls, water will move from the extracellular to intracellular space, and further vascular volume depletion may occur if rehydration and sodium replacement have not been adequate.

Sodium. Studies of urinary sodium losses in patients with DKA show that urinary sodium concentration is 40 to 100 mEq per liter,[71] or the approximately equivalent to one-half normal saline. In spite of the loss of free water in excess of sodium, serum sodium concentration usually is not elevated but decreased[12, 35] because serum hypertonicity draws water out of the cells into the extracellular space, diluting the sodium within that space. Each 100 mg per dl elevation of glucose concentration lowers the

serum sodium by about 1.6 mEq per liter.* As DKA is treated and the blood sugar falls, water moves back into the cells, and the serum sodium concentration rises. Hypertriglyceridemia occurs with severe episodes of DKA, and is a cause of factitious depression of the serum sodium. Sodium is distributed only within the aqueous fraction of serum, but the total serum volume may be elevated by triglyceridemia. Thus, the sodium concentration reported by the clinical laboratory in mEq per liter of plasma may be artifactually low.

Potassium. Potassium loss may be profound during DKA. Intracellular potassium shifts to the extracellular space during acidosis and protein catabolism. Potassium is lost into the urine owing to both the solute diuresis and increased aldosterone activity stimulated by dehydration. Additional potassium loss may occur from vomiting. In spite of potassium depletion, normokalemia or hyperkalemia is the rule during the early phase of treatment of DKA,[32, 38] a result of both the intra- to extracellular shift of potassium and the impairment of renal function. With rehydration and insulin therapy, hypokalemia may occur, a consequence of dilution of circulating potassium, improvement of GFR and accelerated renal losses, and redistribution of potassium back into cells by correction of acidosis and treatment with insulin.[54]

Cardiac arrhythmias are the major complication seen with changes in potassium homeostasis. Myocardial membrane stability and function depend largely on the gradient of potassium across the muscle membrane. Intracellular potassium depletion and consequently a decreased intracellular/extracellular potassium gradient may result in the typical clinical picture associated with hyperkalemia. Electrocardiographic manifestations of hyperkalemia conceivably may be seen in diabetic patients at lower serum potassium concentrations than in normal patients: peaked T waves and, if severe, widening of the QRS complex and asystole. Hypokalemia occurs frequently during therapy of DKA, and is manifested by U waves on the electrocardiogram, as well as myocardial irritability and ventricular ectopic activity. Although delay of potassium therapy for the first hour or two of treatment while expanding the blood volume and reestablishing renal function is acceptable, the presence of a normal or slightly elevated serum potassium concentration should not deter the clinician from replacing potassium losses during the subsequent hours of therapy.[9]

Phosphate. Although serum phosphate concentrations in untreated patients with DKA are usually normal or slightly elevated,[19, 50] body phosphate stores are significantly depleted.[2, 49] Serum concentration of inorganic phosphate is usually well defended by movement from the intracellular space into the plasma, with passive loss through diuresis. As with potassium, serum phosphate levels predictably fall during therapy of DKA.[50, 101] Phosphate depletion and inhibition of red blood cell oxidative metabolism lead to a decrease in red blood cell 2,3-diphosphoglycerate (2,3-DPG) concentration.[2, 11, 23, 49] 2,3-DPG is a glycolytic intermediate

*Correction of serum sodium during hyperglycemia[71]:

$$Na^+ = Na^+ \text{ measured} + 1.6\,(\text{Glucose} - 100)$$

known to be present in high concentrations in red blood cells, which facilitates release of oxygen from hemoglobin to tissues. A reduction of 2,3-DPG level causes the hemoglobin–oxygen dissociation curve to be shifted to the left. As a result, hemoglobin binds oxygen molecules more tightly, and releases them less readily at the tissue level. Acidosis, however, promotes oxygen release from hemoglobin (the Bohr effect); therefore, tissue hypoxia does not occur because of the opposing effects of acidosis and low levels of 2,3-DPG.[3, 11] Profound hypophosphatemia (serum phosphate concentration <0.5–1.0 mEq per liter) can cause muscular weakness, CNS depression, and myocardial dysfunction,[72] but such low concentrations have not been reported in patients with DKA. The clinical importance of phosphate depletion in diabetic patients has not yet been defined. In adults, phosphate therapy prevents hypophosphatemia,[49, 101] and preserves normal hemoglobin oxygen binding,[3] although it does not alter the clinical recovery from DKA.[49, 101] Without phosphate supplementation, children with DKA repair their erythrocyte 2,3-DPG levels more rapidly than do their adult counterparts,[65] and therefore may not require phosphate replacement. A reported complication of aggressive phosphate repletion is symptomatic hypocalcemia and hypomagnesemia,[102] although the child in this report received a quantity of phosphate larger than presently recommended. While phosphate supplementation prevents or repairs hypophosphatemia, its need and overall efficacy are not conclusively known.

Bicarbonate. Serum bicarbonate concentration is always depressed in patients with DKA because extracellular bicarbonate ion is the body's first-line buffer against metabolic acidosis. Although serum bicarbonate concentration is low, little or no bicarbonate deficit is created, because the ketoacid and lactic acid anions in tissues and the circulation are ultimately metabolized by the liver and peripheral tissues to bicarbonate during insulin therapy.[54] While a small quantity of ketone and bicarbonate anion lost in the urine prior to hospital therapy[67, 69] and may contribute to the mild hyperchloremic acidosis that is occasionally seen following resolution of DKA,[1, 67, 70] most patients repair their metabolic acidosis completely without bicarbonate supplementation.[1, 56] The controversy of bicarbonate therapy during DKA is considered below.

Other Consequences of Hyperglycemia. Azotemia is a common occurrence during DKA. Renal dysfunction and increased protein catabolism during DKA increase serum BUN and creatinine.[71] Spurious elevation of the serum creatinine may be seen as a result of the common clinical laboratory method for measuring creatinine (the alkaline picrate assay), which also detects acetoacetate.[7, 64] Newer laboratory assays are more specific.

Prolonged periods of hypertonicity caused by sodium, glucose, or urea have long been known to promote the formation of unidentified osmotically active chemicals in the brain.[5, 6, 60] The brain is enclosed within bony confines and is attached to its osseous vault by bridging veins. If cellular dehydration of the brain were to cause it to shrink away from the skull, bridging veins would tear and subdural hematomas could result. The brain, however, seems not to shrink during periods of systemic hypertonicity,

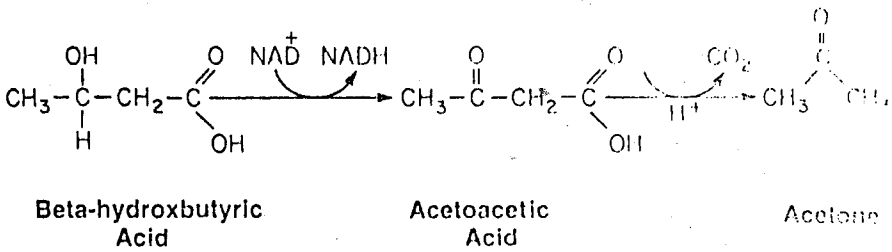

Figure 4. The ketone bodies of diabetic ketoacidosis. Note that β-hydroxybutyric acid (BOHB) is not a ketone and is converted to acetoacetic acid (AcAc) by oxidation. Acetone is formed by nonenzymatic decarboxylation of AcAc, and is not an acid. The common method of measuring serum or urinary ketones only detects AcAc, whereas BOHB is present in the greatest concentration in serum. As DKA is treated, the fraction of AcAc increases while the total ketone body concentration decreases.

analysis of the brain during such hypertonic states reveals that the brain's tonicity has been increased by the presence of osmotically active substances, the nature of which has eluded qualitative analysis (hence the term "idiogenic osmoles"). During hyperglycemia, these substances to a minor extent are glycolytic products of the "polyol pathway,"[20, 39, 77] fructose, sorbitol, and other glucose metabolites, but these substances account for no more than 50 per cent of the total increase in brain osmolality.[5, 6, 14] The formation of idiogenic osmoles may serve to limit the extent of volume contraction of the brain, thus protecting against the formation of subdural effusions or hematomas. The role of sorbitol and idiogenic osmoles in the genesis of cerebral edema during DKA is considered below.

Hyperglycemia therefore causes several important alterations—dehydration, hypertonicity, volume contraction, electrolyte losses, and renal dysfunction, as well as the creation of idiogenic osmoles in the brain.

Consequences of Ketoacidosis

Ketone bodies are synthesized in the liver during DKA (Fig. 4). Beta-hydroxybutyric acid (BOHB) and acetoacetic acid (AcAc) are strong organic acids with pKas of 4.70 and 3.58, respectively;[1] they therefore are completely dissociated at physiologic pH. Although both these species are commonly referred to as ketoacids, only AcAc is truly a ketone. BOHB is oxidized to AcAc, and the relative amount of each species depends on the redox state of the cell. Decreased tissue perfusion, metabolic acidosis, and tissue catabolism will favor reductive metabolism during DKA. Normally the BOHB/AcAc ratio is 3:1, but the ratio may increase during ketoacidosis to 6:1 or even 12:1.[17, 54, 55, 58] The common method of measuring ketone body concentration (e.g., the Acetest tablet or Ketastix) relies on the nitroprusside reaction, which only detects ketones, not BOHB. The major species of ketoacid present during DKA therefore is not routinely measured. Furthermore, the BOHB/AcAc ratio is not known in any given patient and certainly changes during the course of therapy. Therefore the utility of routine determination of serum ketones is of limited value and does not necessarily reflect the well-being of the patient or adequacy of treatment.

DKA, reflecting only a predominance of BOHB, and rise during therapy as oxidative metabolism converts BOHB to AcAc, although the total concentration of ketone bodies actually may be falling.

Metabolic acidosis may affect organ function profoundly. Breathing is stimulated, inducing a partially compensating hypocapnia[71] and the Kussmaul respirations associated with DKA. Hypocapnia during DKA is ubiquitous, and a partial pressure of CO_2 in arterial blood below 20 mm Hg is not uncommon. During metabolic acidosis, minute ventilation increases as pH falls. Older literature suggests that when the arterial pH is below 7.2 or 7.1, respiratory compensation may become attenuated, allowing no further compensation of worsening acidosis to occur.[51]

Hypocapnia causes cerebral vasoconstriction and reduces cerebral blood flow. In healthy awake patients arterial CO_2 tensions below 25 mm Hg are associated with maximal cerebral vasoconstriction. The physiologic significance of hypocapnia in patients with DKA is not known, and has not been addressed since Kety et al. measured cerebral blood flow and metabolism in adult diabetic coma four decades ago, finding that patients with diabetic coma infrequently had significantly depressed cerebral blood flow, while depression of cerebral oxygen consumption was more common and predicted fatal outcomes.[51] A possible relationship of hypocapnia, cerebral blood flow, and cerebral metabolism to the development of cerebral edema has not been explored.

Progressive acidosis leads to circulatory depression because of depression of the vasomotor center, direct depression of arteriolar smooth muscle tone, and direct depression of the contractility of the myocardium. In the early stages of acidosis, these depressant effects are offset by an increase in catecholamine secretion and adrenergic stimulation of the circulation, as well as an increase of serum ionized calcium. With severe acidosis, these compensatory adjustments are insufficient to counteract the direct depressant effects of acidosis.

Although profound metabolic acidosis depresses myocardial performance, it has only a limited effect on the central nervous system.[73] The blood–brain barrier is poorly permeable to ions, including bicarbonate and hydrogen ions. Consequently, the brain is relatively isolated from changes in serum ion concentrations. Carbon dioxide, however, diffuses rapidly into and out of the central nervous system; therefore, CNS pH is normal or even elevated during severe metabolic acidosis,[70] unlike during severe respiratory acidosis, when CNS pH is low, possibly leading to alterations in mentation. Children with DKA are usually awake or arousable in spite of an extremely low systemic pH, while patients with respiratory failure and the equivalent pH are deeply comatose.[73] This concept may be important when considering bicarbonate therapy.

Paralytic ileus and gastric dilatation are common accompaniments of DKA. Bowel ileus may be caused by metabolic acidosis and potassium depletion. Splanchnic circulation is decreased in the presence of dehydra-

occur. Hypocapnia may induce cerebral vasoconstriction. Severe metabolic acidosis may lead to cardiovascular depression, arrhythmias, and collapse inadequately compensated by increased sympathetic activity. Finally, splanchnic blood flow is reduced and paralytic ileus is common.

MANAGEMENT OF THE DIABETIC PATIENT WITH DKA

Successful treatment of the patient with DKA requires knowledge of its pathophysiology, vigilant attention to the patient, and effective use of fluids and insulin. Adherence to the following or any other therapeutic approach is less important than flexibility and individualization of therapy.

Diagnosis

The diagnosis of DKA is seldom difficult. The correct diagnosis is usually suggested by the clinical appearance of a lethargic patient with hyperventilation (Kussmaul's respirations), a fruity character to the breath, and a history of polyuria. In small children who are not known diabetics, however, the diagnosis may be less clear. Frequently, such patients are thought to have bacterial sepsis when they appear with pallor, lethargy, tachypnea, and dehydration, and only with routine laboratory evaluation is the diagnosis suggested.

It is important to consider the underlying cause of ketoacidosis. Frequently, a physiologic stress sets the stage for DKA. Most often that stress is infection. Hypothermia and absence of a hyperpyrexial response to infection are so common in DKA that the absence of fever cannot be used to exclude the possibility of infection.[10, 70, 75] Leukocytosis is common even in uncomplicated DKA and is not necessarily evidence for infection. Although in pediatric practice most triggering infections will prove to be viral, bacteriologic etiologies must be excluded. Urinary sepsis is common in poorly controlled diabetic patients, thus the presence of abdominal pain should suggest the possibility of pyelonephritis or a perinephric abscess as well as other surgical conditions,[15] although nonsurgical abdominal pain is more common. The serum amylase is frequently elevated in DKA.[70] The reason for this finding is not known but does not necessarily signify the presence of pancreatitis. Other frequent precipitating causes include trauma, pregnancy, pancreatitis, and, in adults, myocardial infarction and cerebrovascular accidents. It is wise to remember that common causes of coma also may occur in diabetics and trigger DKA, although DKA itself usually does not cause profound coma.[4] In spite of the many problems that may lead to stress and ketoacidosis, in about half the cases of DKA a precipitating cause cannot be found.

The routine laboratory evaluation of the child with DKA should begin with determination of the blood glucose concentration and a urinalysis, followed by serum electrolytes, calcium, BUN, creatinine, phosphate,

ogram may provide rapid evidence for hyperkalemia (peaked T waves), but electrocardiographic evidence for potassium abnormalities is difficult to interpret from a bedside cardiac monitor with nonstandard lead placement. A standardized flow sheet[93] detailing fluid therapy, insulin therapy, and the laboratory and physiologic response to treatment is invaluable in organizing and monitoring therapy.

Once the diagnosis of DKA is established, therapy should begin immediately, delaying neither for further diagnostic evaluation nor for transfer of the patient to the ward or the intensive care unit. The treatment of the patient with DKA consists of resuscitation, monitoring, and intravenous therapy with fluids, electrolytes, and insulin.

Resuscitation

Only 10 per cent of patients with DKA are comatose when first seen by a physician, but most have alterations in their level of consciousness.[4, 35] The first priority is assessment of the adequacy of the airway and the patient's ability to defend it against secretions or aspiration. The infrequent patient with DKA who is comatose and has obtunded airway reflexes should have his airway secured by endotracheal intubation and gastric decompression by nasogastric suction. Patients who are obtunded or lethargic but arousable and who have evidence for gastric dilatation or ileus (abdominal distention, pain, or absence of bowel sounds) should also have gastric decompression by nasogastric suction. Aspiration pneumonia with subsequent respiratory failure is one of the more common mechanisms of death in this population, and in some instances this complication may be preventable.

The next priority is repletion of the circulating blood volume. Patients with DKA are dehydrated, usually with fluid deficits of about 100 ml per kg. A more precise estimate of fluid losses may be made if the patient's weight can be compared to a recent known weight. Volume expansion is accomplished intravenously by infusing an isotonic glucose-free solution, which will actually be hypotonic in relation to the patient's serum tonicity. Volume expansion alone will ameliorate hemoconcentration, improve hemodynamics, but most importantly, restore glomerular filtration and lower blood sugar. The usual fluid used is normal saline or lactated Ringer's solution in amounts of 10 to 20 ml per kg given over a 1-hour period. Lactated Ringer's solution is an isotonic solution with the advantage of providing less chloride than normal saline, which may reduce the risk of hyperchloremic acidosis that occasionally complicates the recovery of diabetics.[1, 67, 69] Additionally, lactated Ringer's solution provides a small amount of lactate (28 mEq per liter), which is slowly metabolized to bicarbonate over several hours. The small amount of potassium present in lactated Ringer's solution (4 mEq per liter) does not contraindicate its use in the presence of mild hyperkalemia, provided that the patient is nonoliguric.

Monitoring the Diabetic Patient

The [illegible]ent with diabetic ketoacidosis may be cared for on a pediatric ward or in an intensive care unit. The latter is recommended in the cases of infants and toddlers with DKA, in the presence of more severe acidosis

(e.g., pH < 7.1), central nervous system obtundation, or cardiovascular instability, to provide the opportunity for closer observation and invasive monitoring to facilitate frequent laboratory evaluation. Continuous electrocardiographic monitoring is desirable. An indwelling intra-arterial line may be used to provide continuous blood pressure recording as well as vascular access for blood sampling. Obtunded patients, especially small children should have an indwelling bladder catheter for accurate measurement of urine output and chemistries.

The child with mild or moderate DKA may be cared for on a ward. A heparin-locked intravenous catheter provides a convenient and painless means of obtaining frequent blood samples. Continuous electrocardiographic monitoring should be employed if hyper- or hypokalemia exists, if intravenous bicarbonate is administered, or if high-dose intermittent insulin therapy is being used, which are associated with a considerable risk of secondary hypokalemia[2, 9, 16], although ECG alone is inadequate for detecting serum potassium abnormalities and should be used in conjunction with serum electrolyte determinations.

Routine laboratory evaluation includes initial monitoring of blood glucose concentration and acid–base status hourly during initial therapy, after which this can be done 2- to 4-hourly as dictated by clinical response, and electrolytes 2- to 4-hourly as needed. Serum calcium concentration should be closely followed if phosphate is administered. Although repeated measurements of serum ketones is of little value, serial calculation of the anion gap* provides valuable information because both BOHB and AcAc as well as lactate contribute to the anion gap. Partial or full correction of DKA should be anticipated to occur within 12 to 24 hours.

Insulin Therapy

Before 1972 very large doses of insulin were used for the treatment of DKA because of postulated insulin resistance during DKA, which was presumed to resolve during therapy in most patients. In subsequent years, several reports appeared documenting the efficacy of treatment with substantially lower doses of insulin given either by continuous intravenous infusion or by frequent repeated intramuscular injections.[7, 43] Despite many published regimens for the treatment of DKA, several broad conclusions may be made regarding the resolution of DKA when treated with low-dose insulin. The rate of decline of blood glucose is fairly constant in most patients and is not accelerated by the administration of larger doses of insulin, although correction of acidosis may require about twice as much time as correction of hyperglycemia.[54, 90]

Few studies have prospectively compared low- with high-dose insulin regimens. Low-dose insulin is as effective as high-dose insulin in correcting hyperglycemia and acidosis, whereas low dose insulin is not associated with any untoward effects.[4, 46] Hypoglycemia and hypokalemia occur in as many as 25 per cent of patients treated with high-dose regimens.[2, 4] In one

*Calculation of anion gap[65]:

Anion gap (mEq per liter) = $Na^+ - (Cl^- + HCO_3^-)$

Normal value = 8–16 mEq per liter

study,[71] acidosis resolved more slowly in patients treated with low-dose insulin than in the high-dose group, although the differences were not clinically significant. The authors of this study also noted that patients treated with low-dose insulin retained less potassium than those receiving high doses, but nonetheless required less potassium supplementation for treatment of hypokalemia. Plasma insulin concentrations in patients on low-dose regimens approximate physiologic insulin concentrations.[40, 72, 87] The maximal biologic effect of insulin seems to be seen at plasma concentrations of 20 to 200 μU per ml,[24] but the plasma insulin concentrations seen with high-dose regimens result in insulin levels of approximately 1000 μU per ml. Counterregulatory hormone activity declines at similar rates with high- and low-dose techniques.[46] Although at first glance it may seem difficult to reconcile the previously held notion of insulin resistance and the requirement for high insulin doses with the later success of low-dose insulin therapy, treatment with high-dose insulin results in supramaximal plasma concentrations of the hormone that achieve no further biologic effect than doses that produce physiologic blood levels, because of receptor saturation, tachyphylaxis, or receptor insensitivity from acidosis or electrolyte abnormalities. Large doses of insulin may produce plasma concentrations that may predispose to hypoglycemia at a time when blood glucose concentration and pH are returning to normal.

The proven success of low-dose insulin by continuous infusion and its association with fewer complications than high-dose techniques have led us to prefer this therapy for most children with ketoacidosis. Some patients will indeed demonstrate true insulin resistance and will not respond adequately to low-dose insulin, however; and these persons must be carefully monitored and more aggressive insulin therapy should be instituted when clinically indicated.[35] Because infection diminishes the response of blood glucose to insulin,[54] a search for bacterial infection should again be made in patients who demonstrate a slow rate of resolution of hyperglycemia. It is worthy of emphasis that the endpoint of treatment of DKA is not euglycemia but correction of acidosis. Although considerable resolution of hyperglycemia may be accomplished by hydration alone,[11, 71] this is not only adequate therapy for DKA. Occasionally, one encounters patients with significant acidosis but only mild hyperglycemia. These patients still require aggressive therapy with fluids and insulin: the appropriate course of action is not to reduce or omit the insulin, but rather infusion of dextrose to prevent hypoglycemia, while insulin is used to correct ketoacidosis.[54] While one might reasonably delay beginning insulin therapy until the response of the blood glucose and serum potassium to volume reexpansion is seen during the first hour or two of therapy, further delays of insulin administration are unwise.

Our approach to insulin therapy is to establish therapeutic insulin levels in the patient with a bolus dose of 0.1 U per kg of soluble (regular) insulin intravenously, then to begin a continuous infusion of 0.1 U per kg per hr. Because insulin will bind to the walls of intravenous tubing, fluid

subcutaneous injection used because of unpredictable and unreliable absorption in the presence of dehydration and volume contraction.[35, 75] The response to therapy should be carefully monitored, initially with hourly determinations of blood glucose and acid-base status. If the therapeutic response is inadequate the insulin dose should be doubled. When blood glucose has fallen to 250 to 300 mg per dl *and* acidosis has been partially repaired, the insulin infusion rate should be halved and 5 per cent dextrose added to the maintenance fluid infusion, and the response to this change carefully monitored to guard against recurrence of acidosis. If the blood glucose has fallen to 250 to 300 mg per dl but the ketoacidosis has not responded to therapy, the insulin infusion should not be reduced, but rather dextrose should be infused by vein at a rate to maintain the blood glucose at an acceptable level. The rate of dextrose administration can be estimated as follows. The volume throughout which glucose distributes is about 0.3 liter per kg. Thus a 30-kg child has a glucose space of 9 liters. If the glucose has been falling by 100 mg per dl per hour, this amounts to a glucose disappearance rate of 9 gm per hour from this child. This is the additional amount of glucose that needs to be infused. Since 10 per cent dextrose contains 10 gm per 100 ml of dextrose, 90 ml per hour should prevent any further fall of the blood glucose.

In some institutions intravenous insulin administration is by policy restricted to the intensive care setting. Patients with mild to moderate DKA can be managed outside of the intensive care unit either with low-dose frequent intramuscular injections or with conventional high-dose techniques, which are described in other treatises on the subject.[32, 92, 93, 94]

The transition from an insulin infusion to subcutaneous insulin injections may be made when the following criteria are met: blood glucose less than 250 mg per dl, pH greater than 7.30, and serum bicarbonate greater than 15 mEq per liter. Previously known diabetic patients can be returned to their known insulin dose. Newly diagnosed diabetic patients can be anticipated to require about 0.5 to 1.0 U per kg of insulin per day, two thirds of which is given as intermediate-acting insulin, and one third as short-acting insulin. Initially two daily injections provide control. Two thirds of the daily dose is given prior to the morning meal, and the remainder prior to the evening meal. The continuous insulin infusion should not be discontinued abruptly with the first subcutaneous insulin dose, but withdrawn over a few hours to allow time for the subcutaneous dose to be absorbed.

Fluid and Electrolyte Therapy

Assuming fluid deficits of about 100 ml per kg, and as high as 150 ml per kg in the most severe cases of DKA, our practice is to replace fluids as precisely as possible based on the known or estimated deficit, plus measured ongoing urine losses, and maintenance metabolic requirements.

Rapid infusions of fluid for vascular volume reexpansion, cardiovascular resuscitation, or establishment of urine flow should be near isotonic in

the calculated deficit over the first 8 to 12 hours, and additionally infuse an amount of fluid equal to the sum of ongoing urine losses measured at hourly intervals, and insensible water requirements, which may be estimated as 40 per cent of usual maintenance requirements. After the first 8 hours of therapy hyperglycemia should be mild or resolved, and ongoing urine losses need no longer be replaced. The remainder of the calculated fluid deficit is then infused over the next 16 to 24 hours in addition to maintenance fluid requirements of 1000 ml per m^2 every 24 hours. The composition of the hydrating fluid should be determined by the patient's serum electrolyte profile. Because about 70 mEq per liter of sodium has been lost as urine, 0.45 per cent saline is a reasonable solution for intravenous rehydration. Use of normal saline for this purpose will often lead to hypernatremia and may predispose to hyperchloremic acidosis during recovery. Some controversy exists over this issue, however, because this regimen admittedly leads to infusion of large quantities of hypotonic solutions in the face of hypertonicity.[28, 29] Although this can be justified by the large free-water losses of DKA, one author has implicated this practice in the etiology of cerebral edema complicating DKA.[29] Indeed some patients who have died of this complication had documented hyponatremia, though most have not. Prudence would dictate that if hypotonic fluids are used for rehydration of the child with DKA, serum sodium should be followed closely, and the amount of sodium in the intravenous fluid increased if the serum sodium declines.

Potassium administration is a crucial aspect of therapy. Potassium may be withheld during the first hour or two of therapy unless documented hypokalemia exists.[32, 33] After vascular volume reexpansion is accomplished, potassium is added to the intravenous replacement fluid in a quantity of 40 mEq per liter, half as the chloride salt and half as the phosphate (see below). The quantity may be increased to 60 mEq per liter in the presence of documented hypokalemia, but more concentrated potassium solutions should not be infused by peripheral vein. Severe hypokalemia requires placement of a central venous catheter for infusion of concentrated potassium solutions at a rate not greater than 1 mEq per kg per hour, with continuous monitoring of the electrocardiogram, but only rarely are these measures necessary. Serum potassium concentration should be carefully monitored, especially during the first 4 hours of therapy, when it usually reaches its nadir.[32, 34]

We choose to replace phosphate losses with potassium phosphate while periodically monitoring the response of serum calcium and phosphate, although the theoretical benefits of phosphate therapy are unproven. Since only severe hypophosphatemia (0.5–1.0 mmole per dl) is associated with significant morbidity, attempts to correct phosphate rapidly to normal values should not be made, accepting values over 1.5 mmole per dl.

Bicarbonate Therapy. The use of bicarbonate is a controversial issue among physicians who treat diabetic children.[19, 64, 101, 105] Arguments in favor of the use of bicarbonate are that myocardial performance and the response to catecholamines are improved at a pH greater than 7.0, and that the ventilatory response to acidosis may be blunted below a pH of 7.2 or 7.1. In fact, hypotension from myocardial depression or lactic acidosis from low

cardiac output states during even the most severe instances of DKA is quite rare in children, and their ventilatory response is usually well maintained.

Arguments against the use of bicarbonate revolve around three issues. The first is that rapid infusion of bicarbonate and correction of acidosis will shift the hemoglobin–oxygen binding curve to the left as the effect of depressed red cell 2,3-DPG level remains unopposed by acidosis (see above), theoretically with resultant impairment of tissue oxygen delivery.[23] No clinical data support this fear. While this phenomenon was indeed demonstrated to occur in adult diabetic patients treated with very large quantities of bicarbonate and would have necessitated a fourfold increase of cardiac output to overcome the decreased tissue oxygen delivery, no adverse clinical effect was seen in any patient.[11] In a study of children with DKA treated with more clinically relevant doses of bicarbonate, no adverse effect on oxygen binding by hemoglobin could be demonstrated.[65] A second and more valid concern is that bicarbonate therapy causes paradoxical CNS acidosis[8, 70] and diminishes CNS oxygenation.[13] Paradoxical CNS acidosis occurs because, while the brain is well defended against metabolic changes in acid–base status, CO_2 crosses the blood brain barrier readily and lowers CNS pH. Because rapid administration of bicarbonate will raise the peripheral pH, the ventilatory response to metabolic acidosis declines and the arterial CO_2 tension rises. This increase in CO_2 tension is immediately transmitted to the brain, inducing a fall in pH and altering CNS function (Fig. 5). This phenomenon has been documented in both animal models[5] and in humans.[8] Its clinical relevance is obscure. Bicarbonate therapy also has been shown to diminish central nervous system oxygen availability in ketoacidotic dogs given very large doses of alkali.[13] Animals treated with bicarbonate had depressed cisternal CSF oxygen tensions and increased CSF lactate levels, suggestive of impaired CNS oxygenation. The authors also report that the bicarbonate treated dogs became lethargic and vomited. Whether impaired CNS oxygenation was related to changes in hemoglobin–oxygen binding, to alterations in CNS acid–base status, or to other factors, is speculative. The doses of bicarbonate administered in this study were also very much larger than are recommended in clinical practice.

A third argument against the use of bicarbonate is that its use will lead to rapid correction of acidosis with resultant intracellular movement of potassium, and result in hypokalemia. Additional concerns are that bicarbonate administration may accentuate sodium load and contribute to serum hypertonicity.

Only two studies have compared patients with severe DKA treated with and without bicarbonate.[8, 56] No discernible difference in the recovery of these patients was evident, but hypokalemia was six times more common in the bicarbonate-treated group.[8] Whether bicarbonate was given by bolus injection or slow intravenous infusion did not change the incidence of hypokalemia. The rate of resolution of acidosis was similar in both groups. Remember that serum ketones will be metabolized to bicarbonate ion following insulin therapy, and represent a large pool of potential base.

Overall, the theoretical arguments against the use of bicarbonate are more compelling than are the theoretical arguments in its favor, while there is no evidence that bicarbonate therapy improves recovery from

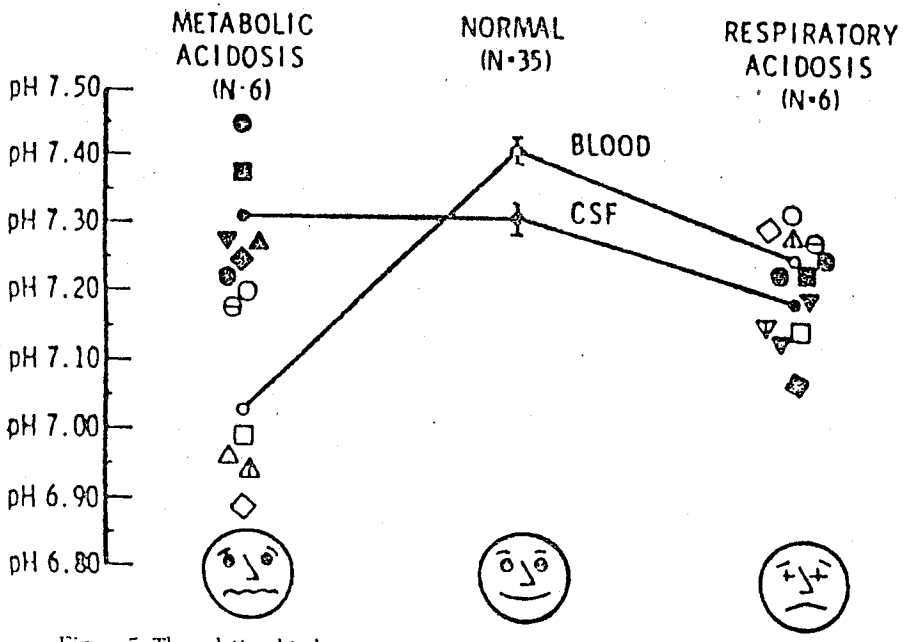

Figure 5. The relationship between systemic acidosis and central nervous system pH and function. CSF pH is near normal during metabolic acidosis but is below normal during hypercapnic acidosis. During respiratory acidosis, mentation is significantly impaired, although it can be near normal during metabolic acidosis. (*From* Posner JB, Plum F: N Engl J Med 277:605, 1967; with permission.)

DKA. It has been my practice to reserve bicarbonate administration for two specific indications, symptomatic hyperkalemia and cardiovascular instability, and otherwise to manage diabetic children without bicarbonate regardless of the arterial pH. Other authors have advocated the use of low-dose bicarbonate given by slow infusion only in the presence of severe acidosis (pH < 7.1) on solely an empiric basis.[32, 35, 47, 48, 54, 88, 101] In the absence of data provided by a controlled prospective study of the use of bicarbonate, one cannot be dogmatic about any approach, and the clinician must remain flexible and willing to change the therapeutic plan based on ongoing clinical and biochemical assessment of the patient.

Table 1 describes typical fluid and electrolyte therapy for a 30-kg child. Administration of excess sodium and chloride in the management of DKA is usual and difficult to avoid, but this may be partially ameliorated by the substitution of lactated Ringer's solution for normal saline during the resuscitation phase.

CNS COMPLICATIONS OF DIABETIC KETOACIDOSIS

*Table 1. Sample Calculation of Fluid and Insulin Therapy for a 30-kg Child with DKA and 10% Dehydration**

	DEFICITS					IV FLUID THERAPY†			INSULIN THERAPY		MONITOR					
	Na	*K*	*Cl*	PO_4	*Solution (%)*	*K*	*Rate*	*Dose*	*Route*	*ECG*	*Glucose*	*pH*	*Na*	*K*	*Phos*	*Ca*
	300	120	360	60						X	X	X	X	X	X	X
					0.9 NaCl	None	300/hr	(None)‡		↓	q1hr	↓	↓	↓	↓	↓
	354	120	354	60	0.9 NaCl	None	300/hr	(None)‡		↓	q2hr	↓	↓	↓	↓	↓
	208	120	208	60	0.45 NaCl§	20 mEq per liter KCl	150/hr	3 U then 3 U/hr	IV	↓	q2hr	↓	↓	↓	↓	↓
						20 mEq per liter kPhos			IV	↓		↓	↓	↓	↓	↓
	106	72	92	36	0.45 NaCl	20 mEq per L KCl	75/hr		↓	↓	q2–4hr	↓	↓	↓	↓	↓
	14	24	−35	12												

*Table 1 describes typical electrolyte losses.
†In addition to these fluids, 40 ml per kg of 0.45 per cent saline should be infused to replace insensible losses, and hourly urine output should be replaced with 0.45 per cent saline until diuresis resolves.
‡Insulin should be started immediately and changed by 1–2 hours. The insulin dose is halved when blood glucose concentration is less than 250–300 mg per dl.
§Dextrose is added when blood glucose concentration is less than 250–300 mg per dl.

acidosis. Although many complications of DKA can be successfully prevented by vigilant patient management and anticipation of physiologic changes, one complication which is seen more frequently in children than in adults remains sporadic, unpredictable, and frequently fatal: idiopathic cerebral edema.

The development of cerebral edema in patients with DKA is not heralded by any warning signs, nor are there any predictive indicators that would allow one to identify patients at risk.[51] Cerebral edema becomes clinically apparent several hours after therapy has begun, at a time when adequate circulation has been restored, severe acidosis has been partially corrected, and blood glucose is falling. All indications suggest that the patient is recovering well. The onset of cerebral edema is marked by an abrupt change in the level of consciousness, abnormal neurologic signs such as pupillary dilatation and decorticate or decerebrate posturing, and rapid progression to deep coma or brain death. Respiratory arrest may occur in association with herniation of the brain stem. The mortality of cerebral edema complicating ketoacidosis is very high.

First described five decades ago[27] and subsequently unreported for the next thirty years, there are now many cases that have been recently described,[29, 34, 36, 37, 41, 45, 57, 62, 83, 91, 96, 100, 103] and most pediatricians who care for diabetic children have encountered at least one case. Although the incidence of this complication is not known, subclinical brain swelling may occur commonly among patients with DKA, and overt cerebral edema may be simply a less frequent end-stage manifestation of a common phenomenon. To date two studies have described changes of cerebral swelling in asymptomatic patients with DKA treated with conventional insulin and fluid therapy,[31, 53] supporting much earlier observations that CSF pressure often rises during the treatment of DKA in patients who remain asymptomatic.[18, 19] Several theories have been advanced to explain the pathophysiology of this complication.

The most frequently invoked theory is that an osmotic dysequilibrium exists between the central nervous system and extracellular fluid during the therapy of DKA,[5, 6] which promotes movement of water along an osmotic gradient into the brain. As discussed earlier, during periods of systemic hypertonicity the tonicity of the brain increases in parallel, owing to the formation of unknown osmotically active molecules within the brain. Theory holds that these organic molecules dissipate or are metabolized more slowly than the rate at which serum tonicity declines, hence during therapy the tonicity of the brain exceeds the serum tonicity, and water movement into the brain is favored.

Experimental evidence for this theory exists but is incomplete. Idiogenic osmoles indeed do occur in the brains of hyperglycemic rabbits.[5, 6] Arieff and his colleague were successful in inducing cerebral edema in a diabetic animal model,[6] and Clements et al. in another animal model.[20] Interestingly, however, the idiogenic osmoles present during the peak of metabolic abnormalities could not be demonstrated at the time at which the rabbits developed edema.[6] Although some authors have speculated that brain glucose concentration may rapidly decline in the course of DKA

this.[3] The contribution of osmotic dysequilibrium to the development of cerebral edema therefore remains speculative.

If one examines all the reported cases of cerebral edema, their common feature is the use of insulin. Although the brain does not depend on insulin for glucose transport, insulin indeed may have some biologic effect on the brain. Arieff and Kleeman were unable to induce significant cerebral edema in diabetic rabbits treated with fluids and peritoneal dialysis alone to correct hyperglycemia and acidosis. Insulin-treated animals developed cerebral edema.[5, 6] Tornheim was able to induce cerebral edema only in rats with DKA by treatment with insulin and fluids, but not with fluids alone.[7] One conclusion that may be drawn is that cerebral edema does not occur unless blood sugar falls below 250 to 300 mg per dl (as it did not in the animals not given insulin), although the blood glucose concentration in the subjects of many case reports remained above this threshold. Another is that insulin was causative.[43] In this regard, Arieff and Kleeman demonstrated that insulin induced an inward flux of sodium, potassium, and water into the brains of experimental animals. The role of insulin in the development of cerebral edema deserves further study.

Although bicarbonate has been implicated as a causative agent in the formation of cerebral edema,[23] many cases reported in the literature were not treated with bicarbonate.[34, 36, 41, 83, 103] Patients with documented subclinical edema were not treated with bicarbonate.[53] Paradoxical CNS acidosis is an accepted clinical phenomenon, but probably plays no role in the development of cerebral edema.

Finally, one investigator has suggested that treatment of diabetics with hypotonic fluid and induction of hyponatremia is causative.[28, 29] While in selected cases hyponatremia may be a factor, most reported cases of cerebral edema have not been hyponatremic. Young and Bradley's original cases, the first reported in the American literature, were hypernatremic.[97] Clements et al. reported that insulin therapy and rehydration with isotonic solutions elevated CSF pressure of experimental animals, even at a time when they were still in negative fluid balance.[20]

Once present, cerebral edema can only be supportively treated with nonspecific measures of neurointensive care. The first priority in the comatose patient is intubation of the airway and hyperventilation to achieve a reduction of intracranial pressure by cerebral vasoconstriction. Mannitol may be effective in reducing brain swelling in this setting,[28, 29] but it should be used with caution. Mannitol can further aggravate hypertonicity, can precipitate renal damage, and can induce rebound increases in intracranial pressure, and its use must be tempered by knowledge that spontaneous recovery without its use has been reported.[62] Doses of as little as 0.25 gm per kg are effective in lowering intracranial pressure and may be safer in hypertonic patients than larger doses that have been previously recommended.[29] Corticosteroids are effective in reducing cerebral edema associated with brain tumors, but it is now widely accepted that they are probably not effective for other forms of cerebral edema, and would be expected to exacerbate the metabolic pathology of DKA. Finally, the prognosis of this

cerebral arterial thrombosis with infarction.[37] Further intensive therapy of the diabetic with cerebral edema should be guided by direct measurement of intracranial pressure.

PREVENTION OF DIABETIC KETOACIDOSIS

Careful management of every case of DKA may help to reduce mortality, but there will be many children with unpreventable complications who will die in spite of our best efforts.[21] To reduce mortality to a minimal requires the prevention of most episodes of DKA.

Prevention of DKA may occur along two lines. The first is patient and family education, with close outpatient follow-up by community physicians. The second is the development of new technologies for insulin administration that circumvent the common problems of poor patient compliance with medical therapies. A laudable goal would be prevention of all episodes of DKA among the population of known diabetics, which will reduce the incidence of DKA by at least 50 per cent. Only new-onset diabetic patients should then develop DKA.

Outpatient Education and Management. Two common reasons that diabetic patients develop DKA are that they do not take their insulin as prescribed, or that their insulin doses are erroneously reduced or even withheld during intercurrent illnesses when insulin requirements may be actually increased. The early symptoms and signs of DKA are almost always recognizable.[40] Lack of proper education and inadequate health care delivery remain major obstacles to preventing many episodes of DKA, and as such should be recognized as public health issues. A frequent misconception among families of diabetic children is that insulin requirements are reduced during viral illnesses when the child consumes less food, when in fact the opposite may be the case. The community physician who cares for diabetic children has the responsibility to correct this error in thinking, and to maintain close contact with families during periods of gastrointestinal illness. If a diabetic child cannot tolerate an adequate carbohydrate intake during an illness, then one may need to hospitalize the patient to ensure intravenous hydration and glucose intake, while at the same time carefully monitoring the urine and blood and adjusting the insulin dose accordingly.

The noncompliant patient presents one of the most challenging and frustrating problems to the pediatrician. Patient education programs, enrollment in diabetes support groups, diabetic summer camps, and other social programs have helped to reduce the magnitude of this problem, but there are always patients and families who resist our best intentions. It is for this population that implanted insulin delivery devices hold the greatest promise.

Several new technologies are on the horizon for diabetic patients. The implanted insulin infusion device, or artificial pancreas, eliminates patient compliance variables and maintains tighter control of blood sugar than

the usual humoral control of insulin secretion. Recombinant DNA techniques have led to the proposal of iatrogenic infection with benign viruses containing the insulin genome. Finally, genetic engineering has made possible the commercial development of a reasonably priced human insulin preparation, which may serve to reduce the incidence of insulin antibody formation and insulin resistance that is common among patients treated with bovine or porcine insulin. Many years will pass, however, before the epidemiologic impact of these programs on the incidence of DKA can be seen.

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Diabetic Ketoacidosis and Cerebral Edema

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Introduction

In 1922 Banting and Best introduced insulin into clinical practice. A decade later the first reported case of cerebral edema complicating diabetic ketoacidosis (DKA) was reported by Dillon, Riggs and Dyer writing in the pathology literature. While the syndrome of cerebral edema complicating DKA was either not seen, ignored, or was unrecognized by the medical community until 3 decades later when the complication was again reported by Young and Bradley at the Joslin Clinic, there has since been a flurry of case reports in the 1960's and 1970's and basic and clinical research from the 1970's to the 1990's leading to our present day acceptance of this as a known complication of DKA, or of the management of DKA.

In fact, we now recognize that the cerebral complications of DKA (including much less frequent cerebral arterial infarctions, venous sinus thrombosis, and central nervous system infections) are the most common cause of diabetic-related death of young diabetic patients (1), accounting for 31% of deaths associated with DKA and 20% of all diabetic deaths, having surpassed aspiration, electrolyte imbalance, myocardial infarction, etc.

Furthermore, diabetes mellitus remains an important cause of hospitalization of young children. The prevalence rate of diabetes continues to grow in all Western developed nations, nearly doubling every decade, resulting in 22,000 hospital admissions in children under 15 years of age for diabetes in the United States in 1994, the majority of which were due to ketoacidosis. With approximately 4 hospital admissions of children for DKA per 100,000 population per year (2), every PICU located in a major metropolitan center will continue to see children with DKA at significant rates in the future, and every

pediatric intensivist will see at least one case of cerebral edema complicating DKA during his/her career.

The Clinical Characteristics of Cerebral Edema Complicating DKA

Cerebral edema complicating DKA is a syndrome unique to pediatrics. While described in a few adults, this complication occurs predominantly in children, most of whom are experiencing their onset of diabetes mellitus with the presentation of DKA (3) (Figure 1).

Figure 1. The age of patients in approximately 30 cases of cerebral edema complicating DKA from the author's case files and that were reported in the literature between 1960 and 1980.

Cerebral edema complicating DKA is generally an unpredictable phenomenon that occurs in children who seem to be metabolically returning to normal, generally 3-12 hours after the initiation of therapy (4-6) (Figure 2).

Figure 2. The time of onset of neurologic changes in approximately 30 cases of cerebral edema complicating DKA from the author's case files and that were reported in the literature between 1960 and 1980.

This description may seem true for the clinician faced with a case of cerebral edema. But as cases are subjected to post hoc scrutiny, and hindsight is liberally applied, it often seems to be the case that neurologic signs, while subtle, sometimes preceded the onset of clinically obvious cerebral edema and neurologic collapse. These symptoms may be increased lethargy and diminished arousability, incontinence, or complaints of headache. On the other hand, many of these complaints or observations may not seem remarkable at the time they occur. Lethargy and complaints of headache in the early hours of morning in a child with an acute viral illness, and who has been vomiting for several days, are truly not unusual, and may only be judged to be significant with the benefit of hindsight.

While it is true that only a small percent (0.5%-3%) of children with DKA will experience catastrophic cerebral edema, several investigations demonstrate that

subclinical cerebral edema is common if not universal during treatment of DKA both in adults (7,8) and children (6). These observations of cerebral edema *during* treatment were expanded by Hoffman, et al. (9,10) who demonstrated that the radiologic and transcranial Doppler evidence of cerebral edema *is present before the initiation of therapy for DKA.*

We therefore recognize that cerebral edema is a common subclinical complication of DKA in children, and that in a very few unfortunate children the cerebral edema becomes clinically manifest, usually with devastating consequences. The cause of the underlying cerebral edema in DKA, and the cause of neurologic deterioration in the minority of children whose cerebral pathology progresses, have been the source of considerable debate over the years. The theories commonly invoked are several:

1. Osmotic dysequilibrium between brain and plasma.

2. Overhydration and hyponatremia.

3. Intracerebral acidosis induced by alkali therapy or the correction of acidosis; accumulation of intracellular Na due to the action of the Na-H membrane exchanger, the antiport (11-13).

4. Alterations in cerebral blood flow (9,14).

This review will discuss the putative role of theories 1 and 2 in the development of cerebral edema during DKA. References pertaining to theories 3 and 4 are provided for those interested in further reading.

The Osmotic Abnormalities in DKA

Several profound metabolic abnormalities exist in the child with DKA; among the most important are disorders in serum glucose and sodium concentrations, which are the principal determinants of secondary changes in the osmolality, osmolarity, and tonicity of the plasma. Because these three terms mean different things but are frequently used interchangeably, it is useful to define them.

By convention, many biological measurements of concentration are expressed as percentages, or as weight in grams per 100 ml of solution. For example, 0.9% saline solution contains 0.9 gm of NaCl per 100 ml of water, 5% dextrose contains 5 gm of glucose per 100 ml of water, and a blood glucose measurement of 80 mg-% means that there are 80 mg of glucose per 100 ml of blood. The accuracy of this measurement relies on laboratory accounting for the solution temperature at the time of measurement.

A measurement that is more biologically appropriate is the molal measurement of concentration, that is, the concentration in moles, millimoles, etc. per 1000 g of solvent, expressed as a lower case "m" (m, mm, µm, etc.). This measurement is independent of temperature. Alternatively, concentration of solute can be expressed in molar measurement, the number of moles, millimoles, etc. per liter of solution, expressed as an upper case "M" (M, mM, etc.). Because solution volume changes with temperature, molar concentration is temperature dependent.

Because biologic membranes are readily permeable to water molecules there is continual movement or exchange of water between various fluid compartments. The forces governing the movement of water are hydrostatic and osmotic pressures. Most important to this discussion is the latter. Quantitatively, osmotic pressures greatly exceed hydrostatic pressures in the body; the magnitude can be appreciated when one realizes that an osmotic pressure difference of only 6 mOsm/L can move as much water as the entire hydrostatic pressure generated by the heart.

Osmotic pressure is a property of solutions that depends on the *number* of osmotically active molecules in solution, not upon the ionic charge of those molecules, the size of the molecules, or the physical-chemical properties of the molecules. Thus 1 gram-molecular weight (1 mole) of a compound (such as glucose) is termed 1 osmole (osmol, Osm). Most biological concentrations are expressed in milliosmolar (mOsm) or microOsmolar (μOsm) concentrations. Ionized molecules (e.g. NaCl) dissociate in solution, and each dissociated ion exerts its own osmotic force. For example, NaCl is principally dissociated in the body, therefore 1 mM of NaCl exerts approximately 2 mOsm of osmotic pressure; 1mM of $CaCl_2$ exerts 3 mOsm of osmotic pressure, etc. Osmolality is the expression of this quantity of osmotically active particles per 1000 gm of water or solvent, while the more commonly used osmolarity expresses the number of osmotically active particles per liter of solvent.

There is a small difference between osmolality and osmolarity principally due to dissolved protein and fat which comprise 6% to 8% of the solutes in plasma, but the difference is negligible when dealing with small concentrations of solute. In general, the serum osmolarity can be estimated to within 10% accuracy by the equation:

$$S_{osm} = 2 \times [Na^+] + [glucose]/18 + [BUN]/2.8$$

However, this equation will underestimate osmolarity in the presence of unusual or unmeasured solutes, such as ketoacids, ketone, and amino acids, all of which may be significantly elevated during DKA.

Tonicity is a term that is used to describe the relative osmolality of solutions; thus a solution is isotonic when it is isosmotic with body fluids. Normal saline and D5W are isotonic with respect to plasma, in that red blood cells will neither expand nor shrink if suspended in those solutions. Hypertonic fluids (5% NaCl, mannitol, etc.) have a greater solute concentration than body fluids, and will cause cellular dehydration and shrinkage due to egress of water from cells. Although the terms tonicity and osmolarity are often interchanged in clinical usage, an alteration of one does not necessarily imply an alteration of another. Tonicity, in this way, can be thought of as the *effective osmolality* (E_{osm}). High concentrations of low molecular weight permeant molecules (urea, ethanol) distribute evenly throughout total body water, and therefore produce no effect on tonicity. Uremia is a common example of a hyperosmolar state but not a hypertonic state. Glucose, however, is not a permeant molecule, therefore hyperglycemia indeed induces a hypertonic state. The effective osmolality or tonicity, can be best estimated using only glucose and sodium in the equation above (plus other exogenous impermeant solutes if any, such as mannitol, glycerol, etc.):

$E_{osm} = 2 \times [Na+] + [glucose]/18$

DKA clearly represents a hypertonic state, as glucose is significantly elevated in concentration in the plasma. It was recognized several decades ago, in studies of hypernatremic dehydration, that over-rapid correction of hypertonic states could lead to cerebral swelling and death. This phenomenon was attributed to the development or generation of what was then termed "idiogenic osmoles," osmotically active substances formed within the cells of the brain that served to counter the extra osmolality of plasma and protect the cells of the brain from shrinkage during episodes of hypertonicity. Experimental animals made hypertonic with exogenously administered compounds (sodium, glucose, mannitol) had concomitant increases in brain osmolality (15). The term idiogenic osmoles was coined because of the inability of investigators to chemically identify these new osmotically active material in the brains of hypertonic experimental animals (Figure 3) (15,16).

Figure 3. Animals made hypertonic have an increase in brain osmolality; the left column represents the osmotically active constituents of a normal rabbit brain; the right column represents the same in a rabbit made hyperglycemic (glucose 1000 mg/dl). The brain osmolality increased both because of a general increase in electrolyte and glucose concentrations, but also because of the generation of about 20 mOsm of unknown osmoles, termed "idiogenic osmoles." (Adapted from Arieff & Kleeman, 1974)

It was not a very large leap to then postulate that these idiogenic osmoles, putatively the result of intra-cerebral glucose metabolism and therefore large molecules, would dissipate slowly leaving the brain hypertonic relative to plasma during restoration of euglycemia during treatment of DKA, and rendering it susceptible to swelling as water moved into the brain along its osmotic gradient (Figure 4). Indeed, idiogenic osmoles are present in experimental animals during experimental hyperglycemia and during induced DKA. The identity of at least some of these osmoles has been established as myoinositol(~1 mOsm/kg), taurine(~3.5 mOsm/kg), and urea (the last, of course, an osmole but not one participating in brain tonicity for reasons discussed above) (15,17).

Figure 4. The theory of idiogenic osmoles producing brain edema:

Fig. 4a. Normal body water compartments. Dots denote sodium ions, and large dots denote glucose molecules.

Fig. 4b. During hyperglycemia, extracellular glucose concentration rises, leading to a preferential loss of water from the intracellular compartment. Water molecules travel in the direction of the arrows, and ultimately are lost in an osmotic diuresis.

Fig. 4c. Later during hyperglycemia, the brain generates "idiogenic osmoles" (denoted by stars) which serve to draw water back into the cerebrum, ameliorating intracellular dehydration.

But what is the evidence that a reduction of hyperglycemia and correction of hypertonicity causes cerebral edema?

The seminal work in this area was completed by Arieff and colleagues, who were unable to establish such a link. In their rabbit model, brain osmolality increased with increasing magnitude and duration of hyperglycemia, by as much as 40 mOsm/kg during 4 hours of hyperglycemia to levels of about 1000 mg/dl. Half of the increase in brain osmolality was accounted for by increases in intracellular ion and glucose concentration, and half of which by the generation of "idiogenic osmoles." However, they noted "when plasma glucose is . . . lowered below 14 mM, cerebral edema occurs which is characterized by a significant augmentation in the cerebral cortex content of Na+, K+, Cl- and water. Idiogenic osmoles are not only retained in the brain under such circumstances, but the quantity which are present during hyperglycemia increases still further as the plasma glucose is lowered towards normal with insulin. By contrast, when the plasma glucose and Osm are lowered by means of peritoneal dialysis and hypotonic saline infusion, an osmotic gradient between brain and plasma does not develop." In other words, experimental brain swelling occurs with the correction of hyperglycemia with insulin, but does not occur with rapid correction of hyperglycemia with dialysis and hypotonic fluids, and without the use of insulin. Arieff, et al. were led to speculate on the role of insulin on membrane ion pumps, and to caution not to correct hyperglycemia below 250 mg/dl.

Strikingly similar results were found by Tornheim, who studied the brains of diabetic rats treated with insulin or fluid alone to correct DKA (18). She wrote, "Treatment with saline alone did not result in central overhydration. The findings of this study suggest that aggressive therapy with fluids and insulin, but not fluid alone, results in global overhydration of the brains of diabetic animals. Prolonged fluid and insulin treatment with a return of blood glucose to normal values causes further and preferential accumulation of edema fluid in the cerebral cortex."

How may we integrate this knowledge into clinical practice, and how does it reconcile with clinical experience? On balance, one may safely conclude that the osmolality of the brain increases during untreated episodes of hyperglycemia, due to an influx of cations, glucose, and the generation of larger complex carbohydrates and amines. However, these substances dissipate rapidly and brain edema does not occur if hyperglycemia is corrected with even massive quantities of isotonic (18) or hypotonic (15) fluids; if however hyperglycemia is treated with a combination of fluids and insulin, the brain accumulates further cations and other osmotically active substances, and brain edema occurs. Because all children with DKA are treated with insulin, the data are consistent with the observation that cerebral edema occurs only after the initiation of therapy (with the exception of a few rare case reports). These data are also consistent with the observation that cerebral edema is a very rare complication of nonketotic hyperglycemic coma (NKHC), even though NKHC is associated with hyperglycemia many times more severe than DKA. NKHC is generally treated with fluid resuscitation alone, but not insulin; in fact, insulin therapy has been associated with cerebral edema in this setting (19). These data cannot, however, be easily reconciled with the several observations of ICP, radiographic, and encephalographic evidence of brain edema before the onset of therapy with fluids or insulin.

Overhydration and Hyponatremia During DKA

As clinicians have sought to understand cerebral edema complicating DKA and identify strategies for preventing it, considerable attention has been turned towards the possible role of fluid therapy while all but ignoring a potential role of insulin in the etiology of cerebral edema.

The first call to arms against aggressive rehydration of children with DKA came from Duck, et al. in 1976 (19), who described 4 cases of cerebral edema and combined their data with the data of another 5 previously reported in the literature. These authors observed that all of the children who developed cerebral edema had received fluid therapy at a rate in excess of 4 L/m2/day during the first 3-15 hours of therapy. Compared to an unmatched group of 21 children from these authors' practice who did not develop cerebral edema, these 4 children had lower average serum sodium concentrations measured at the same hour that cerebral edema occurred (124 vs 131 mEq/L). Unfortunately, the authors do not describe the fluid therapy of this cohort group of 21 children.

Remember, however, that protocols in practice throughout the 1970's called for fluid resuscitation of diabetic patients to be proportional to their degree of dehydration. Most protocols called for initial fluid boluses of 10-30 ml/kg followed by replacement of half

the fluid deficit over the first 8 hours of therapy. If we calculate what this would mean for a 30 kg 0.7 m2 child with "typical" DKA, that is, who is 10%-12% dehydrated, we would prescribe a fluid bolus of 500 ml of isotonic fluid followed by an infusion of hypotonic fluid at 145 ml/hr for a 8 hour fluid total of 1.65 L, half his deficit. This amounts to 2.4 L/m2/8 hr, or 7 L/m2/24 hr, well above the Duck threshold for risk of cerebral edema. In other words, it is hardly surprising that all of Duck's patients with cerebral edema received fluid in excess of 4 L/m2/8 hr because virtually all protocols recommended this for all but the minimally dehydrated child. Duck's analysis, therefore, fails to take into account the severity of DKA and dehydration as a factor in the causality of cerebral edema, and presents us only with a "true-true-unrelated" paradigm.

A decade later the same senior author expanded his observations of the rate of rehydration and the incidence of hyponatremia in the etiology of cerebral edema (20) reporting 9 new cases and comparing them to 39 previously published reports. Without dwelling on the inherent weaknesses of retrospective series, especially ones in which the majority of data is gleaned from secondary sources (published reports) rather than medical records, their findings viewed objectively may actually weaken their argument of fluid management as a cause of cerebral edema, and hyponatremia as a contributing cause or marker. In this series, 10% of cases of cerebral edema occurred following fluid resuscitation at less than Duck's threshold of 4 L/m2/24 hr, again, not surprising given published protocols for the management of DKA. Two-thirds of his reported subjects did not have measured serum sodiums below 130 mEq/L at the time of neurologic collapse, although many had declining sodium values. Once again, Duck did not distinguish between rapid rehydration as an etiology of cerebral edema, versus an independent cause of cerebral edema in the more severely dehydrated children, who received more rapid rehydration by protocol to manage their greater degree of dehydration.

The other author who has written in favor of conservative fluid management is Harris, et al. (21,22). In his earlier paper, Harris retrospectively studied over 200 episodes of DKA in children and adults, and described his prospective experience with a slow-rehydration regimen in 58 subsequent patients. In the former retrospective group, he identified 20 neurologic complications noted as minor (headache, n=13) and major (death or neurologic collapse, n=7), and noted that serum sodium failed to increase in 54% of uncomplicated cases of DKA, but in 95% of so-defined complicated cases ($p<0.01$). In discussing his prospective cohort group who were rehydrated over 48 hrs, he noted that sodium rose in 95% of patients, and no "major" complications occurred. While the behavior of serum sodium was impressive, the absence of complication (even if defined as a headache, and assumed to be 0 in incidence in the slow rehydration group) did not reach statistical significance in comparing the rapid to slow rehydration groups ($p=0.4$ by chi-square calculated from their data).

In the latter Harris paper, the authors describe a 5 year experience of 48 hour hydration in 231 episodes of DKA. They stratified their subjects into mildly and severely dehydrated groups, and observed that there was a statistically significant difference between the groups in admission glucose, BUN, and sodium. They had no major neurologic complications with their treatment protocol, concluding that "gradual rehydration can protect against life-threatening increases in intracranial pressure and brain herniation."

The Harris conclusions that slow rehydration is safe, vis a vis resolution of the abnormalities of DKA, is probably correct, however can one conclude that slow rehydration protects against cerebral edema? To answer this question I would refer the reader to an important and simple biostatistics paper, "If Nothing Goes Wrong, Is Everything All Right?" (23) in which Hanley demonstrates that a zero numerator in a clinical study does not imply zero risk, even with large denominators, but that the 95% confidence interval for stating a 0/n rate is 3/n. In other words, in the Harris study one can state that with 48 hour rehydration the risk of cerebral edema is not larger than 0 + 3/231, or 1.2%, approximately the same magnitude of risk already documented in prior studies without control of rehydration rates. One can hardly argue with the call for prudent fluid therapy and careful monitoring for and management of hyponatremia, but it is premature to state that this will prevent cases of cerebral edema.

The role of hyponatremia is also uncertain. Hyponatremia may play a role in promoting the development of cerebral edema, or it may be a marker for children who are developing cerebral pathology and are manifesting a degree of SIADH on their way to a neurologic catastrophe. Hyponatremia is far from a constant occurrence during the development of DKA: The original case reports of cerebral edema during DKA from the 1960's described children who were hypernatremic, and the Duck and Harris papers describe hyponatremia with varying frequency. Certainly it's difficult to assign a definite etiologic role to a phenomenon which often is not seen during the evolution of cerebral edema.

Finally, several other authors have retrospectively sought an association between fluid therapy, hyponatremia, and cerebral edema, but have failed to demonstrate such a link (3,24). In fact, cerebral edema has been reported in children who received only oral rehydration and insulin (25). The etiologic role of fluid resuscitation is therefore unresolved.

Summary and Conclusions

Severe metabolic and osmolal disturbances occur during routine episodes of DKA, and the latter has been associated with the development of increased cerebral osmolality that has been assumed to be responsible for the development of cerebral edema. However, it is possible to substantially correct hyperglycemia by administering massive quantities of fluid without inducing cerebral edema, and in so doing cerebral idiogenic osmoles dissipate.

Efforts by clinicians to identify a consistent etiology in patients with DKA who develop cerebral edema have not been successful. Neither excessive fluid therapy nor hyponatremia are constant features of the disease. Of some interest is the rarity of cerebral edema during treatment of the much more severe hyperglycemic states during NKHC, while its more frequent occurrence during the management of DKA.

The one common denominator of children who develop cerebral edema complicating DKA is therapy with insulin, and insulin has been experimentally shown in more than one study to be associated with the accumulation of cations and complex carbohydrates in the brain, and the development of cerebral edema during correction of hyperglycemia

in laboratory animals. Insulin may have a direct ion gate effect on glial cells and neurons, or alternatively may act indirectly by accelerating the correction of metabolic acidosis associated with DKA, and thus activating a pH sensitive sodium-proton membrane pump.

Finally, the observation of the presence of subclinical cerebral edema before the initiation of therapy of DKA, and its worsening and persistence during management, is interesting and difficult to integrate into present theories regarding the etiology of cerebral edema.

The calls for careful management of serum sodium and conservative fluid management with a deceleration of fluid resuscitation from over 24 hours to over 48 hours are prudent and cannot be criticized, but it will be several years before sufficient clinical data may be accumulated to determine if such conservative management will reduce the incidence of this frequently devastating and incompletely understood complication of childhood diabetes. Until we understand more about its prevention, then we must remain vigilant to its occurrence and treat cerebral edema aggressively with conventional neuro-intensive care measures to lower ICP and restore cerebral blood flow.

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* a mole is defined as the molecular weight of the substance in grams, equal to Avogadro's number of molecules, 6.023x10^23. [return to text]

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Diabetic Ketoacidosis: Pathophysiology, Management and Complications

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Bratton SL, Krane EJ. Diabetic ketoacidosis: pathophysiology, management, and complications. J Intensive Care Med 1992;7:199–211.

Diabetic ketoacidosis (DKA) is a common and potentially life-threatening complication of diabetes mellitus, the second most common chronic childhood disease [1]. Prior to the introduction of insulin to clinical medicine by Banting and Best in 1922, DKA had a mortality rate greater than 60% [2]. As insulin was introduced into clinical practice, there was a gradual decrease in mortality associated with DKA over the subsequent 30 years. Recent epidemiological data reveal current mortality varies from 0 to 19% [3,4]. DKA continues to be the most common cause of death in patients younger than 24 years of age; it accounts for as many as 50% of deaths of young diabetic patients [5–7]. In elderly diabetics who have coexisting diseases, DKA carries a high mortality [8]. Despite many advances in the care of diabetic patients, the prevalence of DKA is not declining; it accounts for 14% of all diabetes-related hospital admissions [3,4,9].

The incidence of insulin-dependent diabetes mellitus continues to increase worldwide and has roughly doubled in each recent decade [10–13]. Because insulin-dependent diabetes mellitus is increasing, and preventative measures to avoid DKA in diabetic patients have not been successful, the incidence of DKA can also be expected to increase in coming years. Prevention of DKA is the ultimate goal (80% of hospital admissions for DKA occur in treated diabetics) [3,8]. It is necessary for clinicians to understand the pathophysiology and treatment of DKA to care for this increasing diabetic population. We discuss the pathophysiology of diabetic ketoacidosis, its management, and its complications.

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Endocrinology

Serum glucose levels are tightly regulated by the opposing actions of insulin and the counterregulatory hormones glucagon, epinephrine, norepinephrine, growth hormone, and cortisol. Insulin, the only known anabolic hormone of the body, is secreted by the beta islet cells of the pancreas, not only in response to hyperglycemia, but also in the presence of absorbed amino acids and gut hormones after a meal [14]. Glucose uptake into most mammalian cells occurs via a stereospecific passive transport mechanism that displays saturation kinetics. A mobile carrier-mediated model has gained acceptance, in which insulin promotes translocation of carrier molecules from the intracellular pool to the plasma membrane where they bind glucose and then transport it into the intracellular compartment [15]. Only the brain, formed blood elements, and the adrenal medulla have insulin-independent glucose uptake [16,17].

By this mechanism, insulin increases postprandial peripheral glucose utilization; however, insulin also reduces glucose production by inhibition of hepatic glycogenolysis and gluconeogenesis. Fat-cell lipoprotein uptake in adipose tissue and protein synthesis are also enhanced by insulin. In contrast, insulin activity decreases during periods of fasting, but it still exerts some inhibition of hepatic glucose production [16], because glucose production is more sensitive to insulin than glucose utilization [18]. During prolonged fasting, insulin concentrations decrease to basal levels, and 75% of glucose utilization then occurs in the insulin-insensitive tissues. Lipolysis and hepatic glucose production are then released from insulin inhibition.

The counterregulatory hormones antagonize the effects of insulin to modulate or prevent hypoglycemia and to provide extra substrate during periods of stress. Glucagon is the first hormone to respond to stress and hypoglycemia [19]. It is secreted by the alpha islet cells of the pancreas and increases serum glucose concentrations within minutes by acting in the liver, where it stimulates glycogenoly-

Physiology

Hyperglycemia and acidosis produce marked alterations in organ physiology.

Central Nervous System. Most patients with DKA have an altered mental status but typically are arousable. No more than 10% of patients present in a coma [3]; these patients have a twelve-fold increased risk of death [7]. The etiology of coma in DKA is not well understood, although cerebral hypoperfusion, acidosis, and ketosis may all contribute [30]. Cerebral blood flow decreases as a result of hypocapnia in healthy patients, but the effect of hyperventilation during DKA on cerebral blood flow has not been studied. Decreased cerebral oxygen uptake may occur and was associated with fatality in an older study [31].

Several mechanisms may contribute to decreased cerebral oxygen consumption. The degree of systemic acidosis is not well correlated with changes in mental status, but depression of brain pH induced by therapy of DKA may impair central nervous system (CNS) oxygenation (Fig 2) [32,33]. Ketoacids, which serve as an important brain energy substrate in DKA, also depress the sensorium and may enhance coma [30]. Significant hyperviscosity probably does not occur as a result of dehydration, because a change in red blood cell rheology occurs only with more extreme elevations of hematocrit levels than typically occur during DKA.

Cardiovascular System. DKA can affect cardiovascular function through several mechanisms. Acidosis impairs myocardial contractility and decreases the peripheral vasoconstrictor response to catecholamines. Nevertheless, the very high catecholamine levels associated with DKA more than overcome the effects of acidosis on contractility; because dehydration can be profound, hypovolemia is the usual reason for shock in those few children with DKA who present with hypotension. Cardiac dysrhythmias may occur and are primarily a complication of altered potassium homeostasis [17,34]. An electrocardiogram is a rapid screening examination for hyperkalemia; it can reveal peaked T waves, and, if hyperkalemia is profound, widened QRS complexes progressing to asystole.

Renal Function and Serum Electrolytes. The fluid and electrolyte derangements in DKA familiar to most clinicians occur primarily as a result of hyperglycemia and the resultant osmotic diuresis. Fluid losses in DKA are frequently underestimated when based solely on physical examination. Because glucose is not freely distributed to the intracellular compartment during hyperglycemia and insulin deficiency, water will be osmotically drawn to the extracellular compartment, initially preserving the vascular volume despite progressive dehydration. Ultimately, dehydration, volume contraction, and consequently reduced glomerular filtration rates (GFR) occur. Reduction of GFR limits further glucose excretion, thus exacerbating hyperglycemia, hypertonicity, and further cellular dehydration. Severe hyperglycemia in excess of 600 mg/dL denotes not only severe DKA, but also marked dehydration with significant reduction in GFR.

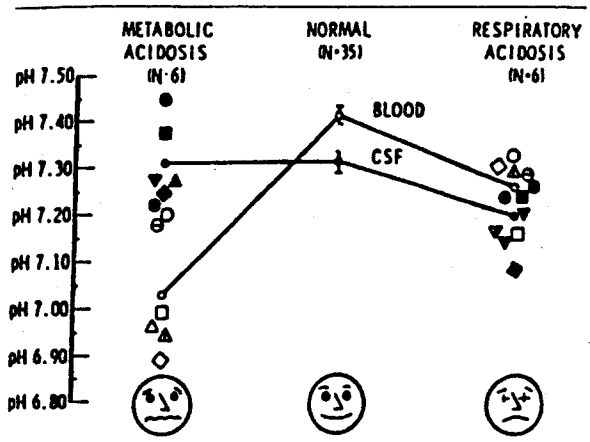

Fig 2. The relationship between systemic acidosis and central nervous system pH and function. Cerebrospinal fluid pH is near normal during metabolic acidosis but is below normal during hypercapnic acidosis. During respiratory acidosis, mentation is significantly impaired, although it can be near normal during metabolic acidosis. (*From* [54], Reprinted by permission of The New England Journal of Medicine, 277:611, 19[illegible].)

During the early phases of DKA, blood glucose concentrations become elevated; however, glycosuria does not occur until the reabsorptive capacity of the proximal renal tubules is exceeded (Fig 3). As hyperglycemia worsens, the reabsorptive capacity of the proximal tubules is exceeded and glucose appears in the urine. Ultimately, a steady state is reached, during which urinary glucose excretion is equaled by the rate of excess glucose production, and the serum glucose remains stable (see Fig 3, nephron 4) until dehydration occurs. At the same time, GFR and the quantity of filtered glucose decrease (see Fig 3, nephron 5) and a new steady state glucose concentration will be established, in which serum glucose will have increased to a new level (see Fig 3, nephron 6–8). Figure 3 demonstrates that severe hyperglycemia can only occur when there is significant reduction in renal function. A serum glucose level of 600 mg/dL suggests

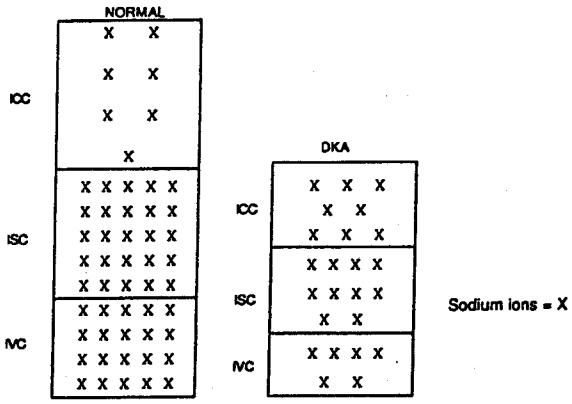

Fig 6. Diagram on left represents normal fluid distribution. The fluid losses in diabetic ketoacidosis initially dehydrate the intracellular compartment (ICC), preserving the extracellular compartments: the intravascular compartment (IVC) and the interstitial compartment (ISC). The sodium concentration of the intracellular fluid is low compared to the ISC and the IVC "diluting" the extracellular sodium concentration.

is osmotically drawn into the extracellular compartment by hyperglycemia (Fig 6). The magnitude of this effect can be predicted based on serum glucose levels as follows. For each 100 mg/dL that the serum glucose level is elevated above normal, the measured serum sodium level will be decreased by 1.6 mEq/L. Furthermore, hyperlipidemia causes a factitious depression of sodium because sodium ions are distributed only in the aqueous fraction of serum, whereas lipids increase the entire serum volume.

POTASSIUM. Potassium losses occur in the kidneys with excretion of urinary ketoacids and as a result of increased aldosterone activity associated with dehydration. Vomiting can further enhance losses. Serum potassium levels, however, are usually normal or high in untreated ketoacidosis [34]. Acidosis and protein catabolism enhance potassium shifts from the intracellular to the extracellular space, and impaired renal function may also contribute to hyperkalemia.

PHOSPHATE. Prior to therapy, serum phosphate concentrations in DKA are typically normal or elevated but decrease with rehydration and insulin therapy. Acidosis causes movement of inorganic phosphate from intracellular phosphate compounds to maintain the extracellular concentration [37]. Urinary losses as a result of rehydration, combined with phosphate ions shift back into the cells during insulin therapy, and resolution of metabolic acidosis frequently results in mild to moderate hypophosphatemia during treatment of DKA.

BICARBONATE AND CHLORIDE. During the evolution of DKA, ketoacids are buffered by bicarbonate and other body buffers, resulting in depressed serum bicarbonate concentrations. The result is an increased anion gap acidosis, and the decrease in bicarbonate approximately equals the increase in the anion gap. Occasionally, patients will present with a superimposed component of hyperchloremic acidosis, which occurs as a result of ketoacid losses in the urine and is typically seen in patients who have been able to maintain a more adequate state of hydration during the evolution of DKA. Although bicarbonate concentrations are low, no true bicarbonate deficit is created, because metabolism of ketoacids and lactic acid by the liver will ultimately restore serum bicarbonate levels to normal [17,36]. During therapy of DKA, rehydration with chloride-containing solutions that replete chloride in excess of chloride losses often causes or exacerbates hyperchloremia [36,38,39].

Respiratory System. The ketoacids betahydroxybutyric acid and acetoacetic acid are strong organic acids ionized at physiological pH values [17]. Chemoreceptors in the CNS sense the resulting acidosis and stimulate a compensatory respiratory alkalosis. All patients with ketoacidosis exhibit hyperventilation and associated hypocapnia, often to remarkable degrees. In children, for example, an arterial carbon dioxide tension ($PaCO_2$) less than 10 mm Hg is not unusual. Hyperventilation and subsequent hypocapnia frequently result in modestly increased arterial oxygen tension (PaO_2) (100–130 mm Hg), which would be predicted from the alveolar gas equation.

Gastrointestinal System. Both acidosis and hypokalemia impair bowel motility; gastroparesis and paralytic ileus are universally present during significant episodes of DKA. Catecholamine secretion decreases splanchnic perfusion. Abdominal pain and emesis are therefore common and may mimic an acute surgical abdominal disease process.

Management of DKA

Diagnosis and Intervention. Treatment of DKA requires a thorough understanding of its pathophysiology and then methodical attention to patient management. We routinely care for young adults and children; however, the management concepts described herein apply to all patients with DKA.

Table 1. Typical Deficits in DKA

Water (mL/kg body weight)	50–150
Sodium (mEq/kg body weight)	5–25
Potassium (mEq/kg body weight)	4–10
Phosphate (mmol/kg body weight)	0.5–4

does not have any known harmful effects after adequate tissue perfusion has been established. Furthermore, less vigorous rehydration diminishes the risk of hyperchloremic metabolic acidosis caused by both excessive chloride replacement and increased urine production with urinary losses of ketoacids [38].

SODIUM. An appropriate intravenous solution needed in most patients with DKA is one-half normal saline containing 40 to 60 mEq/L potassium salts. Fluid replacement should not contain glucose until the serum glucose has decreased to 200 to 300 mg/dL. Glucose should then be added and continued until the patient is able to resume eating.

POTASSIUM. All patients with DKA have potassium depletion, and large potassium requirements should be expected. Serum potassium concentrations may decrease precipitously during rehydration and administration of insulin. Potassium replacement must be guided by frequent measurements of serum potassium levels, because hypokalemic or hyperkalemic cardiac dysrhythmias are life-threatening complications during DKA. Potassium should be administered after the initial fluid resuscitation unless severe hyperkalemia has been documented. Typical intravenous solutions contain 40 to 60 mEq/L potassium salts. To avoid accidents, the potassium infusion should not exceed 0.3 mEq/kg/hr without continuous electrocardiographic monitoring, and intravenous potassium concentrations in excess of 60 mEq/L require placement of a central venous catheter for administration.

PHOSPHATE. Profound hypophosphatemia is rare in DKA; however, moderate hypophosphatemia is common. Phosphate depletion can impair oxidative metabolism and reduce concentrations of red blood cell 2,3-diphosphoglycerate (2,3-DPG), a substance that promotes the release of oxygen from hemoglobin to tissues. Decreased 2,3-DPG levels shift the hemoglobin-oxygen dissociation curve to the left, impairing tissue oxygenation. During DKA, however, the Bohr effect from acidosis opposes the effect of diminished 2,3-DPG and shifts the hemoglobin-oxygen dissociation curve to the right. Therefore, no net change in oxygen delivery is typically seen during DKA [44].

The role of routine phosphate therapy is controversial. Although Fischer and colleagues [45] demonstrated that phosphate supplementation enhanced regeneration of 2,3-DPG, phosphate therapy had no net effect on oxygen delivery. Rapid phosphate repletion, however, may lead to symptomatic hypocalcemia and hypomagnesemia [46]. If phosphate therapy is used, slow infusions are therefore most appropriate. Although phosphate therapy is of uncertain benefit, experience has shown that providing half the potassium replacement as the phosphate salt (and half as the chloride salt) in a continuous infusion is not harmful and in fact decreases excessive chloride administration. When phosphate is replaced, serum calcium and magnesium levels should be monitored every 6 to 12 hours, depending on the severity of the DKA and the rate of phosphate replacement.

BICARBONATE. Bicarbonate therapy continues to be controversial in the treatment of DKA [47–50]. Acidosis has been associated with impaired myocardial performance, decreased peripheral vascular response to catecholamines, depressed CNS function, and increased work of breathing, all suggesting a possible benefit from bicarbonate infusion therapy. However, arguments that mitigate against the use of supplemental bicarbonate are also numerous and are probably more compelling.

Table 2. Sample Calculation: For a 30 kg Child with 10 Percent Dehydration to be Rehydrated over 48 Hours

	Deficits	+	Maintenance (per 24 hr)	=	Total (48 hr)
Water	3,000 mL		(1,750) mL		6,500 mL
Na	300 mEq		(70) mEq		440 mEq
K	210 mEq		(52) mEq		314 mEq

Fluid bolus = 600 mL of Ringer's lactate or normal saline.
440 mEq of Na in 6,500 mL water equals 68 mEq/L or approximately 0.45 NaCl.
314 mEq of K in 6,500 mL water equals 48 mEq/L or approximately 50 mEq/L.
The calculated fluid is 0.45 NaCl with 50 mEq/L of K added to be given at a rate of 123 mL/hour for 48 hours.
Dextrose is added after the blood glucose concentration is below 250 mg/dL.

Table 3. Insulin Therapy Regimens

	Continuous Intravenous Insulin Infusion	Intermittent Bolus Insulin Injection
Initial dose	0.1 U/kg hour	0.5-U/kg, divided as one-half intramuscular & one-half subcutaneously
Maintenance	serum glucose > 250 0.1 U/kg hour serum glucose < 250 and severe acidosis 0.1 U/kg/hr + glucose infusion of 200 mg/kg/hr blood glucose < 250 and resolving acidosis 0.05 U/kg/hr + glucose infusion at 100 mg/kg/hr	subcutaneous insulin every four hours For glucose insulin 800 0.5 – 1.0 U/kg 500-800 0.25 – 0.5 U/kg 200-500 0.1 – 0.25 U/kg

Serum glucose is in mg/dL.
Insulin is regular insulin dosed in U/kg body weight.

perglycemia prevented a general recommendation of treating all patients with DKA with 10% dextrose.

Insulin infusions should be discontinued and the transition made to subcutaneous insulin when acidosis has satisfactorily resolved. Examples of suitable criteria are a blood pH greater than 7.30, a serum glucose level less than 300 mg/dL, a serum bicarbonate level that has increased to at least 15 mEq/L, and a patient who can resume eating. Most diabetics will require an insulin dosage of approximately 1 U/kg body weight/day. The "rule of thirds" can be utilized for a beginning insulin dose in a new diabetic. Two-thirds of the total insulin dose is given in the morning. Of the morning dose, two-thirds is given as an intermediate-acting insulin, and one third as a short-acting insulin preparation. The evening dose is one-third of the total daily insulin dose, divided as half intermediate-acting insulin and half short-acting insulin. Previously diagnosed diabetics may resume their established insulin doses. The continuous insulin infusion should be tapered over an hour after the first subcutaneous insulin injection.

Complications of DKA

Respiratory System. Careful attention to rehydration and electrolyte management can decrease complications from shock, hypoglycemia, and cardiac dysrhythmias. In recent years, several other complications have been recognized. Adult respiratory distress syndrome (ARDS) has been reported during DKA in both adults and several children [62–65]. Noncardiogenic pulmonary edema results from alterations in either alveolar capillary permeability or changes in colloid osmotic pressure, and both have been described in DKA complicated by ARDS. Carroll and Matz [63] reported that diabetics with DKA in whom hypothermia, hypotension, and coma developed had an increased risk of ARDS, with an associated mortality of 80%. A case report of recurrent ARDS during ketoacidosis in one adult patient suggested that microvascular disease associated with long-standing diabetes may have a role in the evolution of ARDS during ketoacidosis [66].

Both insulin and fluid therapies have been implicated in the genesis of ARDS [67–69], a syndrome that is probably multifactorial in patients with acidosis, hypoperfusion, and coexisting medical problems. Hillman [67] has argued that restoration of an adequate intravascular volume with crystalloid infusions is inappropriate because crystalloid redistributes primarily to the interstitial space and may dispose patients to development of pulmonary or cerebral edema. Restoration of perfusion with colloid-containing fluid and then rehydration over at least 24 hours with hypotonic fluid to restore intracellular losses was recommended. In another investigation, however, there was no change in extravascular lung water despite significant decreases in colloid osmotic pressure during treatment of ketoacidosis [68]. Furthermore, a patient has been reported in whom ARDS developed prior to therapy of DKA [62], which implies that the pathophysiological changes that result in ARDS may exist before therapy is instituted. No studies have compared colloid and crystalloid fluid resuscitation during ketoacidosis; therefore, no definitive statement can currently be made concerning this issue and any associated risk of ARDS.

Another pulmonary complication reported dur-

ated various therapeutic interventions and their subsequent effect of decreasing colloid osmotic pressure without clear implication for management of DKA [75,84]. An excessive rate of decrease in serum glucose levels has not been shown to place patients at risk for cerebral edema, although most clinicians still try to lower blood glucose levels by no more than 100 mg/dL/hr. Both hydration rate and tonicity of administered intravenous fluids have been implicated as associations with increased risk of acute cerebral edema. In a retrospective analysis, Duck and Wyatt [84] found that only 10% of patients in whom acute cerebral edema developed received less than 4 L/m^2/day during treatment of DKA. Hypothesizing that as hyperglycemia decreases, an increasing serum sodium concentration diminishes the change in osmolality due to a decreasing glucose concentration, others have evaluated changes in the sodium concentration corrected for hyperglycemia. They concluded that sodium replacement should be sufficient to prevent a decrease in the sodium corrected for hyperglycemia [85]. However, the largest series, published by Rosenbloom [75], did not verify either rate of hydration or tonicity of rehydration fluid as risk factors in the development of acute cerebral edema. Recently, a patient was described in whom cerebral edema developed prior to administration of any rehydration fluid or insulin [86].

Acute cerebral edema is the cause of death in 50% of fatal cases of DKA in children [10,75]. Although approximately half the patients in whom acute brain swelling develops have, in retrospect, a period of neurological change prior to respiratory arrest, it is certainly difficult to prospectively identify children who are less alert than expected. If cerebral edema occurs, appropriate interventions may include mannitol therapy and transfer to an intensive care unit, with assurance of continued hyperventilation by tracheal intubation and mechanical ventilation. Radiological imaging of the brain must be obtained to rule out other causes of coma, such as vascular thrombosis, hematoma, or occult CNS infection, all of which have been reported to mimic idiopathic cerebral edema in DKA [76,87,88]. Intracranial pressure monitoring may be helpful to monitor the patient and to guide further therapy [89].

With rapid intervention and neurological intensive care prior to respiratory arrest, nearly 60% of patients may recover to either good or moderately impaired, but independent, states. If respiratory arrest occurs prior to treatment, fewer than 10% have a satisfactory outcome [75]. Optimal management, therefore, continues to be prevention of DKA; however, after a patient becomes ill, watchful vigilance will help to ensure rapid and aggressive intervention if signs of neurological deterioration occur.

DKA continues to be a frequent and potentially life-threatening complication of insulin-dependent diabetes mellitus. Prevention of DKA with patient education, home glucose monitoring, and readily available health care must be emphasized to decrease DKA-related mortality. Further research is needed to optimize medical management of DKA and to decrease its complications.

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Endocrine Manifestations of Critical Illness in the Child

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The endocrine system helps maintain homeostasis in times of severe stress. The endocrine response, however, may also add to the metabolic derangements which occur during stress. Extensive literature describes the hormonal and metabolic response to critical illness in adults and in animals, but limited research has been done in the pediatric population. Additionally, study of hormonal and metabolic processes in acutely ill children is complicated by dynamic hormonal and metabolic changes related to the age of the patient. This article discusses the major endocrine and metabolic alterations which complicate critical illness. Information specific to the pediatric age group is emphasized whenever it is available.

Antidiuretic Hormone

Antidiuretic hormone (ADH, vasopressin) contributes to the adaptation to changes in intravascular (extracellular) volume by regulating renal clearance of free water. ADH is produced in the hypothalamus, stored in the posterior pituitary gland, and released in response to a number of stimuli. Reduction of extracellular fluid volume by 10 per cent in dogs,[55] an increase in serum osmolarity by as little as 1 per cent,[56] pain, nausea, vomiting, and drugs such as vincristine, chlorpropamide, tricyclic antidepressants, and phenothiazines all stimulate the release of ADH or facilitate its renal effect.

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). Secretion of ADH is termed inappropriate when blood levels of vasopressin, or its clinical effects, remain measurable in a setting in which its secretion would normally be suppressed. Thus, the syndrome of inappropriate ADH secretion (SIADH) is described as (1) serum hyponatremia accompanied by serum hypoosmolality (<270 mOsm per L); (2) urine osmolality greater than serum osmolality, demonstrating diminished free water clearance;

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(3) absence of clinical dehydration or volume depletion; (4) continued natriuresis; and (5) normal renal and adrenal function.

SIADH has been described in several clinical settings in children. Infants and children with central nervous system disturbances, such as head trauma, brain abscess, encephalitis, Guillain-Barré syndrome, subarachnoid hemorrhage, and brain tumors, can present with, or develop, the syndrome. Approximately 50 per cent of children with bacterial meningitis have chemical evidence of SIADH on presentation;[26] both the degree of hyponatremia on admission and the duration of hyponatremia may correlate with long-term neurologic outcome.

Burrows et al.[9] studied 24 children following posterior spinal fusion and found that 5 per cent demonstrated mild SIADH. Patients were asymptomatic except for decreased urine output, and all responded to fluid restriction.

Stretch and baroreceptors in the left atrium and carotid sinus respectively respond to changes in intravascular volume by modulating the release of ADH. Disturbances in ADH release seen with intrathoracic pathology are probably mediated by these receptors. For example, several studies have shown a correlation between acute episodes of bronchial asthma and ADH secretion in both adults[4] and children.[17] Increased ADH release occurs secondary to decreased left atrial filling in the setting of increased pulmonary vascular resistance and/or increased intrathoracic pressure which impairs venous return. Paxson and co-workers[44] studied consecutive admissions to a neonatal intensive care unit and documented significant SIADH associated with 14 per cent of all episodes of pneumothorax and 31 per cent of episodes of lobar atelectasis. The syndrome developed an average of 13.4 hours after the triggering event, and resolved within 1.5 to 4.2 days of treatment with fluid restriction and correction of the insult.

Although high levels of ADH are measured in patients with pulmonary diseases as noted above, few patients develop significant hyponatremia. Nevertheless, it is wise to remember the association between pulmonary pathology and elevated ADH secretion; fluid overload and electrolyte imbalance may result during the course of treatment. Positive-pressure ventilation may also promote diminished free water clearance by decreasing venous return to the heart, thereby lowering left atrial stretch and stimulating ADH production.

Diabetes Insipidus. A relative or absolute deficiency of vasopressin results in central diabetes insipidus, characterized by an inappropriately high urine output for the existing state of hydration. Findings in support of diabetes insipidus include a dilute urine (specific gravity less than 1.010, often in the range of 1.002 to 1.003), an elevated serum osmolality (>280 mOsm per L), and an elevated serum sodium. In a conscious patient with a normal thirst mechanism, free access to water, and normal renal function, serum osmolality and sodium may remain normal, with the condition being manifested as extreme polydipsia and polyuria.

Diabetes insipidus has been described secondary to a number of intracranial disorders in adults and children, and may be either transient or permanent. In a retrospective study of adult craniotomy patients, 50 per cent of patients undergoing surgery for pituitary lesions developed diabetes insipidus;[5] approximately 40 per cent of these cases were permanent. Diabetes insipidus was not seen after surgery in areas other than the hypothalamus or pituitary in this series. In adults, diabetes insipidus has also been described with pituitary abscesses,[33] craniofacial trauma,[29] hypoxemic encephalopathy secondary to carbon monoxide poisoning,[24] respiratory failure,[21] following cardiorespiratory arrest,[48] and after staphylococcal meningitis with brain abscesses in areas other than the neurohypophysis.[20]

In children, diabetes insipidus has been reported after intraventricular hemorrhage[1] and transiently in association with Haemophilus meningitis in a child who ultimately survived with intact neurologic function.[31] Most commonly, diabetes insipidus in children has been associated with brain death. In a review of 45 cases of children with evidence of brain death, Keren[28] found that five (11 per cent) developed diabetes insipidus within 10 to 240 hours after the cerebral insult occurred, and that all of these patients died within 16 to 168 hours of the onset of diabetes insipidus. Outwater[42] reviewed 16 cases of brain death; diabetes insipidus was demonstrated in 14, and in 12 of these the syndrome developed on the day that brain death became clinically apparent. Of the two patients in this series who did not manifest diabetes insipidus, one had Haemophilus meningitis and one had acute renal failure. Two of the patients with diabetes insipidus in this series showed complete spontaneous resolution of the diabetes insipidus within 24 to 96 hours of its onset despite continued clinical brain death. Support was withdrawn while diabetes insipidus was ongoing in other patients. Whether resolution of diabetes insipidus represents small, residual areas of blood flow to the pituitary gland despite clinical evidence of brain death is unclear.

From both the adult and pediatric literature, it is apparent that the development of diabetes insipidus following an hypoxic/ischemic insult to the brain signals an extremely poor prognosis, and may coincide with brain death in many cases. Since the brainstem is relatively resistant to hypoxic damage, brainstem failure implies a very severe insult.

Treatment of diabetes insipidus in the acute care setting involves use of a short-acting vasopressin preparation (pitressin, 8-arginine vasopressin) or a longer-acting preparation (vasopressin tannate or desmopressin (dDAVP), as well as careful attention to balancing fluid input with output. In the setting of cerebral edema, care must be taken to avoid fluid overload after administration of vasopressin. Recognition of the syndrome may be difficult in the patient with diminished renal function, or in the comatose patient unable to express thirst. Careful observation of urine output, urine specific gravity, serum electrolytes, and vital signs will alert the physician to its development.

Glucocorticoids and Glucose Metabolism

Carbohydrate metabolism is often deranged during critical illness. Compared to adults, pediatric patients, particularly infants, are at a relative disadvantage in their ability to maintain glucose homeostasis. Infants and children have higher basal energy expenditure, and require relatively more energy for growth and thermal stability, but their glycogen stores are often lower. When combined with malnutrition prior to their critical illness,

the increased metabolic demand from the illness itself, these patients often develop hypoglycemia.

In the majority of infants and children who are able to mount an appropriate stress response, elevated serum glucose concentrations appear early. This hyperglycemic response is secondary to elevated concentrations of the counterregulatory hormones: catecholamines, glucagon, growth hormone, and cortisol; to increased delivery of substrate from catabolism in tissues (particularly skeletal muscle); and to relatively low insulin concentrations and/or insulin resistance.[34] Later in the course of illness, glucose oxidation rates may decline, along with a change in energy source from carbohydrates to an oxidation of fatty acids, ketones, and amino acids.[11] Cortisol appears to be a particularly important mediator of stress hyperglycemia,[12] and its action in critical illness is reviewed below.

Glucocorticoids are derived from the adrenal gland and are important mediators of the body's stress response. Peripheral effects of glucocorticoids include enhanced hepatic gluconeogenesis, decreased insulin secretion, reduced peripheral glucose uptake, enhanced amino acid uptake by the liver, diminished immune and inflammatory response, and improved myocardial contractility and vascular response to exogenous catecholamines.[46] Glucocorticoid-mediated responses to stress are usually adaptive. Indeed, the lack of an adequate glucocorticoid response to severe illness, such as meningococcal sespsis, may be harmful, resulting in hypoglycemia, hypotension, and other manifestations of Addisonian crisis.

Studies of the cortisol response in severely ill patients followed over time have shown variable patterns. In addition, assessment of cortisol function in infants is complicated by delayed development of a normal circadian rhythm until about 6 months of age.[41] Acquired adrenal insufficiency may be present in a number of critical illnesses and should be suspected in the setting of severe bacterial sepsis[51] or hemorrhagic shock.[25] Baue[6] found low normal cortisol levels initially in a population of adult patients with severe, multiple system injuries, and patients with complications after major thoracic or abdominal surgery. The cortisol levels remained stable throughout the illness, whether the patients survived or not, possibly reflecting a blunted stress response. In acutely ill adults, elevated cortisol levels and increased cortisol release in response to ACTH administration was associated with increased mortality; survivors had lower mean, initial, and ACTH-induced cortisol levels.[18, 39]

When relative or absolute adrenal insufficiency is suspected, treatment should be initiated using appropriate doses of dexamethasone, methylprednisolone or hydrocortisone. If high doses of hydrocortisone are used, mineralocorticoids need not be replaced initially, since hydrocortisone provides sufficient mineralocorticoid activity.[61]

Thyroid Function

Low circulating serum thyroid hormone concentrations are frequently seen in the cirtically ill patient. Whether this represents a protective adaptation to severe stress is not clear; nor is it known if low circulating triiodothyronine (T_3) or thyroxine (T_4) represents tissue hypothyroidism, since few markers of this are available. Such critically ill patients are usually

clinically euthyroid, yet demonstrate normal to decreased total and free T_4, decreased total and free T_3, and elevated reverse T_3 (rT_3). Thyroid-stimulating hormone (TSH) levels are not elevated, and may be slightly decreased. This "euthyroid-sick" syndrome (low T_4–low T_3 syndrome)[58] is distinguished from hypothyroidism by lack of clinical evidence of hypothyroidism, and by the lack of an exaggerated elevation in TSH seen in hypothyroidism after the administration of thyrotropin-releasing hormone (TRH).

A number of adult studies[6, 62] have described an initial fall in T_3 within hours after a severe stress with a coincident rise in inactive rT_3 due to decreased peripheral conversion of T_4 to T_3 and increased conversion of T_4 to rT_3. In more severe injury or illness, total T_4 may also fall; free T_4 may or may not fall below normal. Total T_4 concentration, but not T_3, has been predictive of outcome in critically ill adult patients. Phillips[45] found that total and free thyroxine levels decreased progressively in severe illness; survivors maintained T_4 levels within the normal range while nonsurvivors had subnormal levels before death. In a critically ill adult population, 22 per cent had a low T_4 level, and there was an 84 per cent mortality if the T_4 level on presentation was below 3.0 μg per dl.

Zucker and co-workers[64] studied 9 medical and 18 cardiac surgical patients admitted to a pediatric ICU with various nonendocrine diagnoses. Six of 9 medical patients had the low T_4–low T_3 syndrome within 24 hours of admission. Fourteen of 18 surgical patients had low T_4–low T_3 syndrome by the end of cardiac bypass, and levels declined further over the next 24 hours. TSH levels were normal in all children but one whose elevated TSH concentration led to the diagnosis of primary hypothyroidism. Similar results were found by Carter.[10] Unlike most adult series, the pediatric patients in Zucker's series all survived despite several children having T_4 concentrations less than 3.0 μg per dl.

In a recent study of neonatal screening for primary hypothyroidism, otherwise healthy patients with Down syndrome were found to be affected ten times as frequently as normal infants.[19] Since patients with Down syndrome are often seen in pediatric intensive care settings, it is important to distinguish truly hypothyroid infants from those with euthyroid-sick syndrome in this high-risk population.

Catecholamines

Catecholamines play an important role in the stress response in humans. The physiology of endogenously produced catecholamines (epinephrine, norepinephrine, and dopamine) has been extensively studied in adults and animal models; the available data in pediatric patients or animal models has been reviewed recently.[63] Epinephrine, acting as a true hormone, has potent $alpha_1$, $alpha_2$, $beta_1$, and $beta_2$ effects following release from the adrenal medulla in response to neural stimuli. Norepinephrine is released primarily from presynaptic neurons and acts locally in most situations on the postsynaptic $alpha_1$ and $beta_1$ receptors.

Increased catecholamine release in response to stresses, such as that from hemorrhage, sepsis, head trauma, hypothermia, acidosis, and hypoxia, is considered an appropriate attempt by the body to maintain cardiac

output, blood pressure, and perfusion to vital organs. Secondary effects of elevated catecholamine concentrations are presumably extensions of this stress response, and must be recognized as such. Thus, catecholamines stimulate glycolysis, gluconeogenesis, and lipolysis, inhibit insulin release, and augment glucagon secretion. Through these effects, catecholamines play a major role in producing the hyperglycemia commonly seen in the severely stressed patient.

The ability of human term and preterm infants to mount an endocrine and metabolic response to the stress of surgery has been recently studied.[3] Results indicate that the hyperglycemic response seen immediately postoperatively was most likely due to elevated epinephrine concentrations, but by 6 hours postoperatively the epinephrine levels were returning to normal and hyperglycemia was better correlated with glucagon concentration. The authors noted that the hyperglycemia associated with elevated catecholamine concentrations might have harmful effects in these infants if the serum osmolality were to rise acutely into a dangerous range.

The hypermetabolic state seen in patients with severe burn injury correlates with burn area and with plasma epinephrine and norepinephrine concentrations for several weeks after the injury.[7] Triiodothyronine levels and TSH levels in these burn patients were consistent with the low T_4–low T_3 syndrome, suggesting a possible adaptation to the assumption of metabolic control by the sympathetic nervous system.

Not only do adverse effects occur from endogenous catecholamines, but therapy with catecholamines may also result in several endocrine complications. Dopamine infusions in the range of 2 μg per kg per min in adults decreases hypoxic ventilatory drive[57] and inhibits the release of TSH and prolactin from the anterior pituitary.[27] This suggests that caution should be exercised in using dopamine in patients with chronic hypercarbia who depend on hypoxic ventilatory drive. In addition, since the euthyroid-sick syndrome occurs frequently in critically ill patients, the effect of dopamine-mediated suppression of TSH release is difficult to determine. The usual test of normal thyroid function is to give a dose of TRH and measure the TSH response, but this is not possible in the patient on a dopamine infusion since TSH release is blocked.

Not only may catecholamines influence endocrine function, but the converse is also true. That is, the patient's response to catecholamines may be mediated by endocrine disorders. For example, hypothyroidism and hypocortisolism both decrease beta-adrenergic receptor density on target organs.[8, 16] This results in diminished response to exogenous catecholamines. Conversely, hyperthyroidism increases beta-adrenergic receptor density in many organs[8] and thus enhances the effect of exogenous catecholamines. Corticosteroids also increase or decrease beta-adrenergic receptor density depending on the target organ.[16, 50] Generally, corticosteroids increase beta-adrenergic receptor density in the cardiopulmonary system, and this may mediate a portion of their effectiveness in disease such as asthma or septic shock.

Responsiveness to catecholamines is also influenced by mechanisms other than alterations in receptor number on the cell surface. For example,

system have been documented in both hypothyroidism and hyperthyroidism.[32] Thus mechanisms beyond receptor-catecholamine binding are also influenced by the hormonal and metabolic state of the patient.

Aldosterone

Aldosterone is produced in the adrenal cortex and is involved in conservation of sodium and maintenance of adequate extracellular volume. Kaliuresis occurs secondary to enhanced renal sodium reabsorption. Aldosterone is secreted in response to ACTH, low plasma sodium concentration, and elevated plasma potassium concentration. Its release is also stimulated by angiotensin II, which is derived from the action of renin; release of renin (and therefore release of aldosterone) is stimulated by decreased plasma volume, hypotension, elevated prostaglandins,[47] and increased sympathetic stimulation. Dopamine inhibits aldosterone synthesis and release,[22] and may therefore be useful in clinical settings of secondary hyperaldosteronism when this is not desired. Decreased aldosterone secretion, as seen in relative or complete adrenal insufficiency, can result in inadequate intravascular volume, hyponatremia, hyperkalemia, and hypotension.

Insulin

Insulin is the major anabolic and anticatabolic hormone; it decreases glucose production by the liver, protein catabolism in skeletal muscle, and lipolysis of adipose tissue. Circulating insulin concentrations are decreased during the early response to severe stress, then they rise to normal or elevated levels during prolonged stress.[34] Despite this rise in insulin plasma concentration, the actions of insulin are antagonized by glucagon, epinephrine, cortical, and growth hormone, which results in hyperglycemia. The action of insulin depends on the molar ratio between itself and glucagon.[52] During stress, adrenergic stimulation of the islets causes a concomitant rise in glucagon release and a fall in insulin release so that the molar ratio of glucagon to insulin is increased. Insulin secretion is also inhibited by growth hormone and cortisol.[34]

Besides decreased insulin release, the acute response to stress is characterized by decreased sensitivity to insulin. The exact mechanism of this "insulin resistance" has not been determined, but it also adds to the increase in plasma glucose concentrations commonly seen in the stressed patient.

Glucagon

Glucagon plasma concentration is increased in trauma and sepsis,[34, 39] in cardiogenic shock, and postoperatively in infants,[3] where it is important in regulating plasma glucose concentration by stimulating hepatic glycolysis and gluconeogenesis. Increased glucagon concentration may be partly mediated by increased catecholamine concentrations in response to stress. Besides its effect on glucose homeostasis, several investigators,[23, 43] have shown that glucagon produces a direct positive inotropic and chronotropic effect on the heart in animals and man. Whether this effect is important in the stress response of humans is not

Parathyroid Hormone

Little information is available concerning alterations in parathyroid hormone physiology in critically ill children. Preterm infants on long-term furosemide therapy have elevated parathyroid hormone concentrations;[54] evidence of dystrophic calcification was seen in several infants with hypercalciuria. All these infants had decreased bone mineral content, and all had evidence of abnormal calcific abdominal densities. In critically ill adults receiving massive transfusion therapy, which can produce hypocalcemia, the ability to increase parathyroid hormone release appears intact.[36]

Mineral Metabolism

Hypocalcemia is a common problem in critically ill patients, and may be associated with hypoalbuminemia, sepsis, red cell transfusions, and renal failure.[14] In infants, mechanical hyperventilation producing alkalemia has been shown to decrease total and ionized calcium concentrations, and to decrease serum phosphorus concentration.[59] The determination of hypocalcemia should be based on the presence of a low ionized calcium concentration. Calculated ionized calcium concentration based on total serum calcium, total protein, and pH may be a poor reflection of true ionized calcium concentration in the critically ill patient,[14] emphasizing the importance of directly measuring ionized calcium concentrations in this population.

Hypercalcemia is less frequently seen in the critically ill patient and is usually due to iatrogenic causes, although tumors and sarcoidosis may result in hypercalcemia.[40] In neonates, hypercalcemia has been associated with iatrogenic hypophosphatemia;[38] treatment with supplemental phosphorus resulted in resolution of the hypercalcemia.

Hypophosphatemia may occur within several days of severe injury or illness, possibly secondary to volume expansion and secondary phosphaturia.[35] It is more frequently seen in patients who are malnourished, particularly when their caloric intake is increased, which stimulates phosphorus uptake by cells. Hypophosphatemia may be perpetuated by failure to supply sufficient dietary phosphorus. Since inorganic phosphorus is necessary for the regeneration of high-energy phosphates such as adenosine triphosphate, severe muscle weakness, including respiratory and cardiac failure, may result from severe hypophosphatemia (concentration less than 2.0 mg per dl).[2, 53] Treatment with parenteral phosphate salts is effective in reversing the muscle weakness, but must be given with caution since deterioration of renal function, hypocalcemia,[30] and iatrogenic hyperphosphatemia[13] may result.

Hypomagnesemia is a frequent finding in critically ill adults.[49] A number of causes have been identified,[15] and include gastrointestinal and renal loss (particularly with administration of aminoglycosides[60] or diuretics), endocrine and metabolic problems (such as protein-calorie malnutrition, phosphate deficiency), cardiopulmonary bypass, cardiac glycosides, and massive transfusion.[37] Manifestations of hypomagnesemia include tachyarrhythmias, electrocardiographic changes (similar to those seen with hypokalemia), muscular weakness, seizures, nystagmus, hypotension, hypothermia, and hypocalcemia, which may then produce tetany or stridor.

Hypocalcemia results from impaired parathyroid hormone secretion, which requires magnesium; therefore, magnesium concentration should always be checked in patients with resistant hypocalcemia.

SUMMARY

The stress response in humans commonly includes elevations in plasma concentrations of glucocorticoids, catecholamines, glucagon, growth hormone, aldosterone, and renin, resulting in alterations in the metabolism of glucose and other energy substrates, and in increased sodium and water retention. In severe illness, triiodothyronine and sometimes thyroxine are decreased without evidence of clinical hypothyroidism. Antidiuretic hormone may be elevated in bacterial meningitis and other central nervous system disorders, as well as in acute asthma, chronic ventilator therapy, pneumothorax, atelectasis, and postoperatively. Increased ADH concentration can lead to significant hypoosmolality and hyponatremia with adverse effects on the patient. In the setting of severe intracerebral insults, ADH may be inappropriately low, resulting in diabetes insipidus. Insulin concentrations may be inappropriately low for serum glucose concentration, or insulin may have diminished receptor responsiveness in seriously stressed patients. Either situation leads to hyperglycemia.

Disturbances in calcium, phosphorus, and magnesium homeostasis may occur relatively frequently in the critically ill patient in response to therapeutic interventions, or illness-induced altered metabolism. It is not always clear when an altered metabolic or hormonal state is an appropriate response to a stress, or represents decompensation of the body's mechanisms for coping with that stress. It is important, however to recognize the common responses of the organism to severe illness, and to monitor for treatable abnormalities which occur.

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SPECIAL ARTICLE

Inborn Errors of Metabolism: The Clinical Diagnosis in Early Infancy

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ABSTRACT. Major advances occurring in recent years in the recognition and treatment of inborn errors of metabolism have made it more essential than ever that the physician be familiar with the clinical presentation of these disorders. Although infants with inborn errors of metabolism will continue to be best cared for in centers with expertise in the treatment of inherited metabolic disease, the initial recognition of these disorders remains the responsibility of the practicing physician. A clinical approach to the diagnosis of inborn errors of metabolism in the young infant is presented as well as suggestions for the use of readily available laboratory studies that can serve to identify these infants who will benefit from further evaluation and treatment. *Pediatrics* 1987;79:359–369; *inborn errors of metabolism, genetics.*

Great strides have been made in recent years in the diagnosis and treatment of that group of disorders known as the inborn errors of metabolism. This expansion of knowledge, although providing critical insight into the normal metabolic processes in operation in man, has served to bewilder the clinician responsible for the care of newborn children. Aware of his or her responsibility for the recognition and diagnosis of these disorders, he or she is often at a loss when confronted with a sick infant suspected of having a metabolic disorder. In fact, too often he or she lacks the awareness of the clinicial manifestations of these disorders that would lead to the suspicion of such a diagnosis.

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Although a number of reviews in the past[1,2] have attempted to consolidate our knowledge of the inborn errors of metabolism into a logical clinical approach to the patient suspected of having such a disorder, knowledge and technology have changed so rapidly in recent years that there are currently few up-to-date guidelines on this complex subject.

Although many of the inborn errors of metabolism are individually rare, collectively they are not rare. With current diagnostic methods and mass screening programs operating in a number of states, many of these disorders are being found to be significantly more common than previously believed. There is, in addition, no doubt that there is a significant number of children whose disorders are still undiagnosed. Every geneticist has had the experience of diagnosing an inborn error of metabolism in a child and discovering that the parents have had one or more other children who died in early infancy of vague or undetermined causes. One can presume in such circumstances that the previous children were similarly affected. Autopsy findings in such cases are often nonspecific and unrevealing unless special biochemical studies are done. Infection is often suspected as the cause of death, and, in fact, sepsis is a common accompaniment of inherited metabolic disorders.

Manifestations of inherited metabolic disorders, whether overt and life-threatening or more subtle, are often present in the neonatal period. The significance of the precise diagnosis of metabolic disease, when possible, cannot be overemphasized. Increasingly, these disorders are being successfully managed medically, and when treatment means the prevention of significant mental retardation or death, even when the numbers are small, it is clearly worth pursuing. The remarkably successful dietary

therapy of phenylketonuria[3,4] and galactosemia[5,6] is but one example of this. The development of a number of synthetic formulas deficient in specific amino acids has greatly enhanced the success of dietary treatment of a wide variety of other conditions as well.[7] In addition, the use of coenzyme therapy such as vitamin B_{12} in methylmalonic acidemia,[8,9] pyridoxine in homocystinuria,[10,11] or biotin in multiple carboxylase deficiency[12] can be of dramatic benefit in selected cases. Even the urea cycle defects, some of which were once invariably fatal in the neonatal period, can now be successfully treated using a combination of dietary therapy and novel drugs designed to provide an alternate pathway for waste nitrogen (ammonia) excretion.[13,14] It must be emphasized, however, that the success of most treatment regimens is contingent upon the earliest possible institution of therapy and, therefore, early clinical diagnosis.

As with many devastating illnesses in the neonate, the clinical manifestations of the inborn errors of metabolism are protean and often nonspecific. For many of these disorders, the predominant clinical signs and symptoms are those of poor feeding and lethargy, the same general features seen in neonatal sepsis, a much more common diagnosis in the newborn. For certain disorders, there are more specific findings that might provide a clue to the clinician, and it is important to be aware of these. In general, however, it is a constellation of findings that should alert the physician to the possibility of metabolic disease. Indeed, the clinician should not wait until other more likely diagnoses have been ruled out before considering the possibility but should obtain some simple screening studies for metabolic disorders during the initial evaluation of any sick neonate with appropriate symptoms.

It is the purpose of this review to define that constellation of findings in the newborn that should alert the clinician to the possibility of inherited metabolic disease. The discussion will be confined to those disorders for which manifestations are commonly observed in early infancy and will not include the many disorders (such as most lysosomal storage diseases) that typically present in later infancy or childhood. An additional goal of this discussion will be to provide an approach to the use of some simple laboratory tools in a selective fashion in infants suspected of having metabolic disease.

MAJOR CLINICAL MANIFESTATIONS ASSOCIATED WITH THE INBORN ERRORS OF METABOLISM

A list of those inborn errors of metabolism that have been described clinically in the newborn infant is given in Table 1. This summary cannot be considered complete because it includes only those disorders for which neonatal manifestations have been reported in the literature. It is likely that disorders typically occurring later in childhood may occasionally present in the first month of life. In addition, new disorders causing neonatal disease will undoubtedly continue to be described. For general reference, however, this should serve as a useful guideline. Detailed information relating to most of the disorders listed can be found in recent editions of several reference textbooks.[15,16]

A summary of the major clinical findings seen in neonates with the inborn errors of metabolism and the disorders with which they have been associated is given in Table 2.

A guideline for abnormal laboratory findings found in these disorders is given in Table 3.

Acute Life-Threatening Illness (Lethargy, Coma, Seizures, Persistent Vomiting)

A number of inherited metabolic disorders, most notably the organic acidemias, urea cycle defects, and certain disorders of amino acid metabolism, typically present with acute overwhelming symptoms in the neonatal period. Because they are associated with protein intolerance, symptoms typically begin after feedings have been instituted. The interval between the first protein feeding and clinical symptoms may range from hours to weeks. The initial findings are typically those of lethargy and poor feeding, as seen in almost any sick infant. When such symptoms are not otherwise readily explained, or when other supportive clinical laboratory findings are present, metabolic disease must be considered. Infants with metabolic disorders may quickly become debilitated and septic, and it is, therefore, important that the presence of sepsis not exclude consideration of other possibilities.

An infant with an inborn error of metabolism may come to attention because of apnea or respiratory distress. The apnea in such cases is most often a manifestation of the encephalopathy that may accompany metabolic disorders, whereas tachypnea may be a symptom of an underlying metabolic acidosis. Other evidence of CNS dysfunction is also commonly observed, including abnormalities of muscle tone and seizures.

Vomiting is a striking feature of many of the inborn errors of metabolism associated with protein intolerance, although it is somewhat less common in the neonate than in the older infant. When persistent vomiting does occur in the neonatal period, it usually signals significant underlying disease. Inborn errors of metabolism should always be considered in the differential diagnosis. It is not uncommon to diagnose a metabolic disease in an

TABLE 1. Inborn Errors of Metabolism With Presentation in the Neonatal Period

Disorders of carbohydrate metabolism
1. Galactosemia (galactose-1-phosphate uridyl transferase deficiency)
2. Hereditary fructose intolerance (fructose-1-phosphate aldolase deficiency)
3. Fructose-1,6-diphosphatase deficiency
4. Glycogen storage disease, type I (von Gierke disease, glucose-6-phosphatase deficiency)
5. Glycogen storage disease, type II (Pompe disease, α-1,4-glucosidase deficiency)
6. Glycogen storage disease, type III (limit dextrinosis, debrancher deficiency)
7. Glycogen storage disease, type IV (amylopectinosis, brancher deficiency)
8. Pyruvate dehydrogenase deficiency
9. Pyruvate carboxylase deficiency
10. Phosphoenolpyruvate carboxykinase deficiency

Disorders of amino acid metabolism
11. Maple syrup urine disease
12. Hypervalinemia
13. Periodic hyperlysinemia
14. Hyper-β-alaninemia
15. Nonketotic hyperglycinemia
16. Phenylketonuria
17. Hereditary tyrosinemia
18. Pyroglutamic aciduria (5-oxoprolinuria)
19. Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
20. Lysinuric protein intolerance
21. Methylene tetrahydrofolate reductase deficiency
22. Sulfite oxidase deficiency

Organic acidemias
23. Methylmalonic acidemia
24. Propionic acidemia (ketotic hyperglycinemia)
25. Isovaleric acidemia
26. 3-Methyl crotonyl CoA carboxylase deficiency
27. Multiple carboxylase deficiency
28. Glutaric acidemia, type II (multiple acyl CoA dehydrogenase deficiencies)
29. Ethylmalonic-adipic aciduria
30. Hydroxymethylglutaryl (HMG) CoA lyase deficiency (3-hydroxy-3-methylglutaric acidemia)
31. 2-Methyl-3-hydroxybutyric acidemia (β-ketothiolase deficiency)
32. D-glyceric acidemia

Urea cycle defects
33. Carbamyl phosphate synthetase deficiency
34. Ornithine transcarbamylase deficiency
35. Citrullinemia
36. Argininosuccinic aciduria
37. Arginase deficiency

Lysosomal storage disorders
38. GM_1 gangliosidosis type I (generalized gangliosidosis, β-galactosidase deficiency)
39. Gaucher's disease, infantile form (glucocerebrosidase deficiency)
40. Niemann-Pick disease, types A and B (sphingomyelinase deficiency)
41. Wolman disease (acid lipase deficiency)
42. Farber disease (ceramidase deficiency)
43. Mucopolysaccharidosis type VII (β-glucuronidase deficiency)
44. Fucosidosis
45. I-cell disease (mucolipidosis, type II)
46. Sialidosis type II (neuraminidase deficiency)

Other disorders
47. Congenital adrenal hyperplasia
48. Lysosomal acid phosphatase deficiency
49. Menke kinky hair syndrome
50. Hereditary orotic aciduria
51. Cystic fibrosis
52. Hypophosphatasia
53. Crigler-Najjar syndrome
54. α_1-antitrypsin deficiency
55. Fatty acyl CoA dehydrogenase deficiencies
56. Primary systemic carnitine deficiency
57. Zellweger syndrome
58. Neonatal adrenoleukodystrophy

TABLE 2. Major Clinical Manifestations of the Inborn Errors of Metabolism in the Neonatal Period

Clinical Findings	Associated Disorders (Numbers refer to those listed in Table 1)
Failure to thrive, poor feeding	Essentially all
Vomiting	1–3, 11–13, 16–20, 23–31, 41, 42, 47, 48
Diarrhea	1–4, 17, 20, 41, 51
Lethargy or coma	3, 11–15, 18–20, 23–27, 49, 50, 55, 56
Hypotonicity or hypertonicity	1, 3–12, 14, 15, 18, 22–27, 30, 32–37, 39, 40, 42, 43, 49, 50, 57, 58
Seizures	1–4, 6, 9–11, 13–15, 19–25, 27, 28, 30–36, 42, 44, 47, 49, 52, 55–58
Respiratory distress and/or apnea	3–6, 8–11, 15, 21–25, 30, 33–38, 55
Jaundice	1, 2, 7, 17, 40, 41, 49, 53, 54
Hepatomegaly	1–7, 19, 20, 23, 30, 34, 36–41, 43–46, 54, 56, 57
Coarse facial features	38, 43–46
Abnormal odor	11, 16, 17, 25–28
Dysmorphic features (multiple minor anomalies)	28, 49, 57, 58
Abnormal eye findings (cataract, retinopathy, other)	1, 22, 38, 40, 42, 43, 45, 46, 49, 57, 58
Abnormal hair	20, 36, 49
Macroglossia	5, 38, 42

TABLE 3. Common Laboratory Findings Associated With the Inborn Errors of Metabolism in the Neonatal Period

Laboratory Finding	Associated Disorders (Numbers refer to those listed in Table 1)
Metabolic acidosis	1–4, 6, 8–11, 18, 23–32, 35, 36
Hypoglycemia	1–4, 6, 9–11, 17, 23, 28–30, 48, 55, 56
Hyperammonemia	13, 19, 20, 23–25, 27, 31, 33–37, 55, 56
Elevated transaminases	1, 2, 6, 7, 17, 20, 34, 36, 37, 41, 54–56
Nonglucose reducing substance in the urine	1, 2, 17
Ferric chloride test positive on urine	11, 16, 17
Ketonuria	3, 9, 11, 23–27, 31
Neutropenia	15, 20, 23–25, 33, 50
Thrombocytopenia	20, 23–26
Anemia	17, 18, 20, 23, 41, 50
Vacuolated lymphocytes on peripheral smear	4, 38, 40, 41, 43–46

infant who has already undergone surgery for suspected pyloric stenosis.[17] Among the disorders most notably associated with recurrent vomiting are the urea cycle defects, those disorders associated with hyperammonemia secondary to a deficiency of one of the five enzymes of the urea cycle, the primary pathway for ammonia detoxification in man. In addition to vomiting, affected infants exhibit CNS effects ranging from lethargy to coma and seizures. The obvious diagnostic clue to these disorders is the plasma ammonia level which in acutely and severely ill patients is often dramatically elevated but which in the less severely affected infant may be only episodically elevated. Infants who are not receiving protein, such as those who have been placed temporarily on IV fluids, may or may not show the expected elevation.

The other major group of disorders typically associated with recurrent and overwhelming illness is the group of organic acidemias. Among the most common of these are methylmalonic acidemia, propionic acidemia, and isovaleric acidemia. The list of disorders in this group has expanded dramatically, however, in recent years as new entities are being defined through the more widespread availability of organic acid analysis and through increased awareness of the significance of this type of evaluation. A major feature of most disorders in this group during acute episodes of illness is a profound metabolic acidosis with increased anion gap, readily demonstrable by arterial or capillary blood gases or by measurement of serum electrolytes and bicarbonate. Neutropenia and thrombocytopenia are also commonly observed and further underscore the clinical similarity of these disorders to neonatal sepsis. Hyperammonemia, at times as dramatic as that associated with urea cycle defects, is commonly seen in critically ill neonates with organic acidemias, whereas it is less consistently observed in older infants.

The metabolic acidosis associated with organic acidemias may have significant adverse impact on many different organ systems and may lead to the erroneous diagnosis of a wide variety of other dis-

orders. The author has had the experience of caring for an infant with isovaleric acidemia who on the first day of life had severe metabolic acidosis, a dilated heart, and poor cardiac output. The infant was suspected of having congenital heart disease and underwent cardiac catheterization even though numerous members of the nursery staff had noted that the infant had a very strong odor reminiscent of sweaty feet, a typical finding in isovaleric acidemia. It was even noted in the catheterization laboratory that the blood had a very strong peculiar odor. Yet, it was not until 18 hours later, long after significant heart disease had been ruled out, that the diagnosis of metabolic disease was first considered. Despite attempts at therapy with dialysis and other measures at that point, the child died of the disease. In another situation, a child with methylmalonic acidemia was admitted through the emergency room with severe metabolic acidosis and a tight, distended abdomen with evidence of ileus on a roentgenograph. The history revealed that the child had fed poorly since birth and had repeated episodes of vomiting despite several formula changes. The child was taken to the operating room where most of the small intestine was found to be infarcted, presumably secondary to the acidosis and poor perfusion. Postoperatively, metabolic disease was considered and the diagnosis of the vitamin B_{12}-responsive form of methylmalonic acidemia was made. The child died of the complications of the disease despite the fact that early diagnosis and treatment of this disorder, prior to the terminal episode, should have been associated with a good prognosis.

In summary, then, disorders of protein intolerance should be seriously considered in an infant who has symptoms of acute overwhelming illness or who has a chronic history of poor feeding or vomiting. The following laboratory studies should be obtained: blood gases or measurement of serum electrolytes and CO_2, ammonia, blood glucose, complete blood cell count, and urinalysis. In addition, a ferric chloride test (Phenistix) should be done on urine to screen for maple syrup urine disease, and the urine should be checked for ketones. From these simple screening tests, which should be readily available in any hospital laboratory, a great deal of information can be obtained. Any infant with metabolic acidosis or hyperammonemia with or without other supportive findings should be considered a strong candidate for a metabolic disorder and should be further evaluated for this possibility. Dialysis may be necessary in such infants to reverse the metabolic derangement and can be lifesaving if instituted in a timely fashion. Not all infants with life-threatening metabolic disease will have either metabolic acidosis or hyperammonemia, however. For example, patients with nonketotic hyperglycinemia typically present in the neonatal period with severe CNS manifestations, including seizures and altered muscle tone, but exhibit neither a metabolic acidosis nor hyperammonemia. Therefore, urine and plasma amino acids should also be measured in any infant with symptoms suggestive of a metabolic disease, even when no other supportive laboratory findings are present. Urine organic acid screening should be done for any infant with unexplained metabolic acidosis, hyperammonemia, an abnormal odor, or other findings suggesting the possibility of an organic acidemia. Although not available in most hospital laboratories, organic acid analysis can be obtained in any part of the country through reference laboratories or through referral of samples to medical center genetics units. It is important to insist, however, that any reference laboratory used for this purpose not only provide prompt test results and reference ranges but also provide interpretation of abnormal results.

In any infant with significant metabolic acidosis, a blood lactate level should be obtained. Lactate is the primary metabolite that accumulates in a number of disorders of carbohydrate metabolism, such as glycogen storage disease or disorders of pyruvate metabolism, but is typically not elevated in disorders related to protein intolerance. When pyruvate determinations are available, calculation of the lactate to pyruvate ratio may be helpful in distinguishing primary from secondary lactic acidosis.

Hypoglycemia

Hypoglycemia and its associated symptoms may occasionally be seen in infants with disorders of protein intolerance, as previously discussed, but is more commonly seen in disorders of carbohydrate metabolism or of fatty acid oxidation. Among the best known inborn errors of metabolism associated with hypoglycemia are the glycogen storage diseases of which types I (von Gierke disease or glucose-6-phosphatase deficiency) and III (limit dextrinosis or debrancher deficiency) are the most likely to be associated with manifestations in the neonatal period. The hypoglycemia in these disorders is related to the inability of the liver to release glucose from glycogen; therefore, it is most profound during periods of fasting. In addition to hypoglycemia, hepatomegaly, hypotonia, and metabolic acidosis are prominent features of these disorders. It should be noted here that hypoglycemia is not a feature of glycogen storage disease type II (Pompe disease) because cytoplasmic glycogen metabolism and release is normal in this disorder in which glycogen

accumulates within lysosomes as a result of the deficiency of the lysosomal enzyme α-1,4-glucosidase. The clinical manifestations of this well-described disorder include macroglossia, hypotonia, cardiomegaly with congestive failure, and hepatomegaly. Of these, the cardiomegaly is most striking and may be apparent in the neonatal period. Congestive heart failure is the cause of death in most cases.

A disorder that presents clinically with findings virtually indistinguishable from the hepatic glycogen storage diseases types I and III is fructose-1,6-diphosphatase deficiency, a disorder of gluconeogenesis. A number of other disorders of gluconeogenesis resulting in neonatal hypoglycemia have also been described. The basic immediate treatment of all of these disorders is frequent feedings and glucose administration, and the definitive diagnosis is made by liver biopsy and assay of appropriate hepatic enzymes. In some cases, enzymatic assays can be performed using lymphocytes or cultured skin fibroblasts.

Within recent years, a number of specific inborn errors of metabolism have been defined in infants presenting with symptoms resembling Reye syndrome. Prominent in this group are disorders of fatty acid oxidation such as medium- or long-chain acyl CoA dehydrogenase deficiency. Infants with these disorders typically present with recurrent nonketotic hypoglycemia, but hyperammonemia, elevated transaminases and all of the associated clinical symptoms of Reye syndrome may also be observed. The accumulation of fatty acyl CoAs in these disorders leads to a secondary carnitine deficiency, probably as a result of excretion of excess acyl carnitines in the urine.[18,19] There also appear to be infants with primary systemic carnitine deficiency and similar symptoms,[19] although in some reported cases, the various disorders that may result in a secondary carnitine deficiency have not been completely ruled out. Because of the hyperammonemia and encephalopathy typically observed in the urea cycle defects, infants with these disorders are also often suspected of having Reye syndrome. Hydroxymethylglutaryl CoA lyase deficiency, an organic acidemia, results in clinical findings virtually identical with those of Reye syndrome as well. Clearly, any infant presenting with findings suggestive of Reye syndrome or any older child with atypical or recurrent Reye-like episodes should be evaluated for the possibility of metabolic disease. Although urine organic acid analysis and measurements of serum carnitine may be helpful, specific enzymatic assays are usually necessary for diagnosis of disorders in this group.

Jaundice or Other Evidence of Liver Dysfunction

Jaundice or other evidence of liver dysfunction may be the initial finding in a number of inherited metabolic disorders in the neonatal period. For most of the inborn errors of metabolism associated with jaundice, the elevated serum bilirubin is of the direct-reacting type. This generalization, of course, does not include those inborn errors of RBC metabolism such as glucose-6-phosphate dehydrogenase deficiency or pyruvate kinase deficiency which are occasionally responsible for hemolytic disease in the newborn. The best known metabolic disease associated with jaundice is galactosemia in which the deficiency of the enzyme galactose-1-phosphate uridyl transferase results in an accumulation of galactose-1-phosphate and other metabolites such as galactitol which are thought to have a direct toxic effect on the liver and on other organs. Jaundice and liver dysfunction in this disorder are progressive and usually appear at the end of the first or during the second week of life along with vomiting, diarrhea, poor weight gain, and eventual cataract formation, provided the infant is receiving a galactose-containing formula. When galactosemia is suspected, the urine should be tested simultaneously with Benedict's reagent (Clinitest tablets, Ames Co) and with a glucose oxidase method (Clinistix, Ames Co). The glucose oxidase method is specific for glucose, whereas Benedict's reagent will detect any reducing substance. Therefore, a dipstick result negative for glucose with a positive Benedict's reaction means that a nonglucose-reducing substance is present. With appropriate clinical findings, this is most likely to be galactose. Paper on thin layer chromatography can be used to positively identify the reducing subsance. Similar to the situation with disorders of protein intolerance, the urine test results may be negative if the child is not receiving galactose in the diet.

If the diagnosis of galactosemia is suspected, whether or not reducing substances are present in the urine, galactose feedings should immediately be replaced by lactose-free feedings pending the results of appropriate enzyme assays on RBCs to confirm the diagnosis. Untreated galactosemic babies, if they survive the neonatal period, will have persistent liver disease, cataracts, and severe mental retardation. Many affected infants will die of *Escherichia coli* sepsis in the neonatal period.[20] Treatment of this disorder by simple dietary restriction of galactose, if started early, results in complete reversal of essentially all of the physical manifestations and enables affected individuals to develop normal or near normal intelligence. Many states currently have newborn screening programs for ga-

lactosemia, but it is important to be aware that clinical manifestations of the disorder often appear before the results of screening studies are available.

Another inborn error of metabolism that occasionally is found in the newborn with jaundice, hepatomegaly, and the presence of reducing substances in the urine is hereditary fructose intolerance, which is also characterized by episodes of profound hypoglycemia, vomiting, and metabolic acidosis. This disorder is uncommonly seen in the neonate, however, because most newborns are not immediately exposed to a fructose-containing diet unless they have been given a soy formula with sucrose as the carbohydrate source. In the uncommon event that an infant who has been receiving fructose should present with these findings, this diagnosis should be considered. Once again, analysis of the urine reveals the presence of a nonglucose reducing substance which on chromatography can be demonstrated to be fructose. Treatment of this disorder is by dietary restriction of fructose and results in a complete resolution of all clinical signs and symptoms. Confirmation of the diagnosis is by assay of the deficient enzyme fructose-1-phosphate aldolase in liver tissue; however, this is rarely necessary.

An additional disorder that may be associated with neonatal jaundice is α_1-antitrypsin deficiency, a puzzling disorder that is among the most common of all inherited metabolic diseases.[21] The clinical manifestations of this disorder may be identical with those of traditional neonatal or giant cell hepatitis, and a determination of serum α_1-antitrypsin or a serum protein electrophoresis should be a part of the initial evaluation of all children presenting with this syndrome. α_1-antitrypsin is the major component of the α_1-fraction of serum globulins; therefore, this diagnosis is virtually ruled out by a normal electrophoretic pattern of serum proteins. Quantitative serum α_1-antitrypsin is now available through most hospital laboratories, however, and is the preferred test. Infants found to have a deficient level of α_1-antitrypsin on quantitative analysis should have protease inhibitor testing performed to confirm the diagnosis. There is no specific treatment for the liver disease associated with α_1-antitrypsin deficiency, but approximately half of all affected infants eventually exhibit complete resolution of their liver disease.

An additional disorder in infants who present with liver disease in early infancy is hereditary tyrosinemia. The biochemical hallmarks of this disorder include marked elevations of plasma tyrosine and methionine and generalized aminoaciduria with a disproportionate increase in the excretion of tyrosine, but these findings are relatively nonspecific and may be observed as a secondary phenomenon in other forms of liver disease as well. Until recently, hereditary tyrosinemia was among the most difficult of inborn errors of metabolism to diagnose clinically. The finding of succinylacetone in the urine of patients with this disease has led to a helpful diagnostic test for the disorder.[22] More recently, it has become possible to establish the diagnosis definitively by demonstration of a deficiency of the enzyme fumarylacetoacetate fumarylhydrolase in lymphocytes and cultured skin fibroblasts of affected individuals.[23]

In contrast to the disorders previously mentioned in which there is an elevation of the direct-reacting bilirubin, a persistent elevation of indirect bilirubin beyond the limits of physiologic jaundice, without evidence of hemolysis, is suggestive of the diagnosis of the Crigler-Najjar syndrome. The hyperbilirubinemia in this disorder is related to a partial or complete deficiency of glucuronyl transferase, the liver enzyme responsible for the normal conjugation of bilirubin to bilirubin diglucuronide. There is no effective long-term therapy for some patients with this disorder, but the standard modalities of phototherapy and exchange transfusion may be of benefit in preventing the development of kernicterus in the neonatal period.[24,25] Individuals with a partial deficiency of the enzyme may respond to phenobarbital therapy.[25]

Hepatomegaly

Those disorders associated with hepatomegaly in the neonatal period fall into two general categories, the storage diseases and those disorders associated with liver damage or dysfunction. The latter have been previously discussed. Many of the well-known lipid storage diseases do not typically present in the neonatal period. Among those that may occasionally be associated with hepatomegaly in the neonatal period, however, are GM_1 gangliosidosis type I, Gaucher disease, Niemann-Pick disease and Wolman disease, all of which are also associated with splenomegaly. The glycogen storage diseases that are associated with hepatomegaly in the newborn have previously been discussed and are listed in Table 2. Infants with the mucopolysaccharidoses, such as the Hurler and Hunter syndromes, uncommonly exhibit clinical abnormalities in the first month of life. Indeed, newborns who appear to have the typical features of these syndromes, such as coarse facial features, hepatosplenomegaly, skeletal abnormalities and hernias, are more likely to have GM_1 gangliosidosis. Infants with β-glucuronidase deficiency, also classified as mucopolysaccharidosis type VII, may present in the neonatal period with

features virtually indistinguishable clinically from those of the Hurler-Hunter syndromes as well. I-cell disease or mucolipidosis type II also occasionally is found in the newborn. An infantile form of sialidosis (neuraminidase deficiency) is typically associated with findings at birth.

When one of these disorders is suspected, urine screening tests for mucopolysaccharides and oligosaccharides may be performed. These can be helpful diagnostically but negative results do not rule out the possibility of a storage disorder. In addition, false-positive mucopolysaccharide spot tests are not uncommonly observed in neonates. The definitive diagnosis of most disorders of lipid or mucopolysaccharide metabolism is made by appropriate biochemical studies on leukocytes or cultivated skin fibroblasts.

Coarse Facial Features

Coarse facial features, a classical finding in older infants with mucopolysaccharidoses and oligosaccharide storage diseases, are observed occasionally in neonates with GM_1 gangliosidosis, β-glucuronidase deficiency, I-cell disease, and infantile sialidosis.

Macroglossia

Macroglossia is a typical finding in Pompe disease, or glycogen storage disease type II, as previously described. It has also been described in neonates with GM_1 gangliosidosis.

Diarrhea

Diarrhea is described in relatively few of the inborn errors of metabolism in contrast to vomiting which is seen in so many. Notable exceptions to this are galactosemia, certain cases of cystic fibrosis, and less familiar disorders such as Wolman disease (acid lipase deficiency) and hereditary tyrosinemia.

Abnormal Odor

Abnormal body or urinary odor, most likely to be noted by nurses or mothers rather than physicians, is an important but often overlooked clue to the diagnosis of several of the inborn errors of metabolism and, indeed, may be the most specific clinical finding in such patients. This is best described for phenylketonuria for which the urine was noted to have a peculiar musty odor years before the biochemical basis of the disease was understood. In the acutely ill neonate with an abnormal odor, isovaleric acidemia and maple syrup urine disease are the most likely entities. In maple syrup urine disease, the urine has a distinctive sweet odor reminiscent of maple syrup or burnt sugar. The odor associated with isovaleric acidemia is very pungent and similar to that of sweaty feet.

Abnormal Hair

Abnormal hair, although frequently difficult to evaluate in the newborn, may be a clue to the diagnosis of argininosuccinic aciduria, lysinuric protein intolerance, and Menke kinky hair syndrome.

Dysmorphic Features

At one time there appeared to be a clear distinction between infants with inborn errors of metabolism and infants with dysmorphic syndromes, both of which may be inherited in a similar fashion. Infants with inherited metabolic disease were generally believed to be phenotypically normal at birth with no evidence of major or minor structural anomalies. It is becoming increasingly apparent, however, that inherited metabolic disorders may be associated with consistent patterns of birth defects, suggesting that metabolic derangements in utero may disrupt the normal processes of fetal development. This phenomenon is perhaps best illustrated by the group of disorders recently found to be associated with multiple defects in peroxisomal enzymes, including those involved in fatty acid oxidation and plasmalogen synthesis.[26,27] These include Zellweger syndrome (the cerebrohepatorenal syndrome), neonatal adrenoleukodystrophy, and a number of variant conditions, all of which are associated with dysmorphic features such as epicanthal folds, Brushfield spots, large fontanels, simian creases, renal cysts, and others. Patients with glutaric acidemia type II, one of the organic acidemias, are also reported to have a characteristic phenotype including many similar minor dysmorphic features. It is not at all uncommon for infants with other metabolic disorders to have one or more minor anomalies as well. Therefore, the finding of multiple minor anomalies in an infant should not mitigate in any way against the diagnosis of inherited metabolic disease.

An important phenotypic abnormality associated with one of the more common inborn errors of metabolism is ambiguous genitalia. This is the presenting finding in most female infants with congenital adrenal hyperplasia, and, if not treated appropriately, such infants may subsequently have life-threatening electrolyte disturbances. Affected male infants are usually not recognized until hyponatremia and hyperkalemia develop and cause symptoms. When the diagnosis of the 21-hydroxylase-

deficient form of congenital adrenal hyperplasia is suspected, it can usually be confirmed by demonstration of an elevated 17-OH-progesterone level.

Abnormal Eye Findings

Abnormal eye findings are typically associated with many of the inborn errors of metabolism, although they are not always noted at the time of initial presentation. Cataracts are classically associated with galactosemia and other disorders of galactose metabolism but may be observed in disorders such as Zellweger syndrome as well. Dislocated lenses, seen with both homocystinuria and sulfite oxidase deficiency, may occasionally be noted as early as the first month of life. Retinal degenerative changes are typical of the peroxisomal disorders including Zellweger syndrome and neonatal adrenoleukodystrophy and are observed in a number of other conditions as well. Other abnormalities that may be associated with inborn errors of metabolism include corneal clouding and congenital glaucoma.

ABNORMAL LABORATORY FINDINGS IN INFANTS WITH INBORN ERRORS OF METABOLISM

Laboratory findings that may be associated with an inborn error of metabolism are listed in Table 3. All of the laboratory studies included are routinely performed in most general hospitals and many are included in the evaluation of any sick newborn. Mention has previously been made of many of the disorders associated with hypoglycemia, metabolic acidosis, or hyperammonemia. In Tables 4, 5, and 6, those disorders associated with a positive ferric chloride reaction, urinary reducing substances, and an abnormal urinary odor are listed.

SUMMARY

The first step in the evaluation of any sick neonate, and clearly, the most important one, is a thorough clinical assessment including history and physical examination. In the case of metabolic disorders, the family history is critical, particularly if it reveals previously poorly explained neonatal deaths. A negative family history does not rule out the possibility of inborn errors of metabolism, however, because most disorders in this group are inherited in an autosomal recessive fashion. Findings from the physical examination may alert the clinician to the possibility of a specific diagnosis and then appropriate laboratory tests may be performed in an attempt to verify that diagnosis. Such is the case in the neonate who presents with jaundice,

TABLE 4. Disorders Associated With a Positive Ferric Chloride Reaction

Disorder	Major Compound in Urine	Color
Phenylketonuria	Phenylpyruvic acid	Green
Hereditary tyrosinemia	*p*-Hydroxyphenylpyruvic acid	Green, fading rapidly
Maple syrup urine disease	Branched chain ketoacids	Gray-green
Histidinemia	Imidazolepyruvic acid	Blue-green
Alkaptonuria	Homogentisic acid	Dark brown
Diabetic ketoacidosis	Acetoacetic acid	Cherry red
Melanoma	Melanin	Black
Pheochromocytoma	Catecholamines	Blue-green
Formiminotransferase deficiency	Imidazolcarboxamide	Gray-green
Drug intoxication	Salicylates	Purple
	Phenothiazines	Purple
	p-Aminosalicylic acid	Red-brown
	Lysol	Green
Conjugated hyperbilirubinemia	Bilirubin	Green

TABLE 5. Disorders That May Be Associated With Nonglucose Reducing Substances in the Urine

Disorder	Compound
Galactosemia	Galactose
Hereditary fructose intolerance	Fructose
Hereditary tyrosinemia	*p*-Hydroxyphenylpyruvic acid
Galactokinase deficiency	Galactose
Essential fructosuria	Fructose
Pentosuria	Xylulose
Severe liver disease with secondary galactose intolerance	Galactose

TABLE 6. Disorders Associated With an Abnormal Urinary Odor

Disorder	Odor
Phenylketonuria	Musty
Hereditary tyrosinemia	Musty or cabbage-like
Maple syrup urine disease	Maple syrup or burnt sugar
Isovaleric acidemia	Cheesy or sweaty feet
Glutaric acidemia type II	Sweaty feet
3-Methylcrotonyl CoA carboxylase deficiency	Cat urine
Multiple carboxylase deficiency	Cat urine

hepatomegaly, vomiting, diarrhea, failure to thrive, and cataracts. Most pediatricians would immediately think of galactosemia, test the urine for reducing substances, and institute a galactose-free diet pending the results of definitive enzyme assays. The same is true of Pompe disease in which the findings of macroglossia, hypotonia, hepatomegaly, cardiomegaly, and congestive failure without evidence of structural heart disease are rarely associated with any other diagnosis. When the clinical findings are not so distinctive, on rare occasions, the diagnosis may be suggested by the observation of an unusual feature such as the odor of maple syrup found in the urine of infants with maple syrup urine disease.

In the vast majority of instances, the clinician is not so fortunate. Although the same may not be true for older children, the majority of inborn errors of metabolism that present in the neonatal period are characterized by nonspecific signs and symptoms which in themselves are not useful in making a diagnosis but when observed in combination are suggestive of such a diagnosis.

It is hoped that the guidelines presented in this discussion will assist the physician in the evaluation of such infants. It has not been the purpose of this review to discuss the definitive diagnostic studies leading to a precise diagnosis or to outline specific therapeutic measures. These are best left to those experienced in the management of infants with inherited metabolic disease. Astute clinical diagnosis and simple laboratory studies may provide the assurance that an affected infant will receive the benefits of further evaluation and treatment. If death appears imminent in a newborn suspected of having a metabolic disorder, the following samples should be collected and stored: (1) urine, frozen; (2) plasma separated from whole blood and frozen; and (3) a small snip of skin obtained sterilely and stored at room temperature or 37°C in tissue culture medium, if available, or in 5% dextrose in normal saline. If an autopsy is performed, a sample of unfixed liver tissue should be obtained as soon as possible after death and frozen at −20°C. Additional tissue should be preserved for electron microscopy. These samples can be subsequently transported to a diagnostic center for any studies that appear to be indicated. Postmortem diagnosis is particularly important in this group of disorders because they are essentially all genetically determined; the ability to offer accurate genetic counseling and specific prenatal diagnostic studies for future pregnancies will be dependent on the establishment of a precise diagnosis.

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MULTIPLE CO-AUTHORS BEWARE

A committee at the University of California at San Diego medical school has found that 68 papers have been tainted by the misconduct of researcher Robert Slutsky. The careers of dozens of co-authors have been thrown into question by the October 9 report of an investigative panel, which required scientists to demonstrate their contributions to the research effort to escape suspicion of misconduct. In its recommendations, the committee said departments should develop a way to measure "the type and degree of participation" of faculty in every published work.

From Mervis J: Study sharpens debate on role of co-authors. *The Scientist,* Nov 17, 1986.

Inborn Errors of Metabolism of Acute Onset in Infancy

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The questions below should help focus the reading of this article.

1. When should a newborn infant having nonspecific symptoms be suspected of having an inborn error of metabolism?

2. What three general diagnostic categories of inborn errors of metabolism of acute onset are useful in directing differential diagnosis?

3. What initial studies are appropriate when an inborn error of metabolism of acute onset is suspected?

4. What factors limit the potential for prenatal diagnosis of inborn errors of metabolism?

Pediatricians and neonatologists are frequently presented with ill neonates or older infants whose symptoms have an acute onset and a severe and/or recurrent character. The clinician faced with symptoms that are frequently nonspecific must differentiate among many disorders, usually considering infection, cardiac defects, central nervous system insults, or gastrointestinal problems. Not infrequently, an inborn error of metabolism (IEM) will mimic these more common conditions. Although each individual IEM is rare, throughout the course of a practice the clinician will cumulatively see many patients with such disorders, with various findings. According to a recent estimate, IEM account for as much as 20% of disease among full-term neonates not known to have been at risk.[1] The neonatologist and/or pediatrician will be the first to evaluate an acutely ill neonate or infant, and he or she must be alert to the possibility of an IEM. The implications of failing to entertain such a diagnosis may be formidable. An IEM should be considered early and appropriate screening tests obtained concurrently with assessment of the likelihood of more common causes.

The exact incidence with which IEM occur in the neonatal period or with acute symptoms in early to late infancy is not known. Cumulatively, IEM may represent more than 1 in 5000 live births. Many of these conditions may now be successfully treated. For those with treatment available, *immediate early intervention* yields the best results and may prevent severe mental and physical sequelae as well as death. A number of recent reviews are available as references to aid the clinician in forming a rational differential diagnosis among these disorders.[1-4]

All IEM are single-gene disorders, almost all being inherited in an autosomal recessive or X-linked recessive manner. The implications for the biologic parents of offspring with autosomal recessive disorders are that they, as the obligate carriers of a recessive gene, will have a risk of 1 in 4 for recurrence of similar cases in each future pregnancy. For the X-linked recessive disorders, the recurrence risk depends on the carrier status of the mother. If the mother is a carrier, the risk is 1 in 2 that a son will be affected and 1 in 2 that a daughter will be a carrier. The carrier daughter may partially express the condition. Prenatal diagnosis is available for virtually all of these diseases if the diagnosis is made in the index case.

The clinician's job would be made easier if these disorders could be diagnosed by newborn screening tests. Screening programs for phenylketonuria (PKU) in the 1960s paved the way for other IEM to be included in newborn testing. Most, but not all, states screen for PKU, hypothyroidism, and galactosemia. Several screen for other IEM, including maple syrup urine disease (MSUD), homocystinuria, adenosine deaminase deficiency, hemoglobinopathies, biotinidase deficiency, and congenital adrenal hyperplasia. The limitations of newborn screening in some of the more acute IEM, such as MSUD and galactosemia, are that the results may not be available until after the onset of the clinical symptoms. Thus, although newborn screening for these few IEM is undeniably valuable, for the remainder of the more than 70 genetically distinct IEM occurring in early and later infancy, clinical suspicion is essential for diagnosis.

EDUCATIONAL OBJECTIVE

15. The pediatrician should have knowledge to make an appropriate evaluation of a 2-day-old infant with seizures, vomiting and lethargy, differentiating among sepsis, central nervous system lesion, hypoglycemia, hypocalcemia, metabolic acidosis, and an inborn error of metabolism (methylmalonic aciduria, primary hyperammonemia, urea cycle defect), and develop an appropriate plan for management (Topics, 89/90).

CAH	Congenital adrenal hyperplasia
GSD	Glycogen storage disease
IEM	Inborn error(s) of metabolism
LCAD	Long-chain acyl-CoA dehydrogenase
MCAD	Medium-chain acyl-CoA dehydrogenase
MSUD	Maple syrup urine disease
PKU	Phenylketonuria
SCAD	Short-chain acyl-CoA dehydrogenase
UCE	Urea cycle enzymopathies

Although routine postmortem findings are rarely specifically diagnostic of an IEM, they are necessary to establish the lack of other, non-IEM illnesses as a cause of death. Moreover, the precise diagnosis of an IEM

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in infancy often requires specific postmortem biochemical analyses of fluids and tissues.

The most difficult task for the clinician is to know *when* to consider the diagnosis of an IEM of acute onset and *which tests* to order for evaluation. Certain clinical symptoms and laboratory findings are more common than others for specific IEM. Diagnostic categories, such as metabolic acidosis, hyperammonemia, and hypoglycemia are useful for developing a differential diagnosis; neurologic symptoms and liver dysfunction provide further diagnostic categories. After an IEM is identified, certain issues must be considered concerning treatment in both the acute stabilization phase and the chronic, but more likely specific, therapeutic phase. Confirmation of specific diagnostic tests allows for precise genetic counseling, including prenatal diagnostic information. Finally, it is important that the clinician be prepared when faced with the situation of an acutely ill child who is dying.

An Illustrative Case

W.W., a male infant, first came to medical attention at 20 days of age with a history of "...sleeping...vomiting and not eating." He was born at term, the first child of a young couple; labor and delivery were uneventful. When he went home from the hospital, at 5 days of age, he was receiving proprietary formula. During the next 3 weeks, he slept all but 1 hour per day, took less than 300 mL (10 oz) of formula per day, and "never cried." At 18 days of age he began forceful vomiting.

At 20 days of age, he became comatose and was admitted to a community hospital; he was evaluated for sepsis, and intravenous fluid and antibiotic therapies were begun. His bicarbonate level was 19 mEq/L, and the glucose concentration was 54 mg/dL. On the second hospital day, he had a seizure and, because of continuing coma, was referred to a pediatric hospital.

Evaluations for infection and primary central nervous system pathologic conditions were initially carried out. Findings from ultrasonography of the head were normal; an electroencephalogram appeared abnormal, consistent with diffuse encephalopathy. The anion gap was 19 mEq/L and pH was 7.26. Results of a complete blood cell count were as follows: a decreased platelet count (48 000/fL compared to a normal 200 000 to 370 000). Leukopenia was noted with a white blood cell count of 2600/fL compared to a normal level of 5000 to 19 000/fL). The platelet count decreased to 10 000/fL. Serum ammonia level soon after admission was 1440 μmol/L; repeated testing gave a result of 2200 μmol/L (normal levels are $\leq$ 144 μmol/L). From urinalysis ketones were found to be 1+. Ultrasonography of the kidneys revealed mild bilateral pyelocaliectasis; a voiding cystourethrogram showed unilateral vesicoureteral reflux.

A differential diagnosis was developed and included urea cycle enzymopathies and organic acidurias. The patient was given 10% dextrose intravenously, and peritoneal dialysis was begun to reduce the nitrogen load and/or other accumulated toxic metabolites (hemodialysis was not available). Therapy using compounds to promote excretion of nitrogen was begun. Qualitative evaluation of urinary amino acids by electrophoresis indicated elevation of ornithine/lysine, histidine, and glycine concentrations. Quantitative plasma glycine levels were three to four times the upper limit of normal; this pattern did not support the diagnosis of citrullinemia or argininosuccinic acidemia. Plasma citrulline was present and the glutamine level was not elevated, as expected in a urea cycle enzymopathy. Urine tested for organic acids by gas chromatography-mass spectrometry revealed metabolites consistent with propionic acidemia. Nasogastric therapy with biotin and a formula containing no protein (Mead Johnson 80056) was begun. By the 3rd or 4th day of hospitalization, ammonia levels had become normal, and the infant began to show arousal. Nutritional therapy was tailored specifically during the next few days to include an essential amino acid mixture and specific restriction of the amount of natural protein (in formula form) in addition to the therapy already described. The immediate and extended families were counseled about genetic factors of the condition and future expectations for the infant. The metabolic nutritionist aided in implementation and education regarding the medical dietary treatment. Future follow-up and monitoring were initiated by a specialized IEM team.

SYMPTOMS

The recognition of an IEM in the neonate and infant can be difficult. The neonate has a limited repertoire of clinical symptoms and the findings of an IEM may resemble that of more commonly occurring disorders. The clinical clues that should alert the clinician both to the *possibility* of an IEM and to the *strong probability* of an IEM are listed in Table 1.

Many of these symptoms can also be found in infants with sepsis, respiratory problems, cardiac disorders, gastrointestinal obstruction, renal transport conditions, and central nervous system insults. Several cases are known in which the diagnosis of an IEM was delayed because the initial evaluation was *only* for the more common disorders. Illustrative cases include: surgery for suspected intestinal obstruction in persistent vomiting in the urea cycle disorders; cardiac disease as a secondary finding of an organic aciduria; surgery for ileus in an infant with previous symptoms consistent with an IEM[2]; consideration of a brain biopsy to prove congenital viral infection in a case of MSUD; and the well-known occurrence of *Escherichia coli* sepsis in patients with galactosemia.

It is common for infants with an IEM of acute onset to have had an uneventful delivery, a normal birth weight, and an uneventful early period of days or weeks before the manifestation of symptoms. Exceptions include those patients with apparent seizures occurring in utero and those with dysmorphic features. Although unusual, an increasing number of IEM which appear acutely in infancy are being reported to have associated congenital anomalies (Table 2).

LABORATORY EVALUATION OF IEM

The laboratory evaluation of the IEM can be straightforward. Clinicians may regard many of these tests

TABLE 1. Clinical Symptomatology of Inborn Errors of Metabolism (IEM) in the Neonate or Infant

Symptoms indicating *possibility* of an IEM (one or all)
- Infant becomes acutely ill after period of normal behavior and feeding; this may occur within hours or weeks
- Neonate or infant with seizures and/or hypotonia, especially if seizures are intractable
- Neonate or infant with an unusual odor

Symptoms indicating *strong probability* of an IEM, particularly when coupled with the above symptoms
- Persistent or recurrent vomiting
- Failure to thrive (failure to gain weight or weight loss)
- Apnea or respiratory distress (tachypnea)
- Jaundice or hepatomegaly
- Lethargy
- Coma (particularly intermittent)
- Unexplained hemorrhage
- Family history of neonatal deaths, or of similar illness, especially in siblings
- Parental consanguinity
- Sepsis (particularly *Escherichia coli*)

TABLE 2. Physical Anomalies Associated With Acute-Onset Inborn Errors of Metabolism (IEM)

Anomaly	Possible IEM
Ambiguous genitalia	Congenital adrenal hyperplasia
Hair and/or skin problems (alopecia, dermatitis)	Multiple carboxylase deficiency, biotinidase deficiency, argininosuccinic aciduria
Structural brain abnormalities (agenesis of corpus callosum, cortical cysts)	Pyruvate dehydrogenase deficiency
Macrocephaly	Glutaric aciduria, type I
Renal cysts, facial dysmorphia	Glutaric aciduria, type II; Zellweger syndrome
Facial dysmorphia	Peroxisomal disorders, (Zellweger syndrome)
Cataract	Galactosemia, Lowe syndrome
Retinopathy	Peroxisomal disorders
Lens dislocation, seizures	Sulfite oxidase deficiency Molybdenum cofactor deficiency
Facial dysmorphia, congenital heart disease, vertebral anomalies	3-OH-isobutyric CoA deacylase deficiency

as "exotic" or unusual, a view reinforced by the lack of familiarity of general clinical laboratories with these tests. The commonly available tests, both within the hospital for initial evaluation and available on site from a specialty laboratory or from an off-site reference laboratory are listed in Table 3; the latter may be needed for more specific testing. The first group of tests includes the usual abnormalities that may be seen in IEM disorders. Although the first group may seem elemental, in the author's experience clues available in these tests often are not recognized or heeded (eg, increased anion gap, nonketotic hypoglycemia) or not obtained early enough in the evaluation (ammonia, lactate/pyruvate). These tests are useful, both for initial management and to assess the need for referral. The neonatologist or pediatric intensivist to whom the patient is referred can immediately institute further diagnostic procedures, obtain appropriate consultations, and direct rational therapeutic approaches.

The second group of tests are inexpensive relative to the cost of other invasive tests and acute care facilities. Certainly, the first three tests in this group should be obtained for almost any child whose symptoms include those in Table 1. Early consultation with a regional IEM specialist, either a clinical geneticist or other qualified individual who manages patients with acute onset IEM, is strongly recommended. The National Center for Education in Maternal and Child Health has published a directory of treatment centers for metabolic disorders and is available upon request.[5] Individuals at these centers can help direct specific tests to an appropriate laboratory, prioritize emergency testing, and suggest and implement initial diagnostic and treatment plans before referral.

There is occasional difficulty in interpretation of the screening tests in the case of an IEM (metabolic screening in urine, amino acid quantitation, organic acid identification in urine). A patient receiving intravenous glucose therapy whose urine or plasma was obtained *after* the acute findings may be "partially treated" for his or her underlying condition; diagnostic metabolites may be less obvious than in a specimen taken at the time of acute findings. On the other hand, some "acute phase" metabolites, particularly in the organic acidurias, may mask more diagnostic compounds, requiring a "convalescent" sample for more specific diagnosis. Intravenous amino acid solutions may influence amino acid profiles, although major amino acid elevations or deficiencies are usually apparent. Drug metabolites (eg, valproate) will be found during organic acid analyses, but the laboratory experienced with IEM should be familiar with the majority of these compounds. Galactose and fructose will not be identified in urine if the offending metabolite (lactose or sucrose/fructose, respectively) has been removed from the diet for a few days, or they may not be found in some patients with the disorder. On the other hand, one may find galactosuria in the presence of certain liver dysfunctions, including those caused by some IEM. Measurement of enzyme activity is indicated even if screening for metabolites for a suspected condition does not find them readily apparent, especially with a high index of suspicion.

It is important that screening tests, including those for amino and organic

TABLE 3. Laboratory Tests for Evaluation of Inborn Errors of Metabolism (IEM) of Acute Onset

Commonly Available Tests
- Complete blood count with phase platelet count (leukopenia, thrombocytopenia, anemia)
- Urinalysis (ferric chloride, pH, ketones, Clinistix [glucose]; Clinitest [reducing substance])
- Arterial blood gases (acidosis, alkalosis)
- Serum electrolytes (anion gap; hyperchloremia)
- Blood glucose (hypoglycemia)
- Blood ammonia (hyperammonemia)
- Lactic and pyruvic acids (from serum and cerebrospinal fluid, obtained simultaneously)
- Uric acid (hyperuricemia)
- Liver function studies (eg, elevated transaminases, decreased clotting factors)
- Blood urea nitrogen (low values)

Available Specific Tests for IEM (On-site or From Experienced Metabolic Reference Laboratory
- Quantitative amino acids (plasma, by column chromatography)
- Quantitative amino acids (cerebrospinal fluid, by column chromatography)
- Amino acid screen (urine, electrophoresis)
- Organic acids (urine, gas chromatography and/or gas chromatography-mass spectrometry)
- Carnitine (plasma total and free)
- Very long chain fatty acids (serum)
- β-OH-butyrate (serum)
- Free fatty acids (serum)
- Quantitative orotic acid (urine)
- Galactose-1-phosphouridyl transferase (red blood cell)

More Limited Available Tests, Usually Requiring Clinical Genetics/Metabolic Professional Interface
- Enzyme determination
  - Cultured skin fibroblasts
  - Leukocytes
  - Liver
- Molecular DNA studies (index case)
  - Whole blood leukocytes
  - Skin fibroblasts
  - Liver or other tissue

acids, be obtained *both* during the acute episode (before treatment if possible) *and* during convalescence and/or well periods to more precisely diagnose certain conditions. Because the findings of an IEM may vary from time to time in the same individual, repeated testing during recurrent episodes of illness may be necessary.

It is imperative that the referring clinician include pertinent information for the IEM laboratory for interpretation. This information should ideally include: clinical symptoms and/or suspected diagnosis; content of oral and intravenous intake in the previous 24 to 48 hours; and any medications or contrast dye administered before sampling. Additionally, after direct communication with the specialty laboratory, the clinician should refer these screening specimens and more specific tests to the nearest academic metabolic laboratory with experience in the diagnosis of these disorders to speed the diagnostic process.

DIFFERENTIAL DIAGNOSIS

A summary of the overall evaluation of illness of acute onset in a neonate is given in Fig. 1. IEM of acute onset can be divided into two major diagnostic categories: those with metabolic acidosis and those with hyperammonemia (Figs 2 and 3). The algorithms shown are not inclusive of all such diseases but are useful to begin sorting the majority of them. Hypoglycemia defines another major group and may appear either with or without metabolic acidosis (Fig 2).

Metabolic Acidosis

Many IEM of organic and amin acid metabolism may cause symptoms of metabolic acidosis at onset which may be persistent, recurrent, or severe. Metabolic acidosis is defined as an excess of circulating acid, simultaneously with decreased blood-buffering capacity (low bicarbonate concentration). Acidemia may result when the body can no longer buffer the acidosis (pH<7.35).[6] Clinical symptoms usually include persistent vomiting and tachypnea. Other signs may include hypotonia, lethargy/coma, seizures, or spasticity, indicating severe decrease in central nervous system pH. Chronic metabolic acidemia may involve failure of growth.

Among the laboratory tests used to confirm metabolic acidosis as part of the routine evaluation of a sick infant, measurement of serum bicarbonate levels is most useful. When the serum bicarbonate levels are low, the *anion gap* must be determined. The anion gap reflects the quantity of unmeasured anions, such as lactate, ketone bodies (β-OH-butyrate and acetoacetate), and other organic acids. It is calculated by subtracting the summed HCO_3^- and Cl^- levels from the Na^+ levels; normal values range from 8 to 16 mEq/L. If the anion gap is *increased*, with a normal chloride level, the acidosis is probably secondary to excess acid production; this is most consistently seen with IEM disorders of organic and amino acid metabolism. If the anion gap is *normal* with hyperchloremia, this may be more indicative of bicarbonate loss, such as may occur with intestinal or renal transport disorders, but these findings may also indicate an IEM (Fig 2).

Additional tests useful for the initial evaluation of metabolic acidosis in the infant are the commonly available tests listed in Table 3. Organic acidurias may occur with thrombocytopenia, leukopenia, anemia, or a combination thereof. Hyperammonemia may occur in many organic acidurias; however, urea cycle defects resulting in hyperammonemia rarely cause metabolic acidosis, and more commonly have respiratory alkalosis.

Lactic acid may be primarily ele-

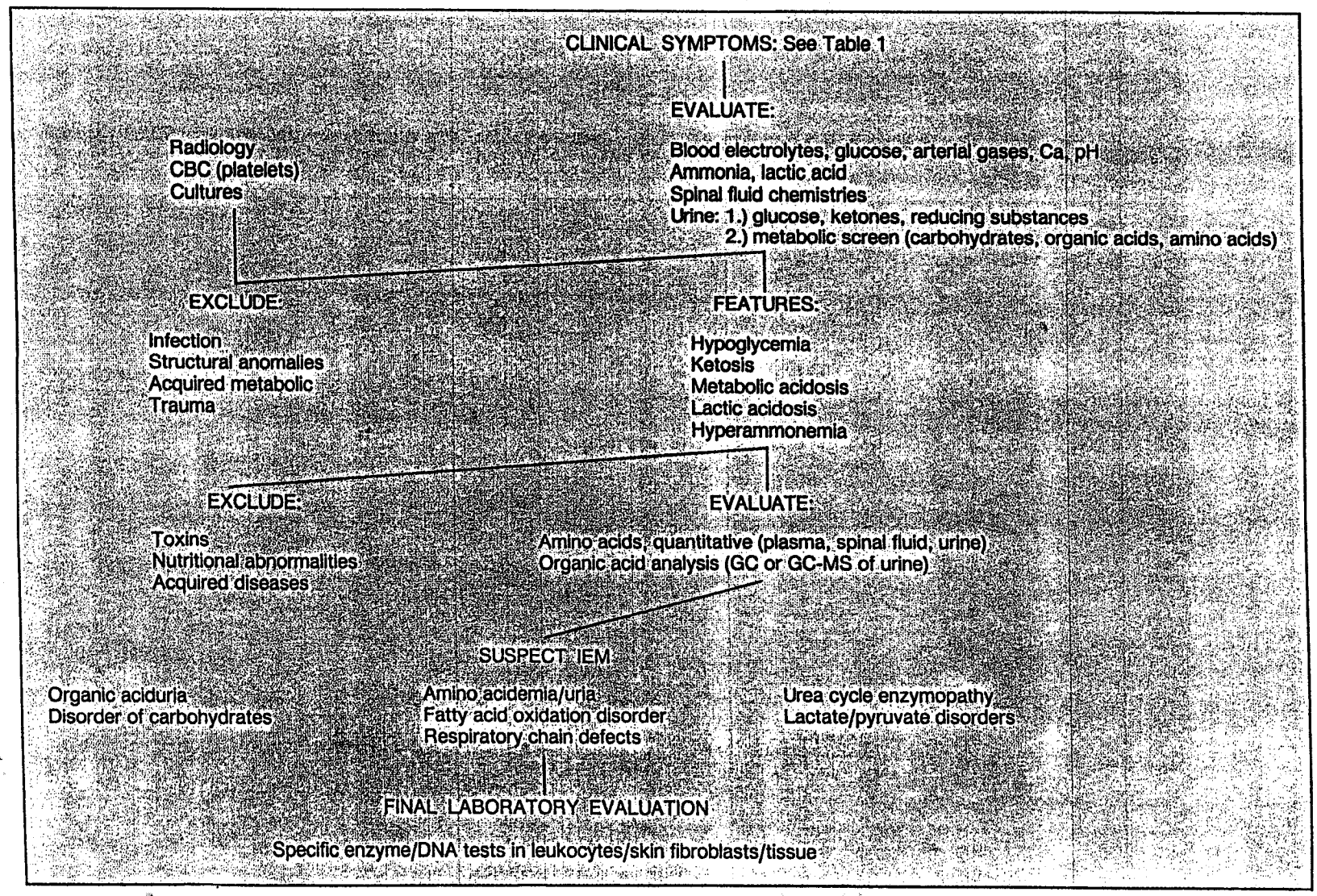

Fig 1. Inborn errors of metabolism in infancy. Abbreviations: CBC, complete blood cell count; GC, gas chromatography; GC-MS, gas chromatography-mass spectrometry. Adapted from Harkness[15] and Holton.

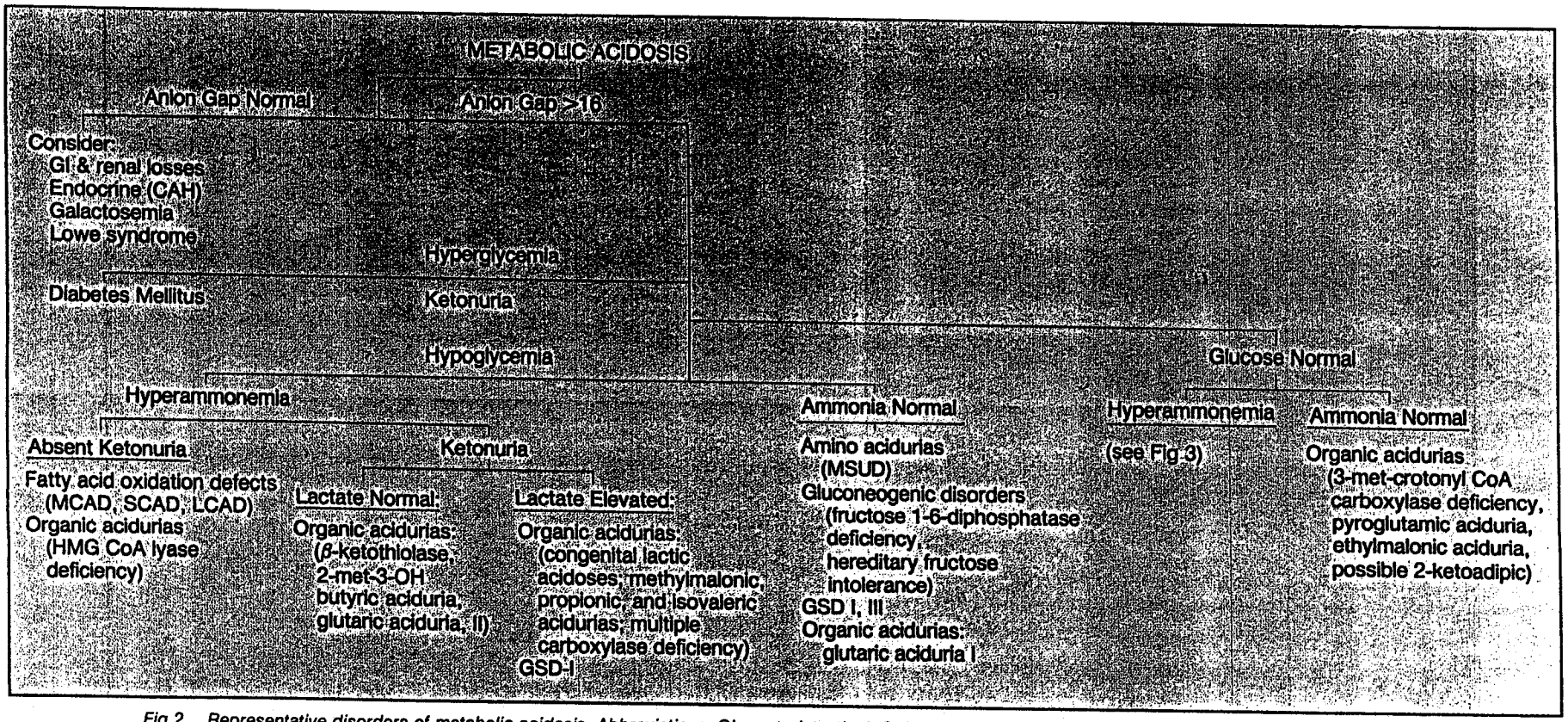

Fig 2. Representative disorders of metabolic acidosis. Abbreviations: GI, gastrointestinal; CAH, congenital adrenal hyperplasia; MCAD, medium-chain acyl CoA dehydrogenase; SCAD, short-chain acyl CoA dehydrogenase; LCAD, long-chain acyl CoA dehydrogenase; HMG, hydroxymethyl-glutaryl; GSD, glycogen storage disease I; MSUD, maple syrup urine disease. Adapted from Greene et al[7] and Barela et al.[9]

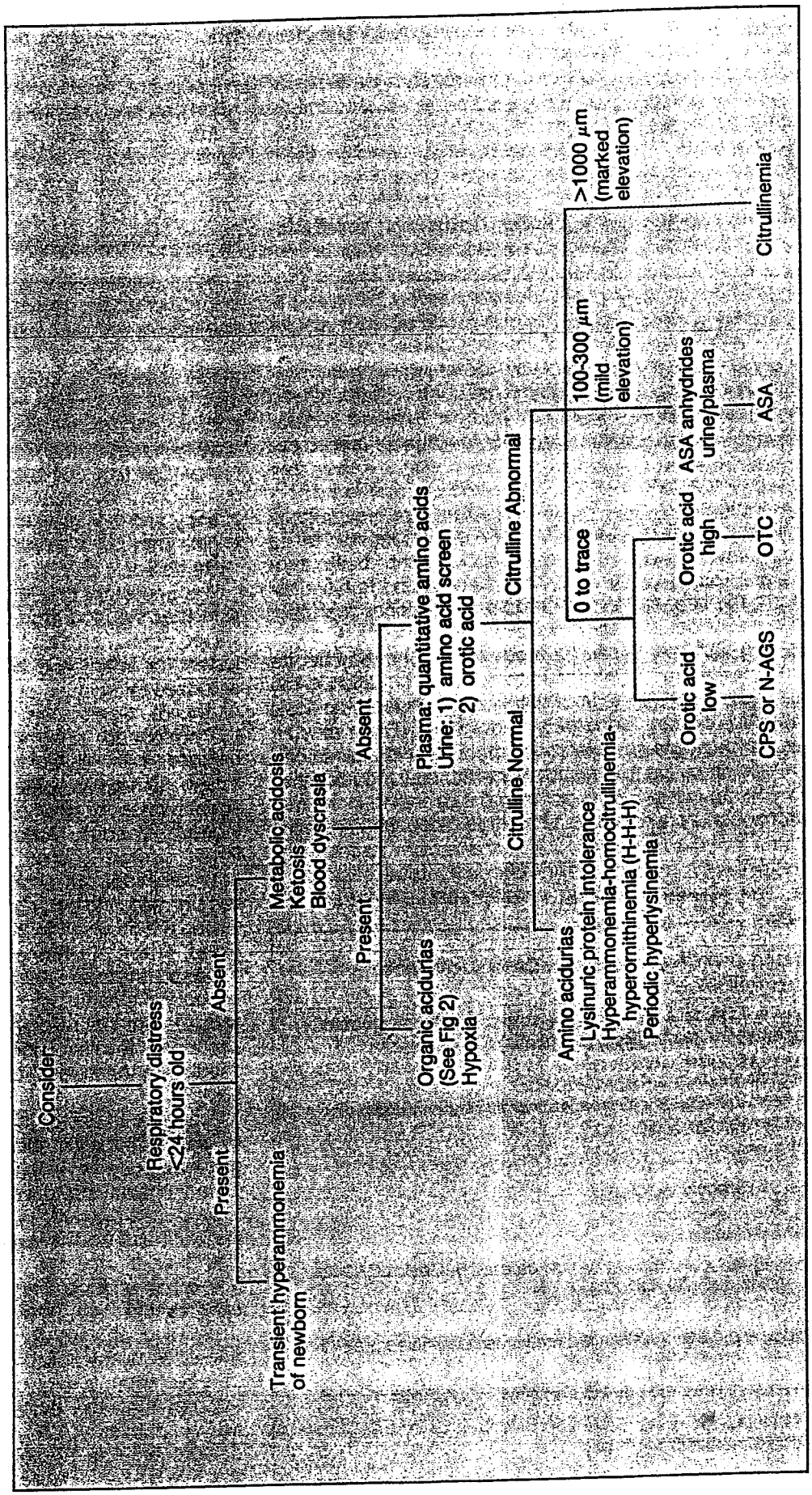

Fig 3. Hyperammonemia in infancy. Abbreviations: CPS, carbamyl phosphate synthetase; N-AGS, N-acetyl glutamate synthetase; OTC, ornithine carbamyl transferase; ASA, argininosuccinic acidemia. Adapted from Hudak et al.[14]

vated in the congenital lactic acidoses or secondarily elevated in organic acidurias, abnormalities of carbohydrate metabolism or hypoxia. Patients with a hypoplastic left heart may have significant lactic acidosis.

These initial laboratory evaluations may lead one to suspect an IEM (Fig 1). A patient with an increased anion gap and normal or decreased glucose level, with or without hyperammonemia or ketonuria, should have urine metabolic screening (amino acid, carbohydrate, and organic acid analysis), amino acids quantitated and identified in plasma, and specific determination of urinary organic acids by gas chromatography or, additionally, by mass spectrometry. Disorders of gluconeogenesis should be considered in those patients in whom hypoglycemia occurs with an increased anion gap and in whom amino acid and organic acid levels are normal.

Organic acidurias form the largest group of disorders to be considered in metabolic acidosis (Fig 2).[2,3] Almost all can be presumptively diagnosed on the basis of acute or convalescent urine test results, thereby allowing chronic therapy to be specifically tailored. Enzyme confirmation of the blocked metabolic step in leukocytes, skin fibroblasts, or liver may be required for more specific therapy, as well as for genetic counseling and prenatal diagnosis. Amino acidurias also require these tests for complete diagnosis.

Other disorders, such as those of gluconeogenesis (eg, fructose-1,6-diphosphatase deficiency) and of fatty acid oxidation (eg, medium-chain acyl-CoA dehydrogenase deficiency [MCAD]) may be carefully evaluated with fasting or specific metabolite-loading tests. However, when an enzyme test is available, this is preferred to fasting studies, because the latter may precipitate severe hypoglycemia. Likewise, galactosemia is relatively easy to confirm with erythrocyte enzyme testing; in the infant who has never received a blood transfusion, one should further evaluate decreased values using a laboratory that subtypes the enzyme forms.

Recently, patients with symptoms similar to Reye syndrome, as well as some with sudden infant death syndrome, have been found to have enzyme defects in mitochondrial fatty acid oxidation (Table 4).[7,8] A major clue to these conditions may be the *lack* of ketone body formation in the face of significant metabolic acidosis and/or hypoglycemia. There may be an increase in the bound plasma carnitine fraction with elevation of these fatty acids and a decrease in the free plasma carnitine. Total carnitine may, therefore, be normal. Accordingly, determination of total and free plasma carnitine and urinary acylcarnitine levels may be useful in these conditions. Carnitine loading with subsequent acylcarnitine measurement has been helpful in diagnosis.[8]

For a discussion of other conditions resulting in metabolic acidosis in the neonate and infant, see the article by Barela.[9]

TABLE 4. Inborn Errors of Metabolism of Acute Onset: Nonacidotic, Nonhyperammonemic Features

Neurologic Features Predominant (Seizures, Hypotonia, Optic Abnormality)
- Glycine encephalopathy (nonketotic hyperglycinemia)
- Pyridoxine-responsive seizures
- Sulfite oxidase/xanthine oxidase deficiency
- Peroxisomal disorders (Zellweger syndrome, neonatal adrenoleukodystrophy, infantile refsum disease)

Jaundice Prominent
- Galactosemia
- Hereditary fructose intolerance
- Menkes kinky hair syndrome
- α_1-antitrypsin deficiency

Hypoglycemia (Nonketotic): Fatty acid oxidation defects (MCAD, LCAD, carnitine palmityl transferase, infantile form)

Cardiomegaly
- Glycogen storage disease (type II phosphorylase kinase b deficiency[18])
- Fatty acid oxidation defects (LCAD)

Hepatomegaly (Fatty): Fatty acid oxidation defects (MCAD, LCAD)

Skeletal Muscle Weakness: Fatty acid oxidation defects (LCAD, SCAD, multiple acyl-CoA dehydrogenase).

Hyperammonemia

Hyperammonemia is a life-threatening condition; affected neonates and infants whose hyperammonemia is undiagnosed may die. Plasma ammonia should be determined in *all* infants with altered consciousness and/or persistent vomiting, which usually appear after 1 to 2 days of normal feeding and behavior. These conditions may occur in early or late infancy and sometimes at later ages in girls with the X-linked form of urea cycle defect.

It is important that the clinician be sure that the laboratory uses control values of ammonia concentration adjusted for infant and neonatal ages and uses techniques of good quality. Ammonia levels can be elevated by prolonged specimen handling, mixture with dead air space in tubes, ammonia-contaminated reagent water, or ammonium heparin tubes.[10] Venous blood is the preferred sample source for ammonia determination, but capillary samples can be used if collected appropriately; values are generally higher in capillary blood. These differences are unlikely to result in failure to detect major ammonia elevations, but capillary samples are not reliable for monitoring lower levels. Abnormal results should be confirmed using venous samples.

Ammonia is one of the major intermediates in the catabolism of nitrogen compounds. It is derived from dietary or body protein (amino acids), is produced primarily in the gastrointestinal tract, and appears in plasma. The liver is the primary organ for maintenance of plasma ammonia levels less than 40 μmol/L (the value depending on method and age). It does this by synthesis of glutamine from glutamate and by urea synthesis through the urea cycle. Urea cycle enzymopathies (UCE), the primary defects of urea production, involve the five enzyme steps of the urea

cycle.[11-14] Deficiency of the cofactor for the enzyme catalyzing the first step of the urea cycle, *N*-acetyl glutamate, can mimic a UCE. All are inherited conditions; ornithine carbamyl transferase deficiency is an X-linked recessive disorder and the rest are inherited as autosomal recessive disorders. Carbamyl phosphate synthetase deficiency may occur acutely or in a later onset form with hyperammonemia. Citrullinemia (argininosuccinate lyase deficiency) and argininosuccinic acidemia (argininosuccinate synthase lyase deficiency) are the other two disorders that occur with hyperammonemia. Therefore, it is of utmost importance to diagnose these conditions, not only because there is therapy available but also because of the recurrence risk for a future child of the same parents (one in four).

Patients with hyperammonemia and acidosis should have full metabolic evaluation. In those patients without acidosis, the plasma quantitative amino acids provide a useful differential aid. Citrullinemia and argininosuccinic acidemia have diagnostic metabolites. Urinary orotic acid distinguishes ornithine carbamyl transferase and carbamyl phosphate synthetase deficiencies. Primary severe hyperammonemia (>1000 μmol/L) without metabolic acidosis in the neonate or infant are usually strong indicators of a UCE (Fig 3). However, some organic acidurias feature marked hyperammonemia as the predominant laboratory abnormality. Transient hyperammonemia of the newborn is a condition that requires early and aggressive treatment. Most of the affected infants recover within days to weeks and apparently do well without further restrictive treatment.[14] These patients have had some of the highest initial ammonia concentrations of the hyperammonemias. Nongenetic conditions producing lesser degree of hyperammonemia may include perinatal asphyxia, valproate therapy, total parenteral nutrition, liver disease, and certain urinary tract infections.

The first two enzymes in the urea cycle (carbamyl phosphate synthetase and ornithine carbamyl transferase) are measurable in liver but not in skin fibroblasts; both argininosuccinate synthetase (citrullinemia) and argininosuccinate lyase (argininosuccinic aciduria) are measurable in skin fibroblasts. The diagnosis of carbamyl phosphate synthetase and ornithine carbamyl transferase deficiencies requires measurement of orotic acid levels in urine or in liver tissue for enzyme confirmation. Molecular DNA analysis of a confirmed affected child with carbamyl phosphate synthetase or ornithine carbamyl transferase deficiency and their parents is currently a prerequisite for prenatal diagnosis in future pregnancies, unless a gene deletion is found. Fetal liver biopsy has been performed in those families in whom molecular studies are not informative. Enzyme determinations in the other UCE and molecular DNA analysis in ornithine carbamyl transferase/carbamyl phosphate synthetase deficiencies are prenatally diagnosable by chorionic villus sampling or amniocentesis.

Treatment of UCE is aimed at reducing the waste nitrogen load (through a decrease in protein intake and the administration of essential amino acids) and the use of alternative waste nitrogen excretion compounds to use and/or bypass the urea cycle. Sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate are currently being evaluated for acute and long-term use to rid the body of waste nitrogen through formation of excretable compounds (hippuric acid and glutamine conjugates).[11-13] Arginine supplementation is required as an essential amino acid in four of five deficiencies; it is used as a major treatment medication in patients with citrullinemia and argininosuccinic aciduria.

Hypoglycemia

Hypoglycemia is another useful category within which to develop a differential diagnosis. When it occurs with metabolic acidosis, an algorithm such as that shown in Fig 2 can be used. Hypoglycemia, particularly with hepatomegaly and of a nonketotic type, should alert the clinician to the possible presence of fatty acid oxidation defects or Reye syndrome. The most common type of the former appears to be due to medium-chain acyl-CoA dehydrogenase deficiency (MCAD) and usually has its clinical onset between 6 and 18 months of age.[7,8] Short-chain and long-chain acyl-CoA dehydrogenase (SCAD and LCAD) deficiencies also occur. These conditions result from the inability of the short-, medium-, and long-chain fatty acids to be metabolized. Most patients are treatable by appropriate metabolic dietary manipulation.

Hypoglycemia and hepatomegaly are also major features of glycogen storage disease (GSD) type I (and sometimes type III), and defects in fructose metabolism. Other causes of hypoglycemia of endocrine origin are discussed in textbooks.

Other Categories

Neurologic Features. Although infants with metabolic acidosis and/or hyperammonemia constitute a significant proportion of patients with acute symptoms, there are several disorders in which the predominant features are neurologic without acidosis or hyperammonemia. These may occur with organomegaly, failure to thrive, dysmorphia, or a combination of the above (Table 4).

Seizures, especially myoclonic, and apnea are common symptoms of nonketotic hyperglycinemia. The elevation of glycine levels results from an apparent defect in glycine cleavage, particularly in the central nervous system. Confirmation of this diagnosis currently requires quantitation of amino acids obtained simultaneously from spinal fluid and plasma. The cerebrospinal fluid to plasma ratio should be <0.03. Recent treatment has included diazepam to control the seizures and sodium benzoate to reduce glycine levels; most patients remain retarded, however, following treatment. This is an autosomal recessive disorder for which to date there is no consistent prenatal diagnostic test. D-glyceric aciduria (an organic aciduria) may occur with seizures and hypotonia. Seizures, in addition to other findings, may occur in patients with molybdenum cofactor deficiency.

Pyridoxine seizures, which have a typical appearance in the newborn period, may have their onset as late as 3 months and be temporarily treated with standard anticonvul-

sants. A trial of pyridoxine therapy should be given to all infants with such seizures[19] to evaluate the possibility of this autosomal recessive condition.

Seizures and hypotonia may be the initial features of the recently elucidated peroxisomal disorders. Those occurring in infancy include Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, hyperpipecolic acidemia, and rhizomelic chondrodysplasia punctata; all are autosomal recessive disorders.[17] Other features that should alert the clinician to such a disorder include ophthalmologic (retinal and lenticular) changes, development of renal cysts, hepatomegaly, and skeletal abnormalities (such as stippled epiphyses), as well as facial dysmorphia. Peroxisomes may be absent, decreased in number, or have decreased function. The best screening test for these conditions is the measurement in plasma of very long-chain fatty acids, because these are uniquely oxidized in the peroxisome.

Liver Dysfunction. Disorders involving liver dysfunction without storage include hereditary fructose intolerance, galactosemia, and hereditary tyrosinemia. Appropriate enzyme tests for galactosemia (galactose 1-phosphate uridyltransferase in erythrocytes) and hereditary fructose intolerance (hepatic aldolase) should confirm the diagnosis. In addition to the suggestive elevations of the amino acids, organic acid analysis for succinylacetoacetate should increase suspicion for the diagnosis of tyrosinemia. Restrictive dietary therapy is available for these autosomal recessive conditions.

Hepatomegaly often appears in association with fatty acid oxidation defects (SCAD, MCAD, and LCAD). Nonketotic hypoglycemia is the alerting sign in these disorders.

Dysmorphic/Physical Features. Several IEM occurring in infancy have dysmorphic features (Table 2); those occurring in the neonate and infant have been listed by Burton.[2] Others may be accompanied by storage of glycogen or a lysosomal substrate resulting in hepatomegaly, cardiomegaly,[18] splenomegaly, or neurodegeneration. Most of these disorders will not occur acutely unless hypoglycemia occurs in a glycogen storage disease or seizures in a neurodegenerative disorder.

Infection. Infants with infection constitute one of the largest groups from which those with IEM of acute onset must be differentiated. On the other hand, galactosemia may *occur with* infection, namely, *E coli* sepsis. Organic acidurias, such as propionic acidemia and methylmalonic acidemia may *mimic* infection displaying acidosis with thrombocytopenia, neutropenia or anemia.

Hemorrhage. Intracranial and/or pulmonary hemorrhage may be one of the clinical signs of IEM of acute onset, particularly as a complication of the hyperammonemia due to a UCE.

TREATMENT

Treatment for the IEM may be divided into the *immediate* steps to stabilize the patient and provide presumptive therapy and the more specific steps to treat the likely condition in the *chronic* state.

Immediate

Hyperammonemia, metabolic ketoacidosis, and hypoglycemia are the more common problems requiring immediate action. Intravenous administration of 10% to 15% dextrose (or an oral glucose polymer solution) to increase caloric intake and appropriate acid-base therapy are frequently necessary. Sodium bicarbonate administration (2 to 3 mEq/kg per 6 hours) is useful. Management requires close monitoring of plasma pH, blood gases, and electrolytes (particularly K^+). Limiting or avoiding oral formula intake removes the source of the offending metabolite, such as protein or specific carbohydrate; this is the first line of treatment.[4] Total caloric intake by intravenous and oral routes should be at least 60 to 70 kcal/kg per day to aid in preventing caloric breakdown in the first 24 to 48 hours. One may choose to use insulin (dosage tailored to case) to aid in utilization of the concentrated glucose solutions given and to inhibit endogenous protein catabolism. In cases in which acidosis is intractable, peritoneal dialysis or hemodialysis may be indicated for removal of toxic metabolites. If the regimens fail to stabilize the infant, a "cocktail" of co factors (such as vitamin B_{12}, biotin, thiamine, riboflavin, pyridoxine, and folate) may be used as an effort to salvage the infant to detect those disorders that would be responsive to a particular cofactor.[20]

When the ammonia level is high (generally greater than two to three times the upper limits of normal), intravenous administration of alternative waste nitrogen compounds is indicated. Peritoneal dialysis or hemodialysis may be required for severe hyperammonemia.[11–14] These compounds and procedures should be administered in the referral specialty center. Exchange transfusions are not as effective as dialysis, and efforts should be made to transport the infant to a center where dialysis is available. If the patient does not tolerate nasogastric feedings, intravenous solutions of glucose (10% to 15%) and of essential amino acids (0.50 to 0.75 g/kg per day) should be begun to prevent further protein catabolism. When tolerated, nasogastric feedings of glucose solutions should be implemented, and when successful, administration of a nonprotein base formula (such as Mead-Johnson 80056) should provide extra caloric intake until a more specific diagnosis can be made. Consultation with a pediatric pharmacotherapeutic specialist and/or metabolic nutritionist is advisable in these cases. Frequent oral (nasogastric) feedings of complex carbohydrates have been useful in certain glycogen storage diseases (GSD, type I).

Lipid can be added to intravenous feedings to increase caloric intake but may be contraindicated in certain fatty acid oxidation defects.

Carnitine, given intravenously and orally has been used acutely to aid excretion of conjugates of accumulating metabolites in many organic acidurias. Its overall usefulness is still being evaluated. Glycine therapy has also been used as an adjunct in disorders such as propionic acidemia.

Careful neonatal and pediatric care is indicated while acute treatment and early evaluation are ongoing, specifically for complications of hypothermia, dehydration, infection, and acidosis.

Chronic

Chronic or long-term therapy includes limitation, but not necessarily total exclusion, of the accumulating substrate(s), if a specific one is identified. One or several amino acids may be restricted in some amino or organic acidurias. Limitation of protein intake (1 to 2 g/kg per day) may be used in organic acidurias and several urea cycle disorders. If a cofactor is required for the metabolic pathway involved, some defects may be responsive to large supplements of that specific cofactor. Oral waste nitrogen excretion therapies are used chronically. Frequent carbohydrate feedings may be used in glycogen storage disorders and in certain fatty acid oxidation defects.

These therapies are lifelong and require intermittent and continuing nutritional, medical, and laboratory monitoring by a team of professionals who specialize in these disorders. Factors that may precipitate recurrent episodes are the inclusion of a restricted substance in the diet (eg, protein), protein catabolism (stress, surgery), and infection, both viral and bacterial. Because patients with these disorders are now able to be treated, information regarding mental and physical development, reproduction, and teratogenic effects on their children is emerging.

TABLE 5. Protocol for Pre- and Postmortem Evaluation of the Dying Infant Suspected of Having an Inborn Error of Metabolism

1. Blood (10–20 mL)
   a. Serum and plasma—
      Separate, freeze in aliquots of 1-2 mL at −20°C; (quantitative amino acids, carnitine, ketone bodies, etc)
   b. Erythrocyte and leukocyte fractions—
      (1) Erythrocytes: Refrigerate (4°C) fraction (selected enzyme, peroxisomal studies)
      (2) Leukocytes: Freeze a fraction at −20°C for possible enzyme/DNA studies
2. Urine (20–30 mL): Store in 5-mL aliquots, −20°C (organic acids, amino acid screening, orotic acid, and others)
3. Vitreous humor (chemistries)
4. Skin (3–4 mm)
   a. Full-thickness skin biopsy taken sterilely (cleansed with alcohol, not iodine, and instruments sterile)
   b. Store in sterile culture medium (or sterile isotonic saline with glucose) and contact fibroblast tissue culture laboratory *immediately*
5. Tissue biopsies (liver, heart, muscle, brain, etc.)
   a. Needle biopsy or immediate autopsy samples of tissue (quick frozen with dry ice (aluminum foil on dry ice) → transferred to prelabeled tightly stoppered tubes; freeze −20°C
   b. Light and electron microscopy; particularly of liver, heart, and skeletal muscle tissues

EVALUATION OF THE SEVERELY ILL CHILD NEAR DEATH

In those situations in which overwhelming complications make stabilization of an infant impossible, there are several steps the clinician can take to increase the likelihood of a specific diagnosis (Table 5).[6,16,21] One should obtain 10 to 20 mL of blood and separate the plasma and the cellular fraction. Urine (20 to 30 mL) can be obtained and stored without preservatives at −20°C. A full-thickness skin biopsy (3 to 4 mm) for fibroblast culture should be obtained and placed in a sterile, isotonic glucose/electrolyte solution and refrigerated. Tissue biopsies of liver, heart, muscle, brain, or other tissues are frequently helpful and should be quickly frozen on dry ice and stored at least at −20°C (preferably at −40°C to −70°C). Additionally, evaluation of tissues by both light and electron microscopy should be undertaken, the latter particularly for evaluation of subcellular organelle morphology (peroxisomes, mitochondria, lysosomes).

Urine can be obtained by a bladder tap for amino acid analysis and organic acid determination by gas chromatography. Cerebrospinal fluid should be retained and frozen (at least 1 to 2 mL) for quantitative measurement of amino acids. X-ray films, computed tomographic scans, and an electroencephalogram should be performed if at all possible. An autopsy, although rarely diagnostic of an IEM of acute onset, will be necessary to exclude nongenetic causes. If an autopsy is not granted, many parents will agree to biopsies of tissues, such as skin and liver. Vitreous humor (freeze after obtaining) has also been of great value in the diagnosis of certain IEM. Parents need to be counseled regarding the recurrence risk for most of these disorders and need to be aware that without a specific diagnosis prenatal detection is virtually impossible.

SUMMARY

The detection of more than 70 inborn errors that are brought to medical attention acutely in the neonate and infant relies on the primary clinician's familiarity with the symptoms with which they present. After consideration, appropriate initial screening laboratory tests can be obtained. Certain conditions, such as metabolic acidosis and/or hyperammonemia, with or without hypoglycemia, will signal the need for further consultation with metabolic specialists, as well as for more specific tests. With the information described in this paper, the primary clinician should be able to be the first effective evaluator among many in a process resulting in a precise diagnosis of these inherited conditions. Treatment is available, in both the acute and chronic phases, for many of these disorders. In virtually all of these conditions, for patients in whom the treatment is incomplete or in whom the disorder is lethal, adequate study should make prenatal diagnosis possible. The recurrence risk of at least 1 in 4 makes the recognition of these conditions important. Thoughtful genetic counseling is essential.

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Self-Evaluation Quiz

6. Inborn errors of metabolism are most often inherited as:

A. Autosomal recessive conditions.
B. Autosomal dominant conditions.
C. X-linked recessive conditions.
D. X-linked dominant conditions.
E. Multifactorial conditions.

7. Among the following, the precise diagnosis of inborn errors of metabolism depends most heavily on:

A. Clinical features.
B. Light microscopic findings in tissues.
C. Electron microscopic findings in tissues.
D. Enzyme assays.
E. Response to therapy.

8. For the infant suspected of having an inborn error of metabolism, the measurement among the following that is *least* likely to be helpful immediately in differential diagnosis is:

A. Blood glucose level.
B. Serum ammonia level.
C. Anion gap.
D. DNA studies in leukocytes.
E. Ketones in urine.

EDUCATIONAL OBJECTIVE

115. The pediatrician should have an appropriate recollection of the presenting features of multiple sclerosis in children and adolescents (Recent Advances, 89/90).

Optic Neuritis and Multiple Sclerosis

Optic Neuritis in Children and Its Relationship to Multiple Sclerosis. Riikonen R et al. *Dev Med Child Neurol.* 1988;30:349.

This is a detailed study of 21 children between 4 and 14 years of age in whom optic neuritis and sudden blindness developed in one or both eyes (62% bilateral). They were followed up for 15 years. Multiple sclerosis developed in 9 children (8 girls). Seven of these children had other signs of central nervous system involvement (2 before the optic neuritis) which made the diagnosis clinically probable. Electroencephalograms did not help the physician make the diagnosis, but scans using magnetic resonance imaging techniques were most helpful with other demyelinating lesions of the nervous system. Thus, these authors, with more refined technology than that available to Carter in 1960 (multiple sclerosis developed in 25% of his patients after 20 years' follow-up), emphasized some helpful clinical and laboratory criteria to link optic neuritis to multiple sclerosis. Optic neuritis may otherwise be idiopathic, postinfectious, or seen with vasculitis.

Optic neuritis, in which the patient looks out and sees nothing and the doctor looks in and sees nothing, is being diagnosed as multiple sclerosis 25% of the time, at least in a Scandinavian population where the incidence of multiple sclerosis is high. (*M. Richard Koenigsberger, MD, Children's Hospital of New Jersey*)

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Cellular and molecular aspects of the renal effects of diuretic agents

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The study of the renal sites and mechanisms of action of diuretics received a major boost by the experiments conducted by the Dallas group in the mid and late sixties [1, 2]. Utilizing clearance techniques and sharp, judicious analysis of free water excretion (C_{H_2O}) and reabsorption ($T^c_{H_2O}$) curves, these investigators set the basis for the present knowledge of the nephron sites of action and rational clinical use of diuretics. Micropuncture and isolated tubule techniques proved most of the inferences and general concepts developed from clearance methodology to be correct [3]. Moreover, clinical studies that aim to assess the nephron sites of action of diuretics (and other drugs) still depend on clearance methods for interpretation.

In the past two decades (70 and 80's) it has become possible to examine in more detail many of the cellular and molecular mechanisms of action of diuretics. These agents are one of the remarkable achievements of the pharmaceutical industry. They are efficacious, relatively innocuous and inexpensive drugs that are life-saving in their short- (such as, in acute hypercalcemia or hyponatremia [4, 5]) as well as in their long-term utilization [6–8]. Most importantly, they are agents that interact with their tissue targets in a reversible way that permits swift modification of dosage and therapeutic goals. The targets for diuretic agents are located along the different segments of the nephron. Potency of these drugs—in practical terms, the degree of salt and water losses they induce—depends precisely on which part of the nephron they affect. Also, on the ancillary effects the agents may exert on systemic and renal hemodynamics.

Recent reviews have emphasized the clinical use and pharmacology of diuretics [9–11]. Therefore, our purpose is to discuss renal tubule transport mechanisms, and the cellular and molecular aspects of the interaction between diuretics and their targets.

Epithelial transport in the principal nephron segments affected by diuretics

Cellular elements in the kidney possess a rich array of transport mechanisms which have been strategically localized along the nephron to insure that the filtrate is converted into a final product that allows homeostasis to prevail. Thus, under normal circumstances, the role of these transport processes is to guarantee that the volume and composition of extracellular fluid, hence the intracellular milieu, remain unchanged.

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It has become apparent that diuretic agents may alter the reabsorption of salts and water and the secretion of various substances by interfering with one or more aspects of a given transport system. Figure 1 schematizes the principal sites of salt and water reabsorption along the nephron and the mechanisms involved. A discussion of these follows.

Proximal tubule

The Na^+/H^+ antiporter is the major mechanism responsible for sodium entry into cells of the proximal convolution [12]. The antiporter is located in the apical (luminal) membrane and its operation is dependent on favorable gradients for sodium (lumen-to-cell) and for protons (cell-to-lumen). The intracellular pH is particularly critical. The gene for the Na^+/H^+ exchanger has been cloned and the predicted model for the membrane model resembles that of the growing family of transporter molecules [13; vide infra].

Two other important mechanisms determine the rate of sodium transport in the proximal tubule. The basolateral cell-membrane sodium pump (Na^+K^+-ATPase) is responsible for maintaining cell sodium concentration approximately 1/10 of that of the luminal fluid and blood. The pump consists of alpha and beta subunits, both of which traverse the membrane [14; vide infra]. Specific inhibitors of the pump (cardiac glycosides) bind to the alpha subunit on the extracellular site, and while some diuretics may lead to non-specific inhibition of the pump [15], none do so at the concentrations used clinically. Needless to say, specific or non-specific inhibition of the pump will lead to diminished net sodium reabsorption by reducing the favorable lumen-to-cell sodium gradient thus impairing the function of the Na^+-proton antiporter.

Carbonic anhydrase is the other critical step in the generation of the appropriate conditions for the functional integrity of proximal tubule sodium reabsorption. Protons secreted in exchange for sodium are generated by the catalytic effect of the enzyme on carbonic acid in the cell. Furthermore, protons secreted into the lumen are buffered by bicarbonate in the filtrate and the catalyzed dehydration of carbonic acid by luminal (brush border) carbonic anhydrase [16]. Inhibitors of carbonic anhydrase have so far been the only diuretics that effectively inhibit proximal tubule sodium reabsorption. They reduce the availability of intracellular protons and induce a luminal acid disequilibrium pH, which impedes proton secretion into the lumen.

Diamox

MOLECULAR ACTIONS OF DIURETICS

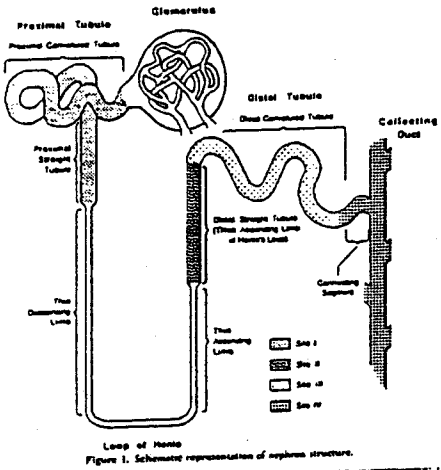

Figure 1. Schematic representation of nephron structure.

Table 1. *Classification of Diuretic Drugs**

DIURETIC AGENT	PRIMARY SITE OF ACTION	MECHANISMS OF ACTION	NATRIURETIC POTENCY (%)†
Mannitol	I	Osmotic diuresis	5
Acetazolamide	I	Carbonic anhydrase inhibitor	5
Ethacrynic acid	II	Exact mechanism unknown‡	15–25
Sulfonyl benzoic acids	II	Block Na+-K+-Cl Cotransport	15–25
Furosemide			
Bumetanide			
Piretanide			
Benzothiadiazines	III	Probable block electroneutral NaCl reabsorption	5–10
Chlorothiazide			
Hydrochlorothiazide			
Phthalimidines	III	Probably blocks electroneutral NaCl reabsorption	5–10
Chlorthalidone			
Quinazolines	III	Probably blocks electroneutral NaCl reabsorption	5–10
Metolazone			
Potassium-sparing agents	IV		5–3
Spironolactone		Aldosterone inhibitor	
Triamterene		Blocks apical sodium reabsorption	
Amiloride		Blocks apical sodium reabsorption	

*Based on chemical structure, mechanism of action, and site of action. Sites of action are discussed in the text and shown in Figure 1.

†Natriuretic potency refers to maximal ability to increase the fractional excretion of sodium.

‡The exact mechanism by which ethacrynic acid blocks tubular reabsorption of sodium and chloride is not completely understood. For further information see Gregor R. Wangensteen: Loop diuretics. Annual Physiol 10:174–183, 1987.

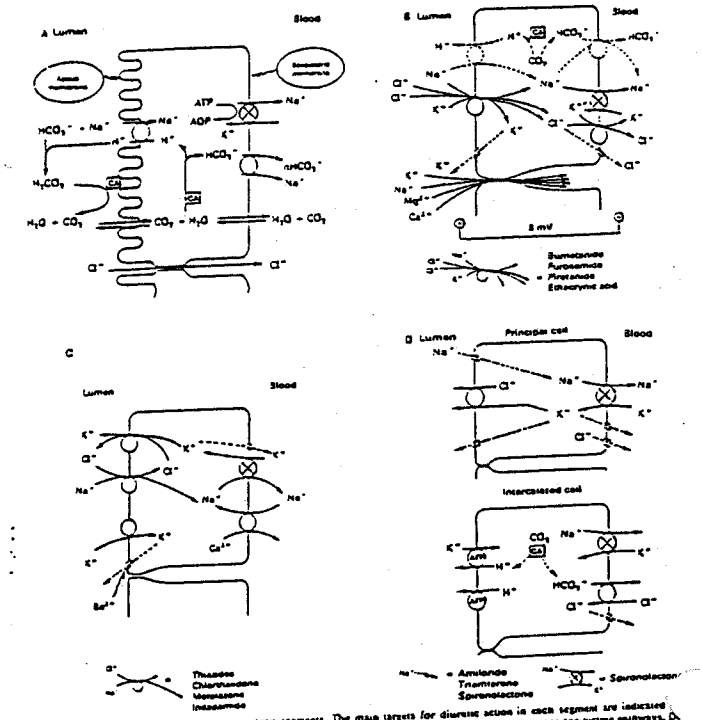

Fig. 1. *Proximal transport systems in various nephron segments.* The main targets for diuretic action in each segment are indicated on each segment are given in the text. The following are worth special attention: 1) Proximal tubule basolateral $Na^+HCO_3^-$ co-transport would be most evident during activation of Na^+/H^+ exchange.

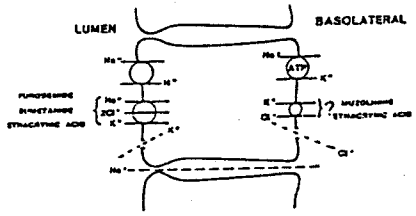

Figure 2 Cell model of the thick ascending loop of Henle. Brace indicate the proposed site of diuretic action.

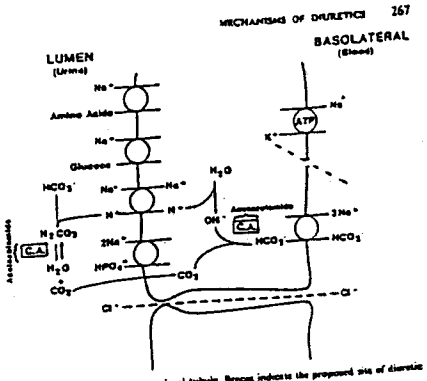

Figure 1 Cell model of the proximal tubule. Brace indicate the proposed site of diuretic action.

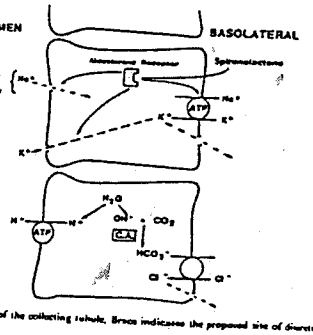

Figure 4 Cell model of the collecting tubule. Brace indicates the proposed site of diuretic action.

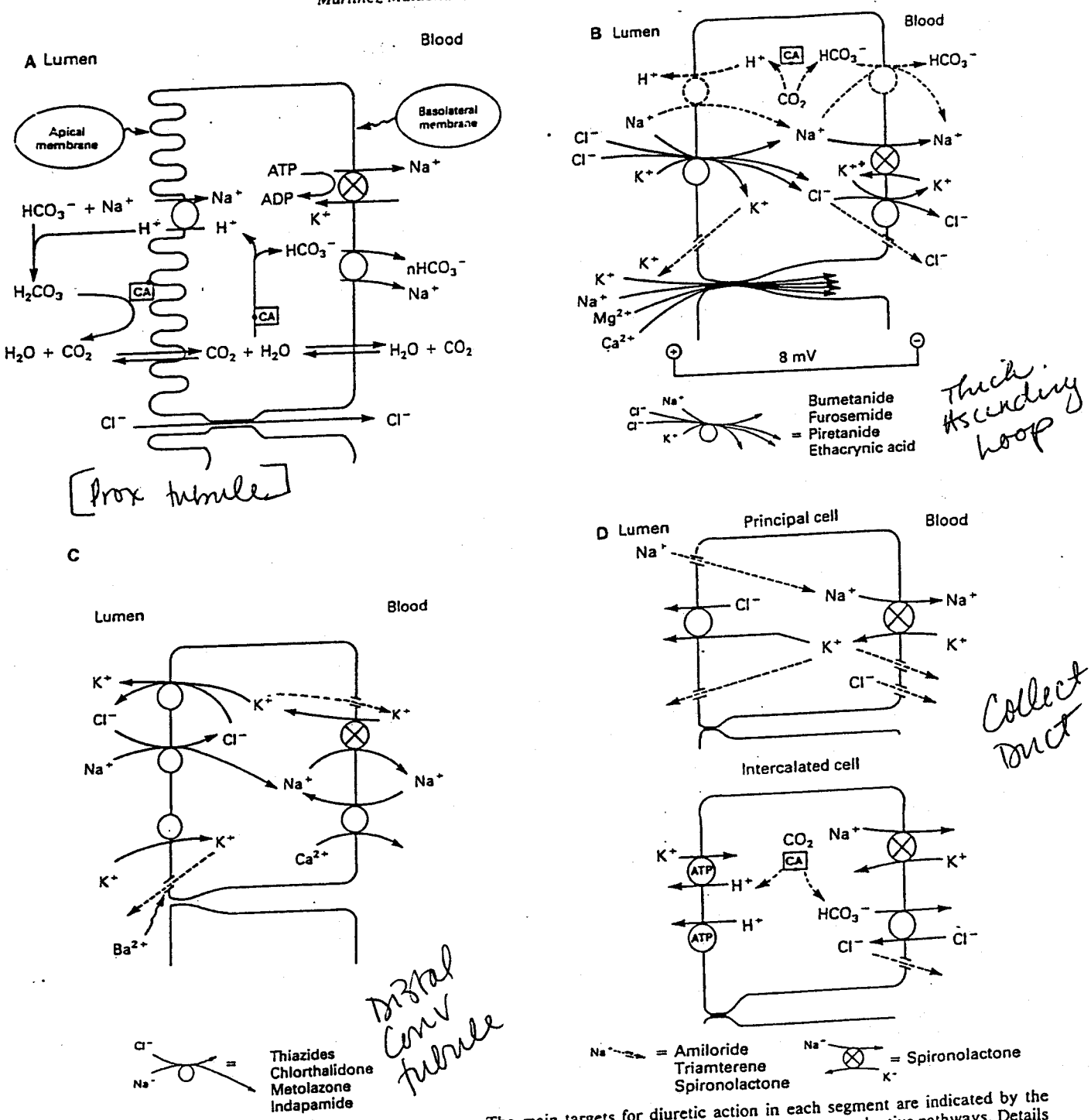

Fig. 1. *Principal transport systems in various nephron segments.* The main targets for diuretic action in each segment are indicated by the appropriate symbol. The sodium-pump is indicated by ⊗; symports and antiports by 0; straight broken lines indicate conductive pathways. Details on each segment are given in the text. The following are worth special attention: 1) Proximal tubule basolateral Na/HCO_3 co-transport, $N = 3$. 2) Thick ascending limb luminal Na^+/H^+ exchanger is under the control of aldosterone. The basolateral Na/HCO_3 co-transport would be most evident during activation of Na^+/H^+ exchange.

Sodium reabsorption into the proximal tubule also proceeds coupled to phosphate, glucose, amino acids and other organic anions. In addition, an electroneutral sodium-chloride reabsorptive process exists. This may be coupled to parallel sodium-proton and chloride-bicarbonate exchange. Evidence also exists for a basolateral 1 Na^+/3 HCO_3^- electrogenic symport [17]. None of these processes appear to be specifically inhibited by clinically useful diuretic doses.

Thick ascending limb (TAL)

This segment of the nephron appears to determine the magnitude of diuresis achieved under most circumstances. This is

probably the case because its reabsorptive capacity is quite high [18]. As a result, inhibition of proximal reabsorption is compensated by high reabsorptive rates in the TAL and the net increase in excretion is modest, poor or none. A complex luminal electroneutral carrier seems to be responsible for the high reabsorptive capacity of this segment. The carrier brings 1 Na^+, 1 K^+ and 2 Cl^- into the cell with energy provided by the basolateral activity of the Na^+,K^+-ATPase pump. Sodium leaves the cell into the blood through the pump, but the fate of chloride is varied. One chloride leaves the cell via an electroneutral KCl symport; the other makes its exit through a conductive chloride channel [19].

The activity of the apical membrane co-transporter aided by the energy generated by the pump-induced sodium gradient raises intracellular chloride and potassium activity above equilibrium, which determines the chloride conductive exit. There being no major potassium conductance across the basolateral cell, it is recycled to the urine via the apical membrane, which exhibits high K^+ conductance. This recycling of potassium in tandem with chloride exit is responsible for the lumen-positive transepithelial potential that drives Na^+ out of the lumen of the TAL via a paracellular pathway. This mode of transport is responsible for an equal number of sodium ions being transported passively through the paracellular space, and through the co-transporter. In addition, the paracellular pathway is the means of passive reabsorption for potassium, calcium and magnesium.

Oberleithner and collaborators [20, 21] have advanced evidence in support for Na^+/H^+ antiport in the apical membrane of the TAL. This urine acidification (cell alkalinization) process and the enhanced apical K^+ conductance is regulated by aldosterone [22].

Distal convoluted tubule

An important regulator of final urine composition, the distal convolution is principally characterized by a luminal electroneutral NaCl symport [23]. The presence of the Na^+K^+-ATPase and a sodium-calcium exchanger in the basolateral membrane together with an apical barium-sensitive potassium conductance impart the rest of the transport characteristics of this segment. The possibility of an apical K-transport mechanism, an outwardly directed (cell-to-lumen) potassium-chloride co-transporter, and an apical potassium conductance has not been conclusively proven.

Studies by Beaumont and collaborators [24] have suggested that a thiazide binding site in isolated renal tubule membranes may represent the NaCl symport (vide infra).

Collecting duct

This is the final segment responsible for major modifications in urine compositions in response to diuretics. In this nephron site principal cells are the predominant cell type and responsible for sodium reabsorption and potassium secretion [25]. As in most transporting cells the basolateral membrane Na^+K^+-ATPase is responsible for transcellular sodium transport; this site also presents potassium and chloride exit steps. The apical membrane exhibits a putative KCl co-transporter, and significant sodium and potassium conductances. The "small" sodium conductance channels are of critical importance in establishing the depolarization of the apical membrane which permits potassium secretion down a favorable electrochemical potential gradient [26]. Of the two potassium channels (high and low conductance) the low conductance seems to be responsible for potassium secretion [27]. Finally, the intercalated (or mitochondrial rich) cell is responsible for hydrogen ion secretion and potassium reabsorption. In states of potassium deprivation an ATP-dependent K-H exchanger in the apical membrane may be responsible for potassium reabsorption and a portion of H^+ secretion (the remainder H^+ secretion is electrogenic). The functional capacity of this exchanger mechanism is not as great under normal conditions. Evidence has been advanced that this ouabain-insensitive K-stimulated ATPase can be blocked by K-H inhibitors [28].

Cellular and molecular aspects of transport systems affected by diuretics

Carbonic anhydrase

This enzyme is found in the cytosol of the renal tubular cells as a high-activity form called CA II. "High activity" refers to its capacity to hydrate CO_2 and dehydrate H_2CO_3, and the form and function of this isoenzyme is identical to that of the CA II of erythrocytes [29]. The other cytosolic isoenzymes described, CA I and CA III, are found in erythrocytes and skeletal muscle respectively, but are not present in the kidney [30]. Recently it has been demonstrated that the carbonic anhydrase activity in microvilli and basal infoldings of renal tubular cells from human kidneys is associated with a strongly membrane-bound enzyme protein. Provisionally called CA IV, this protein seems to be different from the cytoplasmic soluble forms of the enzyme, but it is the type of carbonic anhydrase responsible for the reabsorption of bicarbonate in the proximal tubule [31].

Purification to homogeneity has revealed CA IV to have a molecular weight between 34.4 and 36.7 kDa. Kinetically the enzyme was similar to CA II with respect to hydrase and esterase activities and to inhibition by various sulfonamides. When CA IV is reconstituted into lipid bilayer membranes, it forms channels selective for small cations [32]. The physiological significance of this finding, however, is presently obscure.

Membrane associated carbonic anhydrase proteins have been isolated from rat brain myelin (44 kDa) and bovine lung (42 kDa), but it remains to be shown whether membrane isoenzymes are homologous even though localized in different tissues [31, 33].

The genes of several isoenzymes, including CA II, have been cloned [34]. In the chick brain in situ hybridization has revealed CA II mRNA most intensely in the choroid plexus and in neurons [35]. In addition to its presence in the brain in a structure responsible for fluid and electrolyte transport (the choroid plexus), CA II mRNA levels are induced in parietal cells by carbachol, histamine and gastrin, three of the most potent stimulants of gastric acid secretion [36]. In the syndrome of osteopetrosis and renal tubular acidosis, it has been shown that affected individuals lack CA II in erythrocytes [37]. Moreover, in an animal model for this syndrome, lack of paternal CA II has been demonstrated to be heritable and due to a null mutation at the Car-2 locus on chromosome 3 [38]. Studies of gene expression in the kidney may reveal important information as to the ontogeny and regulation of this critical enzyme in acid-base regulation and, perhaps, of differences induced by

chronic states in which diuretic inhibitors of the enzyme are required.

The sodium-hydrogen antiport

The principal properties of this plasma membrane-bound protein include the following: 1) electroneutrality; it exchanges Na^+ or Li^+ for H^+ with a coupling ratio of 1:1; 2) in membrane vesicles or in intact cells an inward-directed Na^+ gradient drives uphill H^+ efflux and an outward-directed Na^+ gradient drives uphill H^+ influx, thus the transporter is reversible; 3) H^+, Na^+, Li^+ and amiloride all compete for an external binding site in the transporter; 4) H^+ binding to an internal regulatory site exerts an allosteric activation, thus acting as a self-controlled H^+ efflux pathway [reviewed in 39, 40]. Intracellular pH is critical in the control of the transporter; when it rises >7.4 the mechanism comes to a virtual halt, whereas it is activated at low pH with maximal effects detected at pH 6. Numerous growth factors and growth promoting agents (platelet-derived growth factor or PDGF; epidermal growth factor or EGF; fibroblast growth factor or FGF; serum, alpha thrombin, vasopressin, bradykinin, phorbol esters, concanavalin A) stimulate the Na^+/H^+ exchanger by apparently increasing the affinity of the internal modifier site. The relationship of this finding to sodium transport in renal tubule has not been explored [41].

Equally mysterious is the role of second messengers in activation of the antiporter in relation to renal tubule function. Growth factors and other growth promoters activate the hydrolysis of phosphoinositides (PIP_2) leading to the formation of inositol trisphosphate (IP_3) and diacylglycerol. Phospholipase C activation is transduced from the membrane receptors via a GTP-binding protein. The rise in intracellular calcium produced is not sufficient to trigger a pH_i change, therefore, activation is most likely via protein kinase C. In contrast, EGF, and perhaps FGF, may stimulate the antiporter by activating the tyrosine kinase activity of their respective receptors leading to phosphorylation of the exchanger [42].

The Na^+/H^+ exchanger bears some topological similarities to the adrenoceptor molecule. Amiloride, an inhibitor of the Na^+/H^+ exchanger, has only very moderate diuretic potency. Interestingly, it also binds to, and antagonizes, alpha and beta adrenoceptors ($alpha_2$ > $alpha_1$ > beta) even at concentrations below those required to inhibit the exchanger [43]. Stimulation of the $alpha_2$ adrenoceptors activates the Na^+/H^+ exchanger suggesting that catecholamines may be involved in this way in the regulation of sodium reabsorption in the proximal tubule [44]. It seems unlikely, however, that an interaction of amiloride to block adrenoceptors plays a major role at clinically useful doses of the diuretic.

The sequence of a cDNA encoding the human amiloride-sensitive Na^+/H^+ antiporter has been presented [13]. The cDNA includes a non-coding leader of 407 bp, a 2682 bp open reading frame, and a 3′ noncoding sequence. The amino acid sequence predicts a protein of M_r = 99,354 with an N-terminal amphiphatic domain that contains 10 putative transmembrane-spanning segments and two-potential glycosylation sites, followed by a hydrophilic stretch of 395 residues, presumably cytoplasmic. The number of putative transmembrane segments are reminiscent of the $Cl^-HCO_3^-$ antiporter.

The Na^+-K^+-$2Cl^-$ co-transporter

A thorough review of the mechanistic details of this transport system is beyond the scope of this article [for recent reviews see 45, 46], but its major characteristics are given below.

It is essential for identification of this system that it be inhibited by loop diuretics (bumetanide, furosemide, piretanide). There is absolute requirement of two of the ions for transport of the third ion (for example, Na and Cl must be present for K reabsorption to proceed) and it is always electroneutral. Therefore, ion translocation does not alter membrane potential nor does membrane potential affect transport of coupled ions. The stoichiometry of the coupling of ions is very tight and driven by the third ion (such as, K^+ flux-Na^+ flux, driven by Cl^- gradient). Some of the participating ions can be substituted in a restricted way, for example Li^+ for Na^+, Rb^+ or NH_4^+ for K^+, Br^- for Cl^-. Since net ion movement is energized by the ion gradients, there is no direct requirement of ATP hydrolysis for transport. Finally, since the direction of transport is governed by the algebraic sums of the electrochemical gradients of each of the three ions, net transport is reversible.

It has been observed that in isolated TAL preparations with preformed ion gradients, which do not require energy from ATP, ATP enhances the activity of the co-transporter. Furthermore ATP utilization and transport rates bear little relation under these circumstances. In addition, activation of the Na^+-K^+-$2Cl^-$ co-transporter leads to membrane protein phosphorylation, suggesting that phosphorylation of the co-transporter by protein kinases facilitates ion binding and translocation [47].

Utilization of [^{3}H]4-benzoyl-5-sulfamoyl-3-(3-thenyloxy) benzoic acid (BSTBA), which contains a photoreactive benzophenone group, is a potent loop diuretic and competes with its analogue bumetanide for binding sites on dog renal membranes, has permitted the identification of specific photoincorporation of the molecule to a dog kidney protein of approximately 150 kDa [48]. This same group found that when the dog kidney membranes were incubated in media containing Na, K, Cl and 0.2 μM [^{3}H]bumetanide, incorporation of the label resulted in the ~40 kDa region but not in the 150 kDa [49]. Inhibition of the labeling, however, was less than 50% when unlabeled bumetanide was added to the medium, suggesting that the labeled protein(s) are not part of the Na-K-2Cl co-transporter. Most likely they are low affinity bumetanide binding sites such as the basolateral K-Cl cotransport system of the TAL or other transport proteins. In addition, dog kidney membrane proteins of variable molecular weight that incorporate [^{3}H]BSTBA with low affinity, have also been detected [50]. Radiation inactivation studies in rabbit kidney TAL membrane vesicles led Kinne and co-workers to report a 80 to 90 kDa apparent molecular weight for the Na-K-2Cl co-transporter [51].

Evidently, the nature of the protein or protein complex that makes up the co-transporter is not clear. The number of proteins reported raises the question of whether all of them could represent components of the cotransporter, but identification of its structure in TAL remains to be elucidated.

The Na-Cl symport

The early distal tubule (we use the term to signify the earliest portion accessible to micropuncture, that is distal to the macula

Table 1. Inhibition of [^{3}H] metolazone binding to the high affinity site of rat kidney membrane fractions by some thiazide-type diuretics

Drug	K_i, nM
Methychlothiazide	0.43
Metolazone	5.1
Indapamide	29
Hydroflumethiazide[a]	43
Hydrochlorothiazide	146
Chlorothiazide	3630

This Table is adapted from Beaumont et al [24].
[a] Selectively inhibits high affinity site

Table 2. Some compounds that compete for the low affinity [^{3}H] metolazone binding site of rat kidney membranes

Compound	K_i, μM
Metolazone	0.26
Nicardipine	0.62
Nitrendipine	0.65
Verapamil	1.2
Diltiazem	5.8
Nifedipine	15

This Table is adapted from Beaumont et al [24].

densa and ends before connecting and collecting tubule) is residence for a rather unique cotransport system for Na and K, that seems to have an exact replica in the urinary bladder of the winter flounder [52]. The symport is not affected by mucosal K^+ concentration: neither sodium or chloride transport are affected [53]. Net fluxes of Na and Cl are identical and completely interdependent (reduction of one inhibits transport of the other). Thus, it is clear that this system. in contrast to the TAL Na-K-2Cl cotransporter, is K-independent. Moreover, Na transport is not affected by amiloride in doses as high as 15 mM, nor is chloride reabsorption inhibited by the disulfonic stilbene, DIDS, indicating that neither Na^+/H^- exchange nor Cl^-/base exchange determine its operation. The system is not antagonized by carbonic anhydrase inhibitors and insensitive to bumetanide. The former eliminates the possibility of parallel synchronous antiporters, the latter that the system is analogous to that in the TAL [54].

On the other hand, furosemide partially inhibits Na-Cl symport, while thiazides and metolazone completely halt its function [55]. Of interest is that thiazide-like drugs, including metolazone, have no effect on TAL function [56, 57]. Still to be elucidated and fully understood is the significance of the partial furosemide effect (which also occurs in the bladder of the winter flounder).

Two important aspects of the symporter in relation to diuretics are its effects on calcium reabsorption and potassium secretion. It has been shown that thiazides increase calcium reabsorption both in the early distal tubule and in the winter flounder bladder [58, 59]. While the mechanism for this effect is not well understood, it is possible that hyperpolarization of the mucosal membrane by the diuretics could increase calcium entry into the cell through calcium channels [52]. In addition, reduction in the apical reabsorption of NaCl could lead to partial inhibition of the Na-pump. Influx of sodium from blood to cell could activate a Na^+_o/Ca^{2+}_i exchanger which would effect increased net transcellular reabsorption in the presence of enhanced apical Ca^{++} entry.

Of particular interest is the capacity for potassium secretion afforded by the co-existence of apical NaCl and KCl cotransporters in the early distal tubule. Increasing luminal chloride concentration should increase the reabsorption of both ions. The enhanced lumen-to-cell sodium movement will increase the activity of the contraluminal ATPase and lead to increased cell K^+ and thus, because of the favorable cell-to-lumen gradient, increased K^+ secretion [60]. This mechanism may be responsible for the potassium losses seen in loop diuretic administration and in metabolic alkalosis. In the former, increased Cl^- presentation to the NaCl symport would activate K^+ secretion, as has already been discussed. In the latter, the increased luminal bicarbonate or increased sodium (or both) in the early distal tubule would create differences in luminal Na^+ and Cl^- concentrations, poising the epithelium for K^+ secretion.

The thiazide receptor

Studies using metolazone, a quinazoline-sulfonamide which differs from the sulfonamide diuretics in the benzothiadiazine-dioxide ring [61], by Beaumont, Vaughn and Fanestil [24] have indicated the presence of [^{3}H] metolazone receptors in a preparation of rat kidney cortical membranes. Ten percent of the total binding of [^{3}H] metolazone was to carbonic anhydrase, but two [^{3}H] metolazone binding sites were identified: a high affinity (Kd = 4.27 ± 0.37 nM, B_{max} = 0.717 ± 0.058 pmol/mg protein) and a low affinity (Kd = 289 ± 43 nM, B_{max} = 3.92 ± 0.36 pmol/mg protein). Binding to the high affinity site was limited to thiazide-like compounds, whereas several non-thiazides and thiazide-like compounds inhibited binding of [^{3}H] metolazone to the low affinity site (Tables 1 and 2). Metolazone was the most potent inhibitor of the low affinity site. Various classes of calcium channel antagonists also inhibited this site (Table 2) Nicardipine (10^{-4} M) when added to membrane preparations prevented [^{3}H] metolazone binding to the low affinity site.

There was a significant correlation between the pharmacologic potency of the thiazide-like diuretics and their affinity for the high affinity [^{3}H] metolazone binding sites in rat kidney.

Of several tissues examined, the kidney cortex had the highest density of both the high and low affinity binding sites. Chloride, bromide, and iodide (100 mM) inhibited the high affinity binding site more than 50%, suggesting that these halide anions compete with metolazone for a transport site or channel.

In another set of studies with the same preparation, Tran, Beaumont and Fanestil [62] found that sodium increases the affinity of [^{3}H] metolazone for the binding site from Kd = 3.56 ± 0.15 nM to Kd = 1.32 ± 0.1 nM. Chloride, in the presence of 50 mM, Na^+, competitively inhibited [^{3}H] metolazone binding by suppressing the affinity (Kd = 9.27 ± 1.11 nM). The maximal number of binding sites remained unchanged (B_{max} = 0.733 ± 0.049 pmol/mg protein. These investigators proposed that the transporter (receptor) possess sites for Na^+ and Cl^-, and metolazone binds to the Cl^- site. Moreover, Na^+ binding increases the affinity of Cl^- and metolazone to their common site in the transporter. The co-dependency of sodium and

Table 3. Effect of ischemia ± reperfusion on the affinity and binding site density of the high affinity [^{3}H] metolazone receptor of rat kidney membranes

Condition	B_{max} pmol/mg protein	Kd nM
Control	0.555 ± 0.052	2.91 ± 0.18
Ischemic (10 min)	0.058 ± 0.01[a]	6.70 ± 2.62
Ischemic (10 min) + reperfusion (10 min)	0.347 ± 0.086	2.37 ± 0.34

This Table is adapted from Beaumont et al [64].
$N = 3$ to 5.
[a] $P < 0.001$ vs. control

chloride in the salt reabsorptive processes of the rat distal tubule has already been alluded to above.

Using autoradiographic analysis of rat kidney sections previously incubated with [^{3}H] metolazone, Beaumont and associates [63] detected a preferential binding of [^{3}H] metolazone to the early distal convoluted tubule. Labeling was more prominent in the luminal than the peritubular site. Medullary structures remained unlabeled. Interestingly, not all the cells of the distal tubules were labeled, confirming that more than one cell type is present in that segment. The absence of labeling in the proximal tubule reinforced the notion that thiazide actions in the segment are secondary to carbonic anhydrase inhibition.

Beaumont et al [64] looked into the regulation of the thiazide receptor during renal ischemia. Clamping of the renal artery for 10 minutes resulted in a significant reduction in [^{3}H] metolazone sites (Table 3). Reperfusion for another 10 minutes increased receptor binding sites significantly, although it did not reach baseline values. Receptor affinity constants remained unaltered.

Incubation of rat cortical tissue under oxygen (O_2) or nitrogen (N_2) atmosphere at 37°C resulted in a significant decrease in [^{3}H] metolazone receptor density, being more prominent with N_2. Addition of mitochondrial inhibitors (dinitrophenol, rotenone), but not ouabain, further reduced receptor density in the oxygenated tissue sections. Since the reduction in [^{3}H] metolazone receptor binding density in kidney tissue (O_2 or N_2 atmosphere at 37°C for 10 min) was not observed in membrane preparations, the authors suggested that changes in intracellular sodium or reductions in membrane potential are involved in the down regulation of the thiazide receptor in these experimental conditions.

Finally, the same group of investigators [65] measured [^{3}H] metolazone receptor density and binding affinity in a model of genetically determined hypertension, the spontaneously hypertensive rat (SHR). SHRs (15 weeks old) had significant increments in thiazide receptor density when compared to age-matched Wistar-Kyoto rats (WKY) (SHR: $B_{max} = 0.452 \pm$ 0.021 vs. WKY: $B_{max} = 0.375 \pm 0.020$ pmol/mg protein; $P <$ 0.05).

On the other hand, hypertension produced by placing a clip in a renal artery of normal rats (2K-1C model) did not result in significant alterations in thiazide receptor density in either kidney (clipped, $B_{max} = 0.467 \pm 0.033$ vs. unclipped, $B_{max} =$ 0.495 ± 0.028 pmol/mg protein) [66]. Further studies are necessary to elucidate if the rise in thiazide receptor density antedates or is coincidental with the rise in blood pressure in the SHR model.

The clinical correlates of the studies during ischemia and hypoxia, and the SHR are clearly acute renal failure and low renin hypertension. It would be mere speculation to transpose these findings to the clinical setting at the present time, but these studies could set the base for elucidation of the in vivo responses of the ischemic kidney to thiazides (and other diuretics), and of the antihypertensive effects of thiazides in various forms of hypertension.

The relationship between the thiazide receptor and the NaCl co-transporter remains to be elucidated, but it seems that thiazide-binding sites may represent, if not the transporter itself, part of its component proteins.

Amiloride-sensitive sodium channels

A voltage-independent, sodium-specific ion channel that is sensitive to the potassium-sparing diuretic amiloride has been found only in transporting epithelia [reviewed in 67]. The preferential inhibition by amiloride exhibits high affinity, with an apparent equilibrium dissociation constant (K_i) of less than 1 μM. Located primarily in the apical membrane of epithelia, it is involved in transepithelial sodium transport. In addition, it is hormonally regulated [68]. The channel is critical in permitting the entry of sodium into the cells of the renal tubule, and it is rate limiting for the ATPase sodium-pump. Thus, it may well be the single most important step in determining sodium and water balance in the body. Despite this, the only nephron site in which it may be vulnerable to diuretic action, is the collecting tubule, thus we will limit our comments to this structure and refer the reader to Benos's excellent review [67].

Two fundamental criteria that must be met in any attempt to purify the sodium channel are that the probe that binds to the channel protein does so with high affinity, and that the transport function of the protein be maintained at every step of the procedure. To this end, the use of the high-affinity amiloride analogue [^{3}H]-methylbromoamiloride and transport function retention at every step has permitted reconstitution into planar bilayers of amiloride-sensitive single sodium channel activity [69].

Table 4 summarizes some of the present knowledge concerning the characterization of sodium channel proteins. The native sodium channel consists of a heterohexameric complex of subunits, ranging in molecular size from 40 to 300 kDa. In the non-reduced state the complex runs as a single band of 730 kDa, suggesting that the various subunits, of weights indicated in the table, are covalently attached to each other by disulfide bridges. Under non-reducing conditions, [^{3}H]-methylbromoamiloride binds to a component of bovine renal papillary homogenate with an apparent molecular mass of 730 kDa, while under reduced conditions the binding protein is 150 kDa. Both of these proteins are part of the purified epithelial sodium channel preparation and most likely represent the amiloride binding subunit. Reports of multiple polypeptides from bovine kidney that can bind a high affinity analogue of amiloride have opened the question of multiple binding sites versus degradation products of the larger molecule [70]. It should be mentioned that, as is the case with other transport proteins, these are glycosylated and all can be phosphorylated by cyclic AMP-dependent protein kinase [71].

Table 4. Molecular mass ratios of amiloride-binding and epithelial Na^+ channel proteins from different tissues

Source	Method	Native molecular mass *kDa*	Subunit molecular mass *kDa*
at kidney cortex	Radiation inactivation	650	—
g kidney cortex	Radiation inactivation/^{3}H-phenamil binding	185	90–105 (dimer)
cells, bovine renal papilla	^{3}H-methyl-bromoamiloride binding	730	300 150 95 0 55 40

This Table is adapted from Benos [67].

The dimer (two identical subunits of 90 to 105 kDa) discovd in pig kidney cortex, which also is a putative amilorideitive sodium channel, may not be the same as the high ioride-affinity epithelial sodium channel. Its kinetics indie that it may represent a low amiloride-affinity sodium ductive pathway sometimes observed in vesicle uptake eriments and in basolateral membranes of some epithelia .

se of monoclonal and polyclonal antibodies against the fied amiloride-sensitive sodium channel protein have pered the identification of single amiloride-sensitive sodium nnels in rat renal medullary collecting ducts. Staining of the nnels is circumscribed to the apical membrane of principal , whereas the intercalated cells are unlabeled [67].

view of the binding site of amiloride in the epithelial nnel it seems certain that the diuretic effect of this agent is sult thereof.

Spirolactones: Mineralocorticoid receptor antagonists

e discovery of a group of steroid-related compounds with costeroid blocking actions in the late 1950's has helped to e the mechanisms by which corticosteroids modulate inllular events and transport processes in the kidney and tissues [73, 74]. There are two possible mechanisms to in the antimineralocorticoid actions of the spirolactones, n particular, spironolactone: a direct effect on aldosterone esis by the adrenal gland, and inactivation of the mincorticoid receptor in target tissue by competition with the sts (aldosterone) at the receptor site. Most of the experil evidence to date favor the latter mechanism as the minant one, although there is data supporting an effect in al steroid synthesis.

ler [75] found that spironolactone (10^{-5} to 10^{-4} M) ased the synthesis of aldosterone by adrenal tissue ob- from sodium depleted rats. There was a dose dependent ion of dybutiryl cAMP (10^{-5} M), ACTH, potassium and ensin II-stimulated aldosterone production. The concens of spironolactone necessary to achieve the inhibitory n vitro were higher than those needed to inhibit sodium ort in the toad bladder preparation [76, 77], suggesting that the actions of the antagonist at the receptor level are of critical importance for the overall in vivo effect.

Spironolactone, canrenone and canreonate-K inhibit 11-hydroxylase and 18-hydroxylase, and binds to cytochrome P_{450} [78]. Moreover, some of the thio-derivatives of spironolactone, after undergoing further metabolism, are able to destroy cytochrome P_{450} and its apoproteins [79, 80].

Nevertheless, in a recent review [81], Fanestil concludes that these inhibitory actions of spirolactones on aldosterone synthesis play a minor role in the overall antimineralocorticoid effects of these compounds. The most important mechanism of action is, then, on the mineralocorticoid receptor (MR) in target tissues.

Spirolactones displace [^{3}H] aldosterone from its specific receptor in vitro [82–85]. Furthermore, after binding to the MR the spirolactone-MR complex is unable to bind to the nuclear acceptor sites or the hormone responsive elements (HRE's) [86]. The affinity of spironolactones for the MR is lower than that of aldosterone. Wambach and Casals-Stenzel [85] compared the relative affinity of various spironolactone derivatives to rat cytosolic [^{3}H] aldosterone binding sites, and it was 10% of that of aldosterone. They also described that the 17-spirolactone ring is necessary for binding to the MR, as reported by other investigators [82, 87]. It is possible that in vivo activation of some of the spirolactones with closure of the spirolactone ring results in higher in vivo activity than the one detected in in vitro systems.

The MR has been recognized as the spironolactone binding moiety in the mineralocorticoid target cells. Some recent data dispute this conclusion. Luzzani and Glasser [88] looked at [^{3}H] spironolactone and [^{3}H] aldosterone binding to kidney homogenates of adrenalectomized rats. Specific [^{3}H] spironolactone binding was of high affinity and low capacity (Kd = 12.9 ± 0.6 nM; B_{max} = 93.4 ± 3.8 fmol/mg protein). They also found that [^{3}H] spironolactone was displaced preferentially from its receptor by spironolactone > prorenone > methyltrienolone, testosterone, progesterone, aldosterone ≥ estradiol 17, dexamethasone. [^{3}H] aldosterone was displaced by aldosterone > dexamethasone > progesterone, spironolactone, prorenone > testosterone. The spironolactone binding site had low sensitivity to aldosterone and did not bind dexamethasone. Since there were differences in the binding characteristics, hormone specificities and thermal stability between the classic MR and the spironolactone binding site, these authors conclude that this site is distinct from the MR. The preliminary work of Lazar and Agarwal [89] using a 7-alpha-propyl derivative of spirolactone support this conclusion.

Previous studies employing [^{3}H] spironolactone (SC 26304) [86] and [^{3}H] prorenone [84] support that these antimineralocorticoids compete with aldosterone for the same receptor. Marver et al [86] found that [^{3}H] aldosterone and [^{3}H] SC 26304-receptor complex did not bind to nuclei or chromatin whereas the [^{3}H] aldosterone receptor complexes did bind. Similar findings were obtained in kidney homogenates with [^{3}H] prorenone by Claire et al [84]. These studies corroborated the finding of early studies by Fanestil [90] in the adrenalectomized rat.

All these data point to the MR as the common site of the agonist and antagonistic actions of these steroid related compounds. The post-binding events of these agonist-MR or antag-

onist-MR complexes are incompletely understood. If the general view of corticosteroid hormone action in target cells is followed, it would be expected that after entering the cell the mineralocorticoid hormone or the spirolactone compound binds to the MR. The MR possibly exists in the oligomeric form, like the glucocorticoid receptor (GR) in the cytosol [91] or the progesterone receptor (PR), in the nucleus [92] of target cells. The localization of MR within the cell remains unknown as Fanestil points out [93], but the MR distributes to the cytosol in kidney homogenates in buffer [37] and binds to the nucleus in the presence of an agonist (see above).

Most of the data concerning the transformation of the receptor-ligand complex has been obtained from studies involving the GR's [93, 94] and the PR's [81, 95]. Nevertheless, Eisen and Harmon [96] described the activation of the rat renal mineralocorticoid receptor after labeling with [^{3}H] aldosterone in the presence of a GR agonist, RU 28362. This compound prevents binding of the mineralocorticoid to the GR. The authors noted that the activated aldosterone-MR complex is transformed into a DNA binding form and this process involves dissociation of the multimeric receptor complex.

Arriza and co-workers [97] were able to clone the human mineralocorticoid receptor. There is a 94% homology of the amino acid sequence of the DNA binding domain with the human GR and 57% homology in the carboxy terminus (the hormone binding site). Additional studies are necessary to elucidate the reasons that the antagonist-MR complex is unable to interact with the mineralocorticoid responsive elements in the nucleus. It is possible that a process similar to that of the antagonist-PR complex is involved.

The PR is composed of the hormone binding site, a non-steroid, non-DNA binding protein (the 90 Kd heat shock protein or hsp 90), and a nuclear protein (p59) [95]. When the agonist is absent or when an antagonist binds to the hormone binding site, the hsp 90 remains attached to the hormone receptor so the DNA binding domain (which is part of the hormone or ligand binding domain) is not exposed and does not interact with the hormone responsive elements in the DNA. Agonist binding, on the other hand, results in a conformational change of the hormone binding domain that triggers the dissociation of hsp 90 from the receptor-agonist complex and exposes the DNA binding site which interacts with the specific hormone responsive elements. Transcription by RNA polymerase can then be initiated.

Clearly, while competitive antagonism of aldosterone-receptor binding by spironolactone is necessary for its potassium-sparing and diuretic effects, the post-receptor effects responsible for its pharmacological action remain to be elucidated.

Summary

In the past few years, increased knowledge of the nature of transport proteins and their molecular regulation in the translocation of ions across kidney membranes has emerged. We are beginning to better understand the characteristics of the interaction of diuretics with these transport proteins. It is likely that this knowledge will permit further insight into nephron function regulation.

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Continuous infusion of loop diuretics in the critically ill: A review of the literature

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Objectives: **a) To present the pharmacodynamic concepts behind the administration of loop diuretics via continuous infusion; b) to review the clinical trials and reports in critically ill patients that have described this method of drug delivery; and c) to discuss the data.**

Data Sources: **Review of MEDLINE and International Pharmaceutical Abstracts from 1966 to the present.**

Study Selection: **Study design was not a factor in selecting literature for this review. All studies, case reports, and case series describing infusion of a loop diuretic are included.**

Data Extraction: **Cited literature was found in peer-reviewed clinical or basic science journals.**

Data Synthesis: **There is a pharmacodynamic basis for the use of a controlled infusion of the loop diuretics in critically ill patients requiring extensive diuresis. Animal and human volunteer studies have demonstrated a clear improvement in efficiency of diuresis by controlled infusion. Clinical studies in critically ill patients have demonstrated an improved diuretic response with a controlled infusion. Adverse effects appear to be minimal, and the amount of drug required for effect is less than the required amount for bolus administration.**

Conclusion: **Administration of loop diuretics by continuous intravenous infusion may improve diuresis in critically ill patients who require prompt, controllable diuresis, or who demonstrate "diuretic tolerance" to conventional administration regimens. Despite few, well-designed studies using this method of administration in clinical practice, pharmacodynamic concepts support continuous infusion over bolus administration, including decreased dosage requirements, improved diuretic response and few adverse effects. (Crit Care Med 1994; 22:1323–1329)**

KEY WORDS: diuretics; pharmacodynamics; infusion, intravenous; diuresis, drug effects; critical illness; drug delivery systems; kidneys; furosemide; bumetanide; ethacrynic acid

The loop diuretics, furosemide, bumetanide, and ethacrynic acid are potent drugs used under a variety of clinical conditions in critically ill patients. These diuretics are administered orally or by the intermittent bolus intravenous route. When administered intravenously as a bolus injection, these drugs provide a vigorous, prompt diuresis.

However, there are a number of critically ill patients in whom an optimal diuretic response, using conventional dose and administration regimens, does not occur. In such instances, patients are considered "diuretic resistant." Diuretics can also induce a state of "tolerance," where increased amounts of drug over time are needed to produce equivalent effects. Different therapeutic approaches have been devised to overcome "resistance" and "tolerance," including the administration of higher drug doses, changing the route of administration (from oral to intravenous), using two or more diuretics together (often a thiazide along with a loop diuretic) for synergy, or administering these diuretics via continuous intravenous infusion.

In attempts to avoid diuretic resistance, the administration of loop diuretics via continuous infusion has become more common in intensive care units (ICUs). This review focuses on the pharmacodynamic concepts behind the administration of loop diuretics via continuous infusion, and discusses the clinical trials and reports that have described this method of drug delivery.

PHARMACODYNAMICS OF LOOP DIURETICS

Loop diuretics act on the thick ascending loop of Henle in the kidney, blocking the active transport of

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chloride and sodium out of the tubule lumen. In blocking this mechanism, loop diuretics produce a natriuresis, with an accompanying diuresis (1, 2).

Delivery of the diuretic to the tubular lumen is essential for these pharmacologic effects. Loop diuretics gain access to this site via active secretion in the proximal tubule, following the nonspecific transport route for organic acids (3). Once the drug is in the tubular lumen, the diuretic response depends on a drug-receptor interaction (4–8). The delivery time of loop diuretics to the receptor within the tubular lumen correlates well with the diuretic response in both animal and human models (9–11). The time of drug delivery to the receptor appears to be a more important determinant of diuretic response than the route of administration or the total amount of drug administered (10, 11). The significance of the drug delivery time was observed initially in probenecid-furosemide interaction studies (10, 12), where pretreatment with probenecid lengthened the delivery time of furosemide to the receptor site in the tubular lumen and produced a greater diuretic response than furosemide alone. Further work in dogs (11) demonstrated that the diuretic effects of furosemide increased significantly with increasing infusion time. Administering 20 mg of furosemide over infusion times ranging from 10 secs to 8 hrs demonstrated that the 8-hr infusion produced significantly greater urine output and urine excretion of sodium than a 10-sec, 30-min, or 2-hr infusion, without any increase in the total amount of urinary furosemide recovery.

To explain this effect, the ratio of sodium to furosemide excretion rate has been used to describe the efficiency of the diuretic (4). Using pharmacodynamic modeling, a furosemide excretion rate that produces a maximal sodium excretion rate can be determined. This calculated number allows comparison of dosing regimens in terms of drug delivery time to the receptor site and the drug amount that provides maximal efficiency (4). Deviation from the maximally efficient furosemide excretion rate explains the differences seen in diuretic response between oral, intravenous bolus, and intravenous infusion for similar doses of furosemide. The closer the drug excretion rate comes to the rate that is most efficient, the closer the diuretic response comes to maximum (10).

Studies in both animal models and in human subjects (11, 13–18) have demonstrated that a controlled infusion of furosemide or bumetanide results in a greater excretion of both sodium and water than the excretion achieved by equivalent intermittent bolus doses. This improved response occurs despite similar doses of drug administered and similar amounts of drug recovered in the urine.

LITERATURE REVIEW

Considering the pharmacodynamics of loop diuretics, a continuous infusion of furosemide or bumetanide appears to be the most efficient way to administer these agents. However, few well-designed clinical trials have compared infusion vs. traditional bolus administration of these agents. In the few studies that have been performed, most trial designs do not allow for proper comparison of the natriuretic and diuretic response to infusion vs. bolus administration.

Controlled Clinical Trials. Only three controlled trials (15, 17, 19) in critically ill pediatric or adult patients have been reported. In a prospective, randomized trial (17) in pediatric post-open-heart surgery patients, patients receiving intermittent bolus injections of furosemide required significantly higher daily doses of drug than patients receiving continuous infusion to produce urine output of >1 mL/kg/hr. Patients were <3 yrs of age, and 40% of these patients were receiving dopamine infusions for inotropic effect, at doses ranging from 5 to 10 μg/kg/min. Twelve patients received intermittent bolus doses averaging 6.23 mg/kg/day (Table 1). Average urine output for the 24-hr study period was 3.53 mL/kg/day. Eight patients received a continuous infusion averaging 4.9 mg/kg/day ($p < .045$). Mean volume of urine for the study period was 3.36 mL/kg/day. Central venous pressures were monitored throughout the study period, and no differences were observed between the two groups.

In another study reported only in abstract form, Wilbur and Riemersma (15) studied 20 surgical ICU patients receiving a standard dose (not provided) of furosemide over 24 hrs. The patients were divided into two groups: one group received the drug by infusion; the other group received the drug by intermittent bolus injection. Although the actual data were not provided, the group receiving continuous infusion of furosemide (n = 10) demonstrated a significantly greater average urine output (mL/hr) compared with the bolus injection control group (n = 10) for the 24-hr study period. Hemodynamic comparisons were not made, and no information regarding severity of illness or type of surgical procedures performed was reported.

A similar study (19) of 18 adult post-open-heart surgery patients found no significant difference in urine output between a furosemide continuous infusion and intermittent bolus injection. Nine patients received each method of administration. A total of 0.6 mg/kg (mean 45 mg) of furosemide per patient was given during the 12-hr study period (Table 1). All patients were hemodynamically stable and not receiving inotropic or vasopressor agents. Mean urine output

Table 1. Dosing of continuous-infusion furosemide or bumetanide

Study	Drug (age)	Loading Dose	Infusion Rate (mg/hr)	Range	Duration of Infusion (hr)
Controlled Studies					
Singh et al. (17)	F (p)	0.1 mg/kg	2.0	Unknown	24
Copeland et al. (19)	F (a)	None	0.05	Unknown	12
Case Reports					
Lawson et al. (20)	F (a)	None[a]	8.9	4–16 mg/hr	Unknown
Magovern and Magovern (21)	F (a)	20 mg	4.8	4–10 mg/hr	24
Krasna et al. (22)	F (a)	None[a]	Unknown	25–52 mg/hr[b]	Unknown
Rudy et al. (23)	F (a)	None[a]	38.5	Unknown	37.4
Volunteer Studies[c]					
McInnes et al. (13)	B (a)	None	0.25	N/A[d]	4
McInnes et al. (13)	F (a)	None	10	N/A[d]	4
Rudy et al. (16)	B (a)	1 mg	0.912	N/A[d]	12
van Meyel et al. (18)	F (a)	8 mg	4	N/A[d]	8

F, furosemide; B, bumetanide; p, pediatric; a, adult; N/A, not applicable.

[a]These patients failed bolus furosemide before receiving an infusion; [b]Dosage range has been standardized to a 70-kg patient (actual dosage ranged between 0.36 and 0.75 mg/kg/hr); [c]All subjects in the volunteer studies had normal renal function, except in the study by Rudy et al (16). Subjects in this trial had severe but stable chronic renal failure; [d]Dosage range does not apply to this volunteer study.

peaked in the first hour after the bolus dose was administered in the group receiving intermittent injections. More than 70% of the total urine volume for the 12-hr study period was excreted in the first 2 hrs after the bolus. The continuous infusion group did not achieve peak urine output until the third hour of the infusion, but thereafter maintained nearly constant diuresis during the remainder of the infusion period. Although no difference in diuresis was observed between the two groups, patient demographics were not well described. It is difficult to determine if both groups were similar in terms of surgical procedures, use of the intra-aortic balloon pump, time on bypass, severity of illness, or other confounding variables that influence urine output.

Case Reports–Uncontrolled Observations. Four case series of furosemide continuous infusion have been reported (20–23). Lawson et al. (20) reported on the use of continuous infusion furosemide in a series of 10 elderly patients (age range 60 to 75 yrs) with congestive heart failure who did not respond to 120 mg of oral furosemide. All patients began to diurese after initiation of the infusion, averaging 5.05 L/24 hrs (range 2.0 to 14.1). Preinfusion urine output was reported for five of ten patients, and the average increase in urine output with infusion was 5.9 L/24 hrs. Steady-state serum furosemide concentrations measured in eight of ten patients were low (mean 0.68 μg/mL). Patients exhibited a controllable diuresis at serum furosemide concentrations well below concentrations thought necessary for a therapeutic response. Infusion rates ranged from 4 to 16 mg/hr (Table 1). The extent of disease for these patients was not described, and the concomitant use of other diuretics, hemodynamically active drugs, or invasive devices was not discussed.

Magovern and Magovern (21) described a series of six adult post-open-heart surgery patients who were hemodynamically unstable, and receiving continuous furosemide infusions for postoperative diuresis. These patients had undergone either coronary artery bypass grafting (n = 3), mitral valve replacement (n = 2), or heart transplantation (n = 1). Four of the six patients were on an intra-aortic balloon pump, and all patients were receiving inotropic catecholamine infusions to maintain satisfactory cardiac output (cardiac index >2.2 L/min/m^2) during the infusion period. All patients were fluid overloaded by ≥6 L from the preoperative state, but all patients maintained circulating creatinine concentrations <1.6 mg/dL (<141.4 μmol/L). Patients received an initial 20-mg loading dose, and the infusion was begun at 4 to 6 mg/hr (Table 1). The mean infusion rate was 4.8 mg/hr (range 4 to 10), generally lasting 24 hrs. Mean 24-hr urine output was 5.7 L/patient. Cardiac index, central venous pressure, and pulmonary artery diastolic pressure remained relatively constant during the infusion. Inotropic drugs or intra-aortic balloon pumping were decreased or discontinued in all patients during the infusion. No adverse effects were reported.

In a case-series of three reports (22), furosemide continuous infusion was used in adult patients (age range 57 to 74 yrs) who developed acute renal failure post-open-heart (n = 2) or vascular surgery (n = 1) and cardiopulmonary bypass. Urine output decreased to <40 mL/hr for two of the three patients, and to <100 mL/hr for the other patient. Urine output in all three patients failed to increase after fluid challenges or

bolus therapy with at least three 40-mg doses of furosemide, and a one-time challenge with ethacrynic acid. Cardiac output and intravascular volume were maximized before initiating the infusion. Furosemide infusion rates of 0.25 to 0.75 mg/kg/hr were sufficient to produce a return to adequate urine output (range 200 to 300 mL/hr), and all three patients' renal function returned to normal after infusion therapy began (Table 1). The duration of infusions was not noted.

A fourth series (23), reported only in abstract form, consisted of nine adult patients (mean age 58 yrs) with congestive heart failure (n = 4) or acute renal failure (n = 5) who had failed to respond to bolus furosemide therapy (mean dose 358 mg). These patients received a continuous infusion of furosemide at doses of 0.25 to 1 mg/kg/hr, titrated to response (Table 1). Infusion produced a response in seven of nine patients. Response was measured as >150% increase in urine volume or 150 mL of urine within 2 hrs. The mean duration of the infusions was 37.4 hrs, and a mean total of 1440 mg of furosemide was administered. Initial response was observed at a mean of 3.5 hrs, suggesting a delay in delivery of drug to the tubular lumen. Maximal response to infusion occurred at an average of 7.3 hrs. Because of the brevity of the report, severity of illness scores and concurrent hemodynamic support were not disclosed.

Additional reports have been published in the literature describing beneficial responses to furosemide continuous infusions in patients with ascites secondary to malignancy (24) and in patients with cyclophosphamide-induced oliguria (25). The four patients with ascites did not respond to 80 to 120 mg/day of oral furosemide, and 100 to 200 mg/day of spironolactone. A 100-mg furosemide infusion over 16 to 24 hrs produced diuresis volumes of 1060 to 2840 mL (mean 2050) for the infusion period and reduction of abdominal girth (24). All four patients continued to diurese well after the infusion was discontinued.

Volunteer Studies. There have been few healthy volunteer studies (13, 16, 18) of intravenous bolus vs. constant infusion reported for both furosemide and bumetanide (Table 2). In each of these crossover trials, furosemide or bumetanide was delivered by constant infusion and was more effective in producing natriuresis and diuresis than similar doses administered by intravenous bolus. The improvement in response paralleled an improvement in efficiency of the dose administered, as measured by the ratio of sodium excretion rate to furosemide excretion rate. The effect lasted well beyond the end of the infusion (18).

ADVERSE EFFECTS

Adverse effects to the continuous infusion of loop diuretics are uncommon. Early studies of high-dose furosemide in patients with oliguric renal failure (14, 26–32) reported both transient and permanent deafness in patients receiving prolonged infusions of gram doses of the drug. However, the recent case reports and randomized trials have used cumulative doses well below the amounts used in these early studies. Reduction in serum potassium concentration requiring supplementation now appears to be the most frequent and serious problem.

Murphy et al. (33) described interference with a colorimetric assay for serum creatinine determinations when high-dose furosemide infusion was used. This study was a case series report of three pediatric ICU patients with respiratory distress syndrome and septic shock associated with oliguria. The serum creatinine concentrations were monitored using the Jaffe reaction, and in all three cases, after initiation of continuous infusion furosemide, creatinine was unmeasurable in the patients' serum. The doses of furosemide ranged from 9 to 12 mg/kg/hr. The interference was thought to be caused by a metabolite of

Table 2. Volunteer studies of furosemide (F) or bumetanide (B) bolus vs. constant infusion

Study[a]	Number of Patients	Drug and Dose	Infusion Time (hr)[b]	Improvement[c] in Natriuresis (%)	Improvement[c] in Diuresis (%)	Efficiency[d]
McInnes et al. (13)[e]	8	B 1 mg	4	41.3	Unknown	59.9
McInnes et al. (13)[e]	8	F 40 mg	4	24.6	Unknown	Unknown
Rudyetal. (16)	8	B 12 mg	12	25	11.7	31.5
van Meyel et al. (18)[f]	8	F 40 mg	8	46.3 @ 8 hrs	27 @ 8 hrs	55.8 @ 8 hrs
				36.9 @ 24 hr	28.4 @ 24 hr	33.8 @ 24hrs

[a]All subjects in the volunteer studies had normal renal function, except in the study by Rudy et al (16). Subjects in this trial had severe but stable chronic renal failure; [b]All studies administered the same dose as a bolus and as an infusion; this time reflects the duration of the infusion during that portion of the trial; [c]Improvement by infusion over bolus; [d]Efficiency is measured as the ratio of sodium excretion rate to furosemide excretion rate; [e]This study was conducted using both furosemide and bumetanide; [f]This study evaluated results at the end of the infusion (8 hrs) and at 24 hrs.

furosemide that blocks the colorimetric detection of both creatinine and endogenous chromogens.

Wilson et al. (34) described three cases of supraventricular tachycardia associated with continuous-infusion furosemide in infants receiving doses ranging from 0.75 to 1 mg/kg/hr. Arrhythmias occurred 3 to 7 hrs after initiation of the furosemide infusion; one of three patients had hemodynamic changes associated with the arrhythmia, and two patients demonstrated recurrence of the supraventricular tachycardia upon rechallenge with the furosemide infusion. The authors reviewed the charts of 24 additional children who had received furosemide infusion, and identified 22 "control patients" who received similar treatment, with doses ranging from 0.4 to 1 mg/kg/hr without supraventricular tachycardia. The authors concluded the tachyarrhythmia was secondary to rapid changes in the intravascular volume produced by the furosemide infusion; all three patients had a diuresis of 8 to 10 mL/kg/hr, compared with a mean average of 2.5 mL/kg/hr in 22 control patients. The authors speculated that because of the drug's long-lasting effects, an excessive diuresis in the sensitive patient may persist before furosemide infusion has been reduced to the desired response level.

DOSING

Optimal dosing of either furosemide or bumetanide for continuous-infusion administration has not yet been determined. Among the randomized, clinical trials of furosemide administration by continuous infusion, there have been a wide range of starting and maximal doses (Table 1). Some manufacturers (35) recommend that for high-dose parenteral therapy, furosemide should be administered as a controlled intravenous infusion at a rate ≤4 mg/min (≤240 mg/hour). Doses of ≤4 g/day of furosemide have been administered to patients with renal failure and refractory congestive heart failure, either orally, by intravenous bolus, or as an infusion. Several investigators have used continuous infusion at doses as high as 0.75 mg/kg/hr (22) in adults, and 1 mg/kg/hr (34) in infants to achieve a diuretic response. However, most of the literature regarding continuous infusion of furosemide describes hourly doses in the range of 1 to 9 mg.

Brater et al. (9) suggested that there may be a maximum dose for furosemide, based on studies the authors conducted in patients with chronic renal insufficiency. These investigators constructed dose-response curves for single furosemide bolus doses, and 2-hr furosemide infusions of 120 to 160 mg. The authors found that single doses of 160 mg of furosemide are sufficient to reach the upper plateau of the dose-response curve in patients with severe chronic renal insufficiency. This 160-mg maximum dose may not be directly applicable to the critically ill patient with new onset oliguria, but these results suggest that there probably is a maximum dose that varies in relation to renal function.

This variation is probably dependent on the amount of furosemide that enters the urine. Brater et al. (9) found that subjects with severe chronic renal failure delivered only 9.5 ± 1.5% of the total 2-hr infusion dose into the urine over the 24-hr period following administration. Other studies (18) performed in healthy subjects suggested that 71 ± 2% of an infusion dose is recovered for the same collection period. Since a maximally efficient furosemide excretion rate has been derived on an individual basis, it would appear that the maximum dose of the drug may vary according to individual pharmacokinetic parameters and renal function. However, in patients with severe renal disease (9), 160 mg of furosemide was sufficient to reach the upper portion of the dose-response curve. Patients with greater renal function would be expected to reach this plateau with a much smaller dose.

The necessity of a loading dose is unclear. In the volunteer study by Copeland et al. (19), patients in the infusion therapy group did not receive a loading dose of furosemide, but began the infusion at 0.05 mg/kg/hr. Urine output peaked in the third hour of infusion therapy, and remained constant throughout the remainder of the 12-hr study period. Rudy et al. (16) administered a 1-mg loading bolus of bumetanide to the continuous infusion group in their chronic renal failure study; maximum urinary bumetanide excretion occurred within the first hour of infusion therapy, and remained constant throughout the 12-hr dosing period.

Infants in the continuous infusion treatment group of the post-open-heart surgery study by Singh et al. (17) also received a loading dose before infusion began. The mean urine output for the infusion group was greater than the goal rate of 1 mL/kg/hr within the first hour of therapy. Patients in this study, although acutely ill, did not have underlying renal dysfunction.

van Meyel et al. (18) administered a loading dose to patients receiving continuous infusion therapy, and obtained maximal urinary excretion of furosemide in this group at 1 hr into treatment. Furosemide excretion remained constant throughout the study period. Because of this conflicting information, the advantage of a loading dose remains unclear. It appears that patients may respond maximally within 3 hrs of initiating infusion therapy without a loading dose, but as early as 1 hr when a loading dose is used.

COMPATIBILITY AND PREPARATION

Furosemide may be admixed in dextrose 5% injection United States Pharmacopeia (USP), sodium chloride 0.9% injection USP, or lactated Ringer's solution injection USP. Hoechst-Roussel (35) indicated that when the pH of the admixed solution is >5.5, the product is stable at room temperature for at least 24 hrs. To assure that the pH of the admixture is >5.5, company literature (35) recommended that furosemide be diluted to at least a 1:5 ratio. Magovern and Magovern (21) used a solution of 100 mg of furosemide in 100 mL of 5% dextrose in their protocol, but offered no stability data regarding that concentration. Furosemide for injection is commercially available in a 10-mg/mL concentration. This concentration can be used without dilution, and many intravenous controlling devices on the market today can deliver <1 mL/hr with accuracy.

Furosemide may discolor upon exposure to light. Intravenous solutions should be protected from light after preparation and during infusion. Solutions that have yellowed should be discarded. Furosemide solutions should be stored at room temperature; refrigeration may result in precipitation or crystallization (36). Compatibility of furosemide with common medications administered in the critical care setting is listed in Table 3.

Bumetanide is stable in dextrose 5% injection USP, sodium chloride 0.9% injection USP, or lactated Ringer's solution injection USP, and may be admixed in any necessary concentration. This product will be stable for at least 24 hrs (37). Bumetanide is also unstable when exposed to light, and requires protective covering after preparation and during infusion (36). Table 3 lists the compatibility of bumetanide with commonly used medications in the critical care patient. The critically ill patient presents a challenge in the maintenance of adequate fluid balance. There are normal physiologic compensatory mechanisms that often limit the response to diuretics. Certain disease states in this patient population, such as congestive heart failure and renal insufficiency, may also lead to a diminished response to loop diuretics. Traditionally in these instances of poor diuretic response, the amount of diuretic is either increased or the route of administration is changed from oral to intravenous, if such a change is appropriate. However, in some situations of "diuretic resistance" or "tolerance," simply increasing the dose of the drug or changing the route of administration is of limited or no value.

Administration of loop diuretics by continuous intravenous infusion is becoming more common as a means of overcoming "diuretic resistance" or "tolerance" in the intensive care setting, as well as titrating diuresis to clinical conditions. Few well-designed studies examine the differences in diuretic response to bolus vs. continuous infusion in critically ill patients. Despite a scarcity of studies, pharmacodynamic concepts support the administration of loop diuretics by continuous infusion because of improved efficiency, promoting diuresis, and titratability of response to the infusion rate. A further advantage to this method is the theoretical reduction in drug costs associated with smaller doses and the avoidance of adverse effects and toxicities associated with high loop diuretic administration and poly-pharmacy diuretic combinations.

The precise dosing range for loop diuretic infusions has not yet been determined, but clinical studies (17, 19–21) in critically ill patient groups suggested

Table 3. Compatibility of furosemide and bumetanide with commonly administered medications in the critical care setting (36, 38)

Drug	Furosemide	Bumetanide	Drug	Furosemide	Bumetanide
Amikacin	C	-	Heparin	C	C
Aminophylline	C	-	Isoproterenol	I	U
Amrinone	I	-	Lidocaine	C	U
Atropine	C	-	Meperidine	I	U
Chlorpromazine	I	-	Metoclopramide	I	U
Ciprofloxacin	I	-	Morphine	I	U
Diazepam	I	-	Milrinone	I	U
Diphenhydramine	I	-	Netilmicin	C	U
Dopamine	I	-	Nitroglycerin	I	U
Dobutamine	I	-	Prochlorperazine	I	U
Epinephrine	C	-	Quinidine	C	U
Esmolol	I	-	Ranitidine	C	U
Fluconazole	I	-	Sodium bicarbonate	C	U
Gentamicin	I	-	Tobramycin		

C, compatible; I, incompatible; U, unknown compatibility.
Drugs are assumed to be mixed at the Y-site in 1:1 ratios. This information does not correlate with admixture within the same container.

starting at a low hourly dose of 1 to 9 mg of furosemide, and titrating to response. The administration of a small loading dose may be beneficial in decreasing the time to maximal response. Further clinical trials are needed to fully compare the effects of continuous infusion therapy with conventional bolus administration on the diuretic response and patient outcomes in various patient populations.

This dosing strategy may prove valuable since smaller doses of these diuretics may be used to achieve an adequate diuresis and may be better tolerated than repetitive high bolus-dosing administration. Continuous infusion can allow for titration of diuresis, an advantage that may prove critical in severely ill patients. Given this advantage, it seems reasonable that a continuous infusion of furosemide or bumetanide may be the most effective way to administer loop diuretics to critically ill patients who require prompt, controllable diuresis, or who demonstrate "diuretic tolerance" with conventional administration regimens.

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The Pharmacology and Therapeutics of Diuretics in the Pediatric Patient

*Thomas G. Wells, MD**

Diuretics inhibit reabsorption of water and solutes at several sites along the nephron. The usual result is enhanced urinary excretion of water and electrolytes. In certain pathologic conditions, however, water and solute excretion may be paradoxically decreased. A basic knowledge of renal structure and physiology is essential to understanding mechanisms of diuretic action and effects on urinary electrolyte excretion and plasma electrolyte concentrations. Much of the work done to establish the anatomy and function of the nephron has been accomplished in vivo and in vitro in animals. Subtle differences exist between species; thus, conclusions about human renal physiology must be carefully considered. Furthermore, age has a profound effect on the physical maturation of the nephron, on glomerular and tubular function, and, therefore, on diuretic pharmacokinetics and pharmacodynamics. Although diuretics have been used extensively in infants and children, relatively few controlled studies have been undertaken to clarify the pharmacokinetics and pharmacodynamics of these agents in the pediatric population. Following a brief discussion of renal development and physiology, available information concerning the pharmacology and therapeutics of diuretic use in children is considered. Mechanisms of fluid retention and edema formation have been reviewed elsewhere.[24, 47, 233, 234, 274]

BASIC STRUCTURE AND FUNCTION OF THE DEVELOPING KIDNEY

Although rapid development of the kidney occurs during gestation, significant structural and functional changes continue to occur during the first several years of postnatal life. The effects of postnatal renal maturation on diuretic pharmacology are most significant in preterm neonates, term neonates, infants, and, to a lesser extent, young children. Diuretic pharmacology in older children and adolescents does not appear to differ significantly from young and middle-aged adults.

Embryology

Three structurally distinct but temporally overlapping stages of renal maturation occur in the developing fetus. The first stage, formation of the pronephros, begins

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during the third week after conception.[183] The pronephros, which is thought to be nonfunctional in humans, undergoes rapid involution, disappearing by the fifth week of gestation.[183, 270] As the pronephros involutes, it is replaced by the developing mesonephros. The mesonephros, consisting of rudimentary functioning glomeruli and proximal and distal tubular structures, begins to develop during the fourth or fifth week after conception.[143] Urine produced by the mesonephric kidney passes through the mesonephric duct and into the cloaca. The human mesonephros, like the pronephros, is a transient structure. It undergoes regression during the third month of gestation, disappearing by the twelfth week after conception.[183]

The third stage of renal development, formation of the metanephric kidney, begins during the fifth week of gestation.[143] Formation of the metanephric kidney is dependent on contact between the ureteric bud, a diverticulum arising from the mesonephric duct, and the mesenchyme of the nephrogenic ridge. The ureteric bud elongates dorsally and cephalad to meet the caudal end of the nephrogenic ridge. During the fifth week, the ureteric bud begins to undergo dichotomous branching. As it divides, it is surrounded by the expanding mesenchyme. Continued division and remodeling of the ureteric bud eventually forms the ureter, renal pelvis, calyces, and collecting ducts. An incompletely understood interaction between branches of the ureteric bud and the mesenchyme results in the formation of nephron vesicles, the early progenitors of the definitive nephrons. Although this process begins during the eighth week of gestation, the developing nephrons do not become functional until the 11th or 12th week.[270] By the 20th week of gestation, each kidney contains approximately 500,000 nephrons.[306] Nephrons formed before 20 weeks of age are thought to mature into juxtamedullary nephrons, whereas those forming after 20 weeks of age become cortical nephrons.[306] Nephronogenesis continues until 34 weeks of gestation, at which time each kidney contains approximately 1 million nephrons.[306]

Microdissection studies have demonstrated that glomerular size increases rapidly during the first year of life and continues at a slower rate throughout childhood and adolescence.[88] Proximal tubular length undergoes more dramatic growth, increasing three to five fold during the first year of life and doubling again by late adolescence.[88] Substantial lengthening and anatomic differentiation of the loop of Henle occurs during the same time. Anatomically, glomerular maturation appears to occur in a centrifugal pattern, with juxtamedullary glomeruli maturing earlier than cortical glomeruli.[306]

Nephron Structure and Function

The nephron contains several anatomically and functionally distinct segments (Fig. 1). Arterial blood enters the glomerular capillary network through the afferent arteriole. Fenestrations in the endothelium lining the capillary network are freely permeable to water, ions, and larger molecules. The glomerular capillary basement membrane (GBM) lies between the endothelium and the visceral epithelium. Under normal circumstances, the filtration pores in the GBM establish a size and charge barrier, limiting the passage of macromolecules such as albumin and immunoglobulins into the glomerular ultrafiltrate while not appreciably impeding the passage of water, nitrogenous wastes, glucose, or small ions. Diuretics are small molecular weight compounds that circulate in plasma bound to plasma proteins or as free (unbound) drug. The unbound drug fraction is freely filtered, whereas little of the bound fraction crosses the filtration barrier. The ultrafiltrate enters Bowman's space, a narrow passage lying between the visceral epithelium and the parietal epithelium of Bowman's capsule. Bowman's space converges at the urinary pole of the glomerulus to become contiguous with the lumen of the proximal tubule.

Proximal Tubule. The proximal tubule is composed of two anatomically distinct segments, the proximal convoluted tubule (or pars convoluta) and the proximal

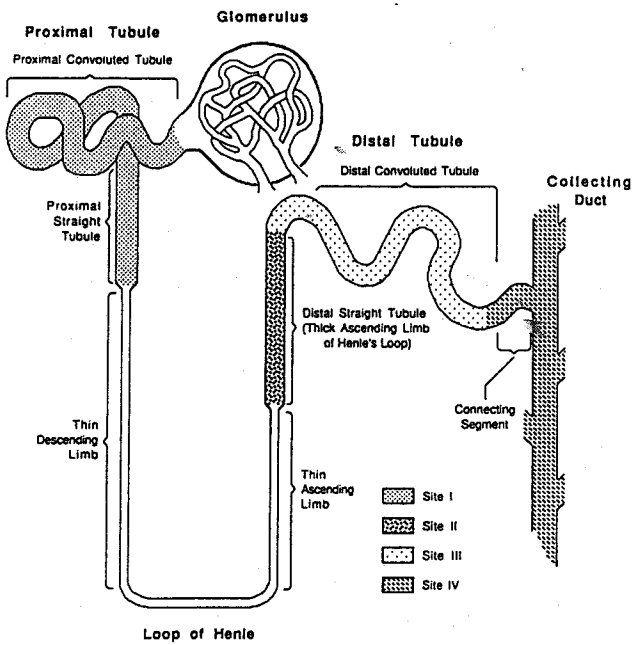

Figure 1. Schematic representation of nephron structure.

straight tubule (or pars recta). The abrupt transition from the squamous cells of the glomerular parietal epithelia to tall, columnar cells signals the beginning of the proximal convoluted tubule. The luminal surface of the columnar epithelia has a well-developed brush border that provides an extensive surface area for reabsorption of water, electrolytes, glucose, amino acids, and other substrates. Reabsorption, the movement of solutes and water from the tubular lumen through or between the epithelial cells lining the tubule into the interstitium or peritubular fluid, is distinguished from secretion, the transport of water and solutes in the reverse direction (from the interstitium into the tubular lumen). Many mitochondria are present within the epithelial cells of the proximal convoluted tubule, indicating a functional capacity to generate substantial amounts of ATP necessary for energy-dependent transport. Transition from the convolutions and columnar epithelium characteristic of the proximal convoluted tubule to a generally straight tubular structure lined by cuboidal epithelium marks the beginning of the proximal straight tubule. The proximal straight tubule has a less extensive brush border and fewer mitochondria than the proximal convoluted tubule, indicative of a lesser ability for active reabsorption.

Reabsorption of glucose and most other sugars occurs primarily in the proximal tubule.[347] Energy-dependent glucose reabsorption is facilitated by a carrier located

on the brush border of the luminal surface and is coupled to sodium reabsorption in a one-to-one ratio.[246] In children with untreated diabetes mellitus, the concentration of glucose in the ultrafiltrate exceeds the reabsorptive capacity of the proximal tubular transport system, resulting in distal delivery of large amounts of glucose. Distal sites lack significant capacity for carrier-mediated reabsorption of glucose, although small amounts of glucose can be absorbed.[48] When glucose remains in the tubular lumen, raising the osmolality of the luminal fluid and thereby reducing reabsorption of water from distal nephron sites, an osmotic diuresis ensues. Mannitol, another simple sugar, lacks a system for carrier-mediated reabsorption and thus always induces an osmotic diuresis in children with intact renal hemodynamics and nephron function.

Under normal circumstances, approximately 60 to 70 per cent of the filtered sodium is isosmotically reabsorbed from the proximal tubule. In addition to cotransport with glucose and other sugars, several additional mechanisms for sodium reabsorption exist in the proximal tubule (Fig. 2). Passive sodium reabsorption has been coupled with reabsorption of organic acid metabolites, inorganic sulfate and phosphate, and acidic, basic, and neutral amino acids.[250] A sodium-hydrogen ion (Na^+/H^+) exchanger on the luminal membrane of the tubular epithelial cell permits urinary acidification and countertransport of sodium.[203] Energy-dependent sodium-potassium exchange occurs on the peritubular (basolateral) surface of the tubular cell. This exchange requires not only adenosine triphosphate (ATP) but a membrane-bound pump protein, Na^+/K^+-adenosine triphosphatase (ATPase).[60, 142] Passive coupling of sodium and bicarbonate reabsorption along the basolateral surface has also been demonstrated.[154]

The proximal tubule is responsible for bulk reabsorption of water and many other solutes. With respect to diuretic therapy, reabsorption and secretion of water, potassium, calcium, and magnesium are of particular interest. Tubular handling of other solutes has been recently reviewed.[153, 154]

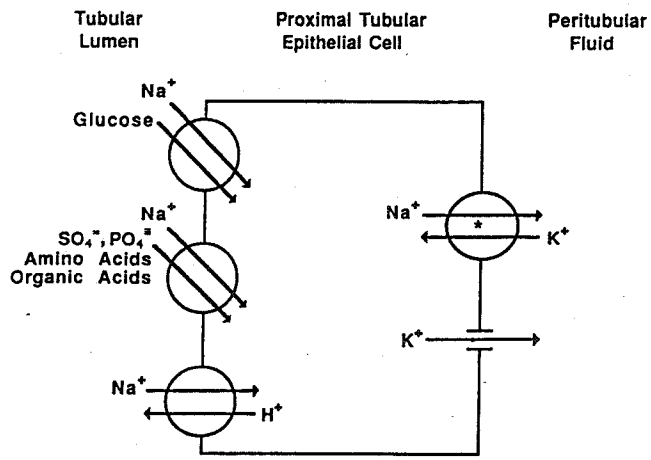

Figure 2. Transepithelial sodium reabsorption in the proximal tubule. (* = ATP → ADP.)

Under normal circumstances, approximately 70 to 80 per cent of filtered water is isosmotically reabsorbed by the proximal tubule. As solutes are actively and passively reabsorbed, an osmotic gradient develops across the tubular epithelium. This osmotic gradient provides the driving force for water reabsorption.

Potassium reabsorption in the proximal convoluted tubule is proportional to that of sodium and water. In the proximal straight tubule, and perhaps in distal segments of the proximal convoluted tubule, however, potassium secretion has been demonstrated.[138] Net potassium balance across the proximal straight tubule appears to be dependent on potassium load.[138] Reabsorption appears to be a passive process, driven by differences in transepithelial potassium concentrations. Other factors, including urine flow rate, acid-base balance, glomerular filtration rate, and extrarenal perturbations can affect potassium reabsorption in the proximal tubule.[170]

In plasma, a complex equilibrium exists between calcium bound to plasma proteins, ionized (free) calcium, and complexed calcium (that which is not ionized but can be ultrafiltered). In children with normal plasma protein concentrations, approximately 40 to 50 per cent of the total plasma calcium circulates bound to proteins (primarily albumin). Complexed calcium and ionized calcium freely pass through the glomerular filtration barrier, whereas protein bound calcium passes only in minute amounts. Thus, ultrafilterable calcium represents only about 55 to 60 per cent of the total serum calcium.[209, 250] In patients with reduced serum albumin concentrations, the proportion of ultrafilterable calcium will increase. Of the ultrafilterable calcium, approximately 50 to 70 per cent is reabsorbed in the proximal tubule. Both passive and active mechanisms of tubular calcium reabsorption are thought to occur.[253] A calcium-magnesium (Ca^{++}-Mg^{++})-ATPase has been identified along the basolateral surface of tubular cells.[150] It appears to have greatest activity in the distal convoluted tubule and cortical collecting duct, intermediate activity in the proximal convoluted tubule and medullary thick ascending limb of the distal tubule, and lower activity in the proximal straight tubule, the cortical thick ascending limb of the distal tubule, and the medullary collecting duct. In animal studies, high concentrations of loop diuretics have been shown to inhibit calcium pump activity.[190]

Loop of Henle. Generally thinner epithelial cells containing fewer mitochondria and a less extensive luminal surface area are characteristics of the descending and ascending thin limbs of the loop of Henle. Functionally, the loop of Henle plays an important part in the ability to generate a concentrated urine, though the exact mechanism is unclear. The lack of large numbers of well-developed energy-forming mitochondria suggests that passive transport processes predominate in this tubular region. A more complete discussion of the structural and functional differences between cortical and juxtamedullary loop segments can be found elsewhere.[139, 270]

Loop segments, located deep within the kidney, have been difficult to study using in vivo models. The descending limb of Henle's loop, however, is thought to be permeable to sodium, potassium, chloride, water, and urea. Permeability to calcium in the thin descending limb appears to be low, whereas permeability in the thin ascending limb is not well characterized.[137] Under normal circumstances, water reabsorption occurs, and the osmolality of the tubular fluid and the concentrations of urea, sodium, and chloride increase along the descending limb. The thin ascending limb is thought to be relatively impermeable to water but highly permeable to chloride. Intermediate permeabilities to sodium and urea are postulated. Significant passive reabsorption of sodium and chloride occurs along the thin ascending limb. At the same time, urea is secreted into the tubular lumen. The osmolality of tubular fluid falls along the thin ascending limb, becoming nearly isosmotic on entering the distal tubule. Differential reabsorption of urea, electrolytes, and water along the loop of Henle appear to play a significant role in the generation of the countercurrent concentrating mechanism, although the exact mechanisms are uncertain.[139]

Distal Tubule. After traversing the thin loop segments, the modified filtrate passes into the thick ascending limb of Henle's loop (also known as the distal straight tubule or the pars recta of the distal tubule). Cuboidal or low columnar cells line the tubular lumen in the thick ascending limb. An abundance of elongated mitochondria associated with invaginations of the basal membrane and a high concentration of Na^+/K^+-ATPase suggest that quantitatively significant energy dependent reabsorption of sodium occurs in this tubular region.

Reabsorption of up to 25 per cent of filtered sodium and chloride occurs in the medullary and cortical portions of the thick ascending limb. Active sodium transport across the basolateral membrane against a concentration gradient provides the driving force for secondary active transport of sodium, potassium, and chloride occurring at the luminal surface (Fig. 3). Potassium, cotransported with sodium and chloride, leaks back into the tubular fluid resulting in a lumen positive–cell negative voltage difference, which in turn drives basal chloride reabsorption. Because the thick ascending limb is relatively impermeable to water, the osmolality of the tubular fluid falls progressively as solute reabsorption occurs. Approximately 20 to 25 per cent of the filtered calcium is reabsorbed in this nephron segment. Both active and passive mechanisms appear to be operative.[263] Additionally, up to 50 to 60 per cent of filtered magnesium may be reabsorbed in the thick ascending limb.[231]

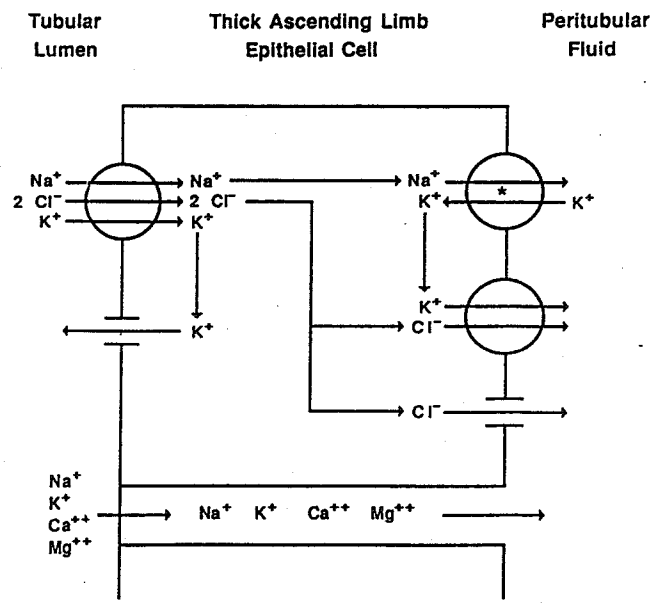

Figure 3. Transepithelial reabsorption and secretion of water and electrolytes along the medullary thick ascending limb. Passive reabsorption of sodium, potassium, calcium, and magnesium occurs through intercellular spaces. (* = ATP → ADP.)

Tall columnar epithelial cells line the distal convoluted tubule (pars convoluta). Like the cells of the proximal convoluted tubule, abundant mitochondria are present. The brush border on the luminal surface of these cells, however, is not as extensive as that of the proximal tubule nor do they possess the extensive ability for pinocytosis of macromolecules. The distal convoluted tubule extends to the transitional region between the distal tubule and the collecting duct. Modified filtrate reaching the distal convoluted tubule is hypotonic. Under normal circumstances, net reabsorption of sodium and net secretion of potassium occur in the distal convoluted tubule. Sodium is actively reabsorbed throughout the entire segment, whereas potassium secretion occurs only in the more distal portion, corresponding to the connecting segment between the distal convoluted tubule and the collecting duct.[259] The distal convoluted tubule is relatively impermeable to water.

Only about 10 per cent of the filtered calcium remains in the tubular fluid at the origin of the distal convoluted tubule.[260] In contrast to the proximal tubule, calcium and sodium reabsorption in the distal tubule appears to disassociate.[242, 263] A more recent study has suggested that in the late segments of the distal tubule, calcium reabsorption may be enhanced when sodium reabsorption is inhibited by amiloride.[56] Parathormone, phosphate loading, increased distal bicarbonate delivery, and chronic administration of thiazide diuretics can increase calcium reabsorption in the distal tubule.[167, 242, 260] In animal studies, reabsorption of up to 90 per cent of the calcium entering the distal tubule has been demonstrated.[263]

A connecting segment, a transitional segment of varying length, joins one or more distal tubule(s) to the collecting duct. The connecting segment appears to retain many of the transport features of the distal tubule, including active sodium reabsorption and potassium secretion. It also shares some structural and functional similarities with the collecting duct.[84, 270]

Collecting Duct. The collecting duct extends from the connecting segment in the renal cortex through the medulla to the ducts of Bellini, which terminate as slit-like openings in the renal papillae.[177] Two cell types, principal and intercalated cells, line the collecting duct. Principal cells are thought to be the target for aldosterone-mediated effects.[270] The intercalated cells, though less numerous than principal cells, contain greater numbers of mitochondria and unique tubulovesicular structures near the luminal surface of the cells.

The entire length of the collecting duct appears to be sensitive to antidiuretic hormone (ADH). When stimulated by ADH, the cells of the collecting duct reabsorb water across the luminal surface, producing a concentrated urine. Impaired urinary concentrating ability has been recognized to accompany potassium deficiency.[25] Evidence suggests that this may result from ADH insensitivity, possibly mediated by altered regulation of adenylate cyclase.[33, 153] ADH may have both qualitatively different and quantitatively less significant effects on other tubular sites.[70] Diuretic-induced volume depletion may stimulate ADH-mediated water reabsorption.

Final regulation of urinary sodium and potassium excretion occurs along the collecting duct. Determinants of serum sodium concentration and total body fluid balance, which in turn affect excretion of sodium, potassium, and water, have been reviewed elsewhere.[117, 227] Potassium secretion along this segment correlates directly with the rate of delivery of sodium and water.[130] As with other tubular segments, Na^+/K^+-ATPase appears to play a role in active sodium reabsorption, although regulation of its activity in this segment appears to differ. Both dietary sodium restriction and chronic potassium loading have been shown to increase Na^+/K^+-ATPase activity along the cortical collecting duct.[98, 100] Experimental data suggest that aldosterone is a potent stimulator of Na^+/K^+-ATPase activity in the connecting segment and cortical collecting duct but has little effect on other tubular segments.[100, 180] Aldosterone appears to stimulate synthesis of a protein subunit of Na^+/K^+-ATPase.[224] Thus aldosterone, by stimulating production or activation of

Na^+/K^+-ATPase, may enhance energy-dependent sodium-potassium countertransport, resulting in increased sodium reabsorption and potassium secretion. Aldosterone may promote sodium reabsorption by other mechanisms as well.[130]

Atrial natriuretic peptide (ANP) influences sodium, chloride, and water transport in the collecting duct. ANP binding sites have been identified along the collecting duct in the inner medulla, and recent evidence suggests that ANP may act to inhibit sodium reabsorption in this segment.[38, 253] Release of ANP occurs in response to volume overload (atrial distention) and results in induction of both natriuresis and diuresis.[173] The effects of ANP on renal blood flow and glomerular filtration rate, which may affect water and sodium transport, have been the subject of much controversy and are reviewed elsewhere.[23, 103, 174, 314] When synthetic ANP was administered to adult volunteers, the resulting natriuresis appeared to be dose dependent, although long-term administration may result in loss of effect.[103, 314] The effects of ANP on renal sodium and water excretion may be partially separable.[103]

Normally less than 10 per cent of the filtered calcium enters the collecting duct and less than 2 per cent is excreted. Significant calcium reabsorption is thought to occur in the cortical collecting duct.[242] This finding is consistent with the demonstration of significant Ca^{++}-Mg^{++}-ATPase activity in the same segment.[150]

Other hormonal mechanisms, including circulating digitalis-like factors, arachidonic acid metabolites, angiotensin II, serotonin, and the kallikrein-kininogen-kinin system, may affect renal water and electrolyte transport. Also, α-adrenergic and dopaminergic innervation may influence transport by altering renal blood flow and perhaps through direct effects on the renal tubular epithelium. Regulation of the mediators for these hormonal and neural mechanisms is under study. Discussion of these topics is beyond the scope of this review.

Developmental Renal Physiology

Maturational changes in renal blood flow, glomerular filtration rate, and tubular secretory processes affect the clearance of drugs excreted by the kidney. Age-related differences in the pharmacokinetics and pharmacodynamics of diuretics parallel developmental changes in renal maturation.

Body composition studies show that the total body water content of the developing fetus decreases as gestation progresses.[95] Preterm newborns delivered at 28 to 32 weeks of gestation have an approximate total body water content of 83 per cent and an extracellular water space equal to 53 per cent of body weight.[94] At term, total body water content decreases to 78 per cent.[94] By the sixth postnatal day, total body water and extracellular water fall to 73 and 39 per cent, respectively.[143] Thus under normal circumstances, a significant but variable loss of water, primarily from the extracellular fluid compartment, is expected during the first few days of life. Total body water content, expressed as a percentage of body weight, declines further during the first year of life.[94] Larger apparent volumes of distribution for certain diuretics in neonates and infants may be due in part to a relatively expanded extracellular fluid compartment. The variability seen in estimates of the volume of distribution may in part reflect significant interindividual variation in total body water content and intracellular and extracellular water.[95]

Estimates of renal blood flow (RBF) and renal plasma flow in neonates, measured by clearance of paraminohippurate (PAH), tend to underestimate true values because tubular secretion of PAH is decreased in the neonatal period.[129] Despite this limitation, measured PAH clearances double between 30 and 35 weeks of gestation and almost double again by term (40 weeks).[143] During the first week of postnatal life, PAH clearance further increases by approximately 50 per cent.[143] Thereafter, PAH clearance rises more slowly until adult values are achieved between 12 to 24 months of age.[143]

PAH is a small molecule and is not highly bound to plasma albumin.[108] Furthermore, PAH is an organic anion and as such, enters the urine not only by glomerular filtration but also by the same transport mechanisms by which many diuretics enter the urine.[108] Therefore, tubular immaturity with respect to organic anion transport may decrease the rate of entry into the urine of diuretics highly dependent on this transport mechanism to reach distal sites of action. The delayed onset of action, lower total body and renal clearances, and prolonged effect of many diuretics in newborns may result in part from the decreased rate of transport into the urine.

The glomerular filtration rate (GFR) is significantly lower in neonates than in adults and, at birth, may be as low as 1 ml per minute in preterm neonates.[121, 163] In neonates of at least 34 weeks' gestation, GFR measured in the immediate postnatal period increases as gestational age and body weight increase.[16, 121, 163, 246] In younger neonates, controversy exists as to whether renal function correlates best with gestational or postconceptual age.[16, 121, 163, 246] A body weight independent increase in GFR occurs during the first several days of postnatal life.[12, 121] The latter rise in GFR correlates with an increase in RBF and is likely the result of a reduction in renal vasoconstriction accompanied by a redistribution of intrarenal blood flow.[121, 143] During infancy, GFR increases with age, reaching normal adult values between 1 and 2 years of age.[12] Observed increases in GFR depend not only on renal maturation but also on nonrenal factors (e.g., cardiac output, circulating catecholamines, direct renal innervation, endogenous and exogenous toxic exposures).[17]

With respect to diuretic therapy, several maturational aspects of renal tubular function are important. Postnatal maturation of the organic anion transport system has already been mentioned. Other relevant factors include age-related changes in the ability of the tubule to reabsorb solutes and to produce a concentrated or dilute urine.

As previously mentioned, the proximal tubule undergoes a tremendous increase in length and surface area during the first year of life.[62] In preterm neonates, proximal tubular reabsorptive capacity for many solutes appears to improve with advancing gestational age. For example, maximal tubular reabsorption of glucose is highly dependent on gestational age.[16] When plasma glucose levels were less than 100 mg per dl in neonates less than or equal to 34 weeks' gestation, glucosuria occurred in 13.3 per cent of neonates.[16] In another group of preterm (29 ± 0.6 weeks' gestation) infants, tubular reabsorption of glucose fell progressively as serum glucose concentrations rose from 129 to 222 mg per dl.[262] Maximal tubular reabsorption of glucose appeared to occur at serum glucose concentrations of approximately 152 mg per dl, a much lower value than normally observed in older children and adults.[262] As expected, osmotic diuresis may result when the maximal tubular reabsorption of glucose is exceeded. The incidence of glucosuria decreases dramatically in term infants.[16]

Tubular reabsorption of sodium increases, and fractional excretion of sodium decreases with increasing gestational age.[16, 240, 254, 263] In neonates at 26 to 28 weeks' gestation and in term neonates, tubular reabsorption of sodium averaged 91.8 and 99.6 per cent, respectively.[16] In preterm neonates, negative sodium balance may occur despite high sodium intake.[72] Because preterm infants have difficulty conserving sodium, concomitant diuretic therapy risks significant sodium depletion.

During the first few postnatal days, neonates are capable of forming urine that varies in osmolality from 30 to 50 mOsm per liter up to approximately 350 to 700 mOsm per liter depending on gestational age.[12, 50, 205] The abilities to produce and secrete vasopressin are well developed at birth, but neonates are relatively insensitive to its antidiuretic effect.[12] As a result, urine-diluting capacity in neonates is equivalent or slightly superior to adult capacity. The maximal urinary concentrating

capacity in neonates, however, is significantly less than normal adult concentrating capacity. In both term and preterm infants, urine concentrating ability increases an average of 30 to 50 per cent during the first 6 weeks of life, but remains well below maximal concentrating ability in adults.[206] Slower increases in concentrating capacity may be observed during the remainder of the first year and the entire second year of life.[206] Maximal concentrating capacity usually approaches adult levels between 1 and 2 years of age.[206]

Despite greater fractional excretion of sodium and insensitivity to vasopressin, preterm neonates may have difficulty excreting sodium and water loads.[10, 11, 164] Low GFR and increased activity of the renin-angiotensin-aldosterone axis may partially explain these observations. The lower observed maximal concentrating capacity may predispose neonates and young infants to dehydration during diuretic therapy especially when concurrent illnesses reduce fluid intake.

PHARMACOLOGY OF DIURETIC AGENTS

Diuretics have been classified according to several schema employing various structural and functional criteria. In this review, diuretic agents are loosely classified by both mechanism and site of action (Table 1). Factors that may reduce or enhance the efficacy of individual diuretics or groups of diuretics are considered.

With the exceptions of mannitol and spironolactone, all diuretics currently in widespread clinical use block tubular reabsorption of electrolytes and water through a direct interaction with transport systems located on the luminal surface of renal tubular epithelia. To reach their prospective sites of action, these diuretics must

Table 1. *Classification of Diuretic Drugs**

DIURETIC AGENT	PRIMARY SITE OF ACTION	MECHANISM OF ACTION	NATRIURETIC POTENCY (%)†
Mannitol	I	Osmotic diuresis	5
Acetazolamide	I	Carbonic anhydrase inhibitor	5
Ethacrynic acid	II	Exact mechanism unknown‡	15–25
Sulfamyl benzoic acids	II	Block Na–K–2 Cl Cotransport	15–25
Furosemide			
Bumetanide			
Piretanide			
Benzothiadiazines	III	Probably block electroneutral NaCl reabsorption	5–10
Chlorothiazide			
Hydrochlorothiazide			
Phthalimidines	III	Probably blocks electroneutral NaCl reabsorption	5–10
Chlorthalidone			
Quinazolones	III	Probably blocks electroneutral NaCl reabsorption	5–10
Metolazone			
Potassium-sparing agents	IV		2–3
Spironolactone		Aldosterone inhibitor	
Triamterene		Blocks apical sodium reabsorption	
Amiloride		Blocks apical sodium reabsorption	

*Based on chemical structure, mechanism of action, and site of action. Sites of action are discussed in the text and shown in Figure 1.

†Natriuretic potency refers to maximal ability to increase the fractional excretion of sodium.

‡The exact mechanism by which ethacrynic acid blocks tubular reabsorption of sodium and chloride is not completely understood. For further information see Greger R, Wangemann P: Loop diuretics. Renal Physiol 10:174–183, 1987.

first enter the filtrate. Two basic mechanisms for entry into filtrate are operative. First, these agents are relatively small molecules that are filtered easily through the glomerulus. In general, the fraction of a diuretic in the plasma that enters the glomerular filtrate is inversely proportional to plasma protein binding. Second, many of these agents are secreted into the proximal tubular lumen by the organic anion or cation transport systems. These systems involve carrier-mediated active transport. Thiazide and loop diuretics are secreted into the lumen by the organic anion transport system, whereas triamterene and amiloride are secreted by the organic cation transport system.[92] Competition with other organic ions for carrier proteins may influence the rate or extent of entry of diuretics into the tubular lumen. Probenecid, a well-known inhibitor of the organic anion transport system, may reduce the diuretic efficacy of agents secreted by this mechanism.[303] Tubular secretion of other organic anions, including penicillins, salicylates, and indomethacin, may competitively reduce the rate of transport of anionic diuretics into the tubular fluid. The H_2-receptor antagonists ranitidine and cimetidine have been shown to inhibit organic cation transport competitively.[192, 193] The clinical significance of competitive secretory inhibition is likely to be greater for agents that are highly dependent on these systems for clearance and in patients with a reduced population of functioning nephrons.

Dopamine, although generally not considered to be a diuretic, may enhance urine output in certain volume-replete oliguric states and will be briefly considered. Dopamine has been shown to increase renal blood flow, glomerular filtration rate, and urine output when administered in low doses (0.5 to 3.0 μg per kg per minute) to oliguric patients.[64, 71, 108] Low-dose dopamine stimulates dopaminergic receptors in renal and certain other vascular beds, resulting in a decrease in renal vascular resistance and a redirection of blood flow toward cortical glomeruli.[64] Further increases in the dose of dopamine result in stimulation of α_1 and α_2 receptors leading to systemic vasoconstriction and increased blood pressure.[104] Renal vasoconstriction and the resultant decline in renal blood flow may occur at higher doses. Dopamine-mediated stimulation of α-adrenergic, β-adrenergic, and dopaminergic receptors appears to be dose dependent and subject to significant interpatient variability.[64] A new selective dopamine-1 agonist, fenoldopam, has been shown to lower blood pressure and to increase renal blood flow and sodium excretion in adults.[4, 308] Fenoldopam and similar agents remain to be studied in pediatric patients.

Osmotic diuresis occurs when a freely filtered, pharmacologically inert solute is not reabsorbed or metabolized to a significant degree along the renal tubule, resulting in an increase in water and solute excretion. Although many endogenous substances may induce an osmotic diuresis, mannitol is the most frequently administered therapeutic osmotic diuretic. Arguably, iodinated radiographic contrast agents, which have attributes of osmotic diuretics, may be administered more frequently, but their primary use is diagnostic and not therapeutic. Chemically, d-mannitol is a small (molecular weight = 182) polyhydroxyalcohol molecule. Intravenous administration of mannitol raises extracellular osmolality, inducing a shift of free water from the intracellular to the extracellular fluid space.[299] The resulta
expansion of the intravascular volume results in increased RBF and GFR
Mannitol is freely filtered at the glomerulus, is not reabsorbed or met
any significant extent along the nephron, and does not directly inh
transport. Instead, delivery of a greater osmolar load to al
decreases water and electrolyte reabsorption. Isosmotic so
proximal tubule is slowed as the concentration of sodi
and the lumen to cell concentration gradient
reabsorption in the loop of Henle is dimin
concentration gradient. The net result

smaller increase in sodium excretion.[299, 300] The magnitude of the resultant free water clearance is directly related to the initial state of hydration.[299]

Carbonic anhydrase, a zinc-containing enzyme, catalyzes both the hydration of CO_2 and the reverse reaction, the dehydration of carbonic acid. In humans, carbonic anhydrase is located primarily in the proximal convoluted tubule, the thick ascending limb of Henle's loop, and the distal convoluted tubule, with smaller amounts observed in the collecting duct.[215] Administration of acetazolamide, the first potent carbonic anhydrase inhibitor, blocks reabsorption of up to 80 per cent of the bicarbonate present in proximal tubular fluid, ultimately resulting in the excretion of up to 30 per cent of filtered bicarbonate.[215] A modest obligatory increase in urinary excretion of sodium and potassium accompanies acetazolamide-induced bicarbonaturia, whereas chloride excretion is usually reduced. Despite its proximal site of action, acetazolamide is a relatively weak natriuretic agent, usually resulting in excretion of as little as 3 to 5 per cent of filtered sodium.[216] This appears to be due in part to extensive distal sodium reabsorption and to the presence of carbonic anhydrase–independent pathways for bicarbonate reabsorption.[215, 216] Prolonged use may result in the development of hyperchloremic metabolic acidosis, limiting the usefulness of acetazolamide for chronic diuretic therapy.

loop diuretics

The loop diuretics are potent saliuretic agents that act at the luminal surface of the thick ascending limb of Henle's loop. Furosemide and structurally similar loop diuretics (sulfamyl benzoic acid derivatives) reversibly bind to the Na^+–K^+–2 Cl^- transporter on the luminal surface of tubular epithelial cells, effectively blocking reabsorption of these ions. Ethacrynic acid blocks sodium and chloride reabsorption in the thick ascending limb by mechanisms that are not completely understood, but appear to be different from the furosemide-like diuretics.[113] Because reabsorption of approximately 25 per cent of the filtered sodium occurs in this tubular segment, inhibition of luminal sodium transport results in delivery of significantly larger amounts of sodium to distal nephron sites, normally resulting in a brisk natriuresis. In addition, the sulfamyl benzoic acid derivatives may have a minor effect on proximal tubular sodium reabsorption.[154, 184]

Lasix - blocks Na, K, Cl reabs in thick ascending loop

Loop diuretics have a significant effect on potassium homeostasis. Potassium reabsorption in the thick ascending limb is reduced. As sodium is reabsorbed at aldosterone-sensitive distal nephron sites, tubular secretion of potassium is enhanced. Both mechanisms appear to contribute to the kaliuresis observed following administration of loop diuretics. Enhanced urinary excretion of magnesium and calcium also occurs during loop diuretic therapy. The mechanisms of altered reabsorption of calcium and magnesium are not completely understood, although inhibition of Ca^{++}–Mg^{++}-ATPase activity may be contributory.[190]

Of the thiazide diuretics available in this country, chlorothiazide and hydrochlorothiazide have been used most often in infants and children. Metolazone, though not structurally a thiazide, shares certain pharmacologic properties with the thiazides and will be considered with these agents. Thiazide diuretics were initially developed during experiments designed to explore structure-activity relationships of modified carbonic anhydrase inhibitors. As a result, thiazide diuretics retain the ability to inhibit carbonic anhydrase to a variable degree. The diuretic efficacy of thiazides, however, appears not to be highly dependent on this property.

Thiazides

Thiazides appear to be most active at the distal convoluted tubule.[282] Although the exact mechanism of action is unknown, inhibition of sodium and chloride reabsorption distinct from the effects produced by loop diuretics has been demonstrated in animals.[281] It has been suggested that parallel exchange of Na^+–H^+ and Cl^--HCO_3^-, possibly under the control of carbonic anhydrase, is inhibited by thiazide diuretics.[282] Variable inhibition of proximal tubular sodium and water reabsorption also has been demonstrated, although reabsorption of excess sodium

in the loop of Henle blunts this effect.[282] Thus combinations of loop and thiazide diuretics may act synergistically to enhance urinary sodium excretion.

Under normal circumstances, the distal convoluted tubule receives approximately 10 per cent of filtered sodium. Accordingly, thiazide-induced inhibition of sodium and chloride reabsorption in the distal convoluted tubule has a natriuretic potential that is intermediate between loop diuretics and acetazolamide or potassium-sparing agents, resulting in urinary excretion of 5 to 8 per cent of filtered sodium.[216] Urinary potassium excretion generally is increased by thiazide diuretics, whereas calcium reabsorption in both the proximal and distal tubules appears to be enhanced.[282]

K+ sparing

Three potassium-sparing diuretics are occasionally used in pediatric therapeutics. Spironolactone is a competitive inhibitor of aldosterone. Thus, it is generally less effective when aldosterone secretion is not stimulated. Spironolactone inhibits sodium reabsorption and potassium secretion in the aldosterone-sensitive portions of the distal convoluted tubule, connecting segment, and collecting duct. Triamterene and amiloride appear to have similar mechanisms of action. Like spironolactone, both inhibit sodium reabsorption and potassium secretion in latter portions of the distal nephron. Their mechanism of action, however, differs from spironolactone in that neither drug competitively inhibits the effects of aldosterone. At physiologic concentrations, amiloride and triamterene appear to inhibit entry of sodium and exit of potassium and hydrogen ion across the luminal surface of the principal cells of the collecting duct.[91, 130] The effectiveness of the potassium-sparing diuretics is enhanced by concurrent treatment with thiazide or loop diuretics (which increase distal sodium delivery).

PEDIATRIC DIURETIC THERAPEUTICS

Limited information regarding the pharmacokinetics and pharmacodynamics of diuretics in children is available. Extensive therapeutic experience with many of these agents in children has been reported, however. Rather than omitting a discussion of the pharmacokinetics of these agents in which pediatric data are lacking, selected data from adult studies will be provided. Brief descriptions of important pharmacokinetic concepts are contained in Table 2. Pediatric dosing guidelines for commonly administered diuretics are summarized in Table 3.

Mannitol

Mannitol is currently the most widely used osmotic diuretic. It is poorly absorbed from the gastrointestinal tract and, when used therapeutically, is generally administered by the intravenous route. The pharmacokinetics and pharmacodynamics of mannitol in children are not well described. In adults, significant interindividual variability with respect to pharmacokinetic parameters exists.[128] The apparent volume of distribution of mannitol correlates well with extracellular fluid volume.[299] The onset of action following intravenous administration of mannitol is relatively rapid. After an initial rise during mannitol infusion, plasma osmolality falls rapidly owing to movement of water into the vascular space and renal elimination of the drug.[299] Rapid renal clearance of mannitol predicts a relatively brief diuretic effect in patients with normal renal function. In adults, the mean elimination half-life varies from 1.2 to 2.17 hours.[9, 53] In children with increased intracranial pressure, the duration of action was reported to be 4.1 to 4.4 hours.[175] As expected, elimination of mannitol in anephric patients occurs at a reduced rate and significant accumulation may occur if dosing intervals are not adjusted appropriately.

Administration of mannitol results in a net increase in water and sodium

Table 2. *Definitions of Pharmacokinetic Terminology Used in Text*

Absorption: Process of uptake of a compound from the site of administration into the systemic circulation. The extent and rate of absorption depend on the route of administration, the physical form (capsule, tablet, solution, etc.) and chemical properties (lipid solubility, pKa, etc.) of the drug, and on host factors at the site of absorption (vascularity, blood flow, surface area exposure, membrane permeability, and contact time at absorptive sites). The absorption rate constant (k_a) and half-life ($t_{1/2_a}$) provide estimates of the rate and duration of drug absorption.

Bioavailability: Fraction of the dose of a drug that reaches the systemic circulation following extravascular administration. Bioavailability is dependent on absorption from the site of administration and, for orally administered drugs, presystemic clearance (e.g., first-pass hepatic metabolism), which may reduce the amount of unaltered drug reaching the systemic circulation.

Distribution: Partitioning of a drug into various tissues and organs. Drugs may reach tissue concentrations that are much less or much greater than concomitant serum concentrations.

Volume of distribution (Vd): Hypothetical volume of fluid into which a drug appears to distribute with a concentration equal to that of plasma. In children, the volume of distribution of a drug is expressed most often as L/kg or L/m^2.

Elimination: Removal of a drug from the body. The primary means of drug elimination are renal excretion (by glomerular filtration or tubular secretion) and hepatic biotransformation followed by renal elimination or biliary secretion. Other routes (e.g., pulmonary) are less important to diuretic elimination. The elimination rate constant (k_{el} or k_β) and half-life ($t_{1/2}$ or β) provide estimates of the rate and duration of drug elimination. The elimination half-life is that period of time during which the serum concentration decreases by 50%.

Clearance: Description of the rate at which drugs are eliminated from the body. Clearance (Cl) is expressed as the volume of blood from which a drug is completely removed during a given period of time. Clearance is expressed most often in units of ml/min or L/hr/kg. The latter term is more commonly applied in children as it corrects for differences in body weight.

excretion, the magnitude of which is dependent on hydration status.[290] Urinary excretion of potassium, calcium, and chloride are variably increased.[158, 290] In general, magnesium excretion is not changed or modestly increased by osmotic diuretics.[158, 231, 232]

Mannitol has been used in various clinical situations. It has been widely used in children and adults to lower intracranial pressure acutely.[122, 243, 271] Problems associated with mannitol therapy in brain-injured patients have included variable penetration of the drug into the cerebrospinal fluid (CSF), rebound rise of intracranial pressure, and disturbances in serum electrolytes and blood viscosity.[9, 60, 122, 199] Overly aggressive therapy with mannitol may result in reversal of the serum to CSF osmotic gradient, resulting in a paradoxical increase in intracranial pressure.[199]

Mannitol has been used prophylactically in patients undergoing cardiopulmonary bypass in an attempt to reduce the incidence and severity of hypoxic renal injury.[315] Once acute renal failure has been established, mannitol therapy is likely to be of less value.[290]

Several potential adverse effects of mannitol have been noted.[122, 290] Expansion of the extracellular fluid volume in patients with oliguric renal failure may result in heart failure and pulmonary edema. Profound hyponatremia has been reported in association with acute mannitol intoxication, whereas chronic administration of mannitol may result in hypernatremia owing to excretion of water in excess of sodium.[60, 299] In children with acute tubular necrosis, the nephron often becomes permeable to mannitol allowing back diffusion and, hence, loss of the diuretic effect. Mannitol should not be mixed with blood products as crenation and agglutination of red blood cells may result.[225]

Acetazolamide

As a diuretic agent, acetazolamide is used primarily for short-term or intermittent therapy when alkalinization of the urine is a desired therapeutic goal. Acetazolamide is rarely used to treat chronic disorders associated with fluid retention, although it has been used to treat other chronic conditions in infants and children. Recommended pediatric doses for acetazolamide are listed in Table 3.

Acetazolamide can be administered orally or intravenously. Following oral administration, acetazolamide is rapidly and completely absorbed. Oral bioavailability, measured as urinary recovery of unmodified drug, appears to be 70 to 90 per cent.[318] In a small number of adult patients, the apparent volume of distribution of acetazolamide averaged 0.20 liters per kg.[165] Acetazolamide is extensively bound to plasma proteins.[279] Unaltered drug enters the urine primarily via proximal tubular secretion and is eliminated by renal excretion, with a mean apparent elimination half-life of 4.1 hours.[166] Despite extensive plasma protein binding, significant quantities of the drug are apparently removed during hemodialysis.[279] Onset of action occurs within minutes after an intravenous dose and within the first hour after an oral dose. Following an intravenous dose, maximal urinary bicarbonate excretion and urine flow rates are achieved during the first hour. The peak effect following oral administration occurs after 2 to 4 hours. The duration of effect is variable, ranging from 4 to 5 hours after intravenous administration to 8 to 12 hours following tablet administration.

Acetazolamide has few serious adverse effects. As expected, chronic use results in bicarbonate depletion and mild hyperchloremic metabolic acidosis, but profound metabolic acidosis is unusual. Hyponatremia and hypokalemia are occasionally observed and generally mild. Chronic alkalinization of the urine potentially contributes to the development of nephrocalcinosis and nephrolithiasis in patients who have hypercalciuria or are receiving concurrent furosemide therapy.[5] Additionally, acetazolamide enhances phosphaturia and decreases urinary citrate excretion, both of which may contribute to calcium stone formation.[215] Nausea, vomiting, anorexia, alterations in the taste of carbonated beverages, polyuria, paresthesias, and lethargy have been observed.[34, 108] Aplastic anemia, thrombocytopenia, and agranulocytosis have been reported in patients with glaucoma receiving orally administered acetazolamide to lower intraocular pressure.[88] In 80 per cent of affected patients, the onset of adverse hematopoietic effects occurs during the first 6 months of therapy.[88] Hirsutism has been attributed to long-term acetazolamide therapy in a 2-year-old child.[304]

Acetazolamide has not been used extensively as a chronic diuretic in children. In general, the clinical usefulness of acetazolamide has been restricted to specific clinical situations. In patients with severe acute rhabdomyolysis, alkalinization of the urine and increased urine flow rates may reduce renal tubular injury. Acetazolamide has been used to alkalinize the urine in children with salicylate poisoning, thereby enhancing pH-dependent urinary excretion of salicylic acid.[83] Maintaining an alkaline urine enhances solubility of many weak acids, including cystine and uric acid. Oral bicarbonate supplements generally have been used to maintain a chronically alkaline urine pH, although in some patients, acetazolamide has been used as adjunct therapy.[215] In older children with cystinuria, combined therapy with acetazolamide and sodium bicarbonate has been used effectively to enhance cystine solubility.[89] Recent evidence suggests, however, that reducing sodium intake and urinary excretion may result in more effective reduction of urinary cystine excretion.[133] Currently, acetazolamide is not used in the chronic therapy of pediatric hypertension or congestive heart failure. Other therapeutic uses of carbonic anhydrase inhibitors have been reviewed previously.[34, 215, 244]

Acetazolamide has been used in adults to treat the severe metabolic alkalosis

Table 3. *Diuretic Dosing in Pediatric Patients**

DRUG	DOSING INFORMATION *(Dosage, Route, Interval)*	DOSAGE ADJUSTMENT *Renal Failure*	*Liver Failure*	COMMENTS
Acetazolamide	PO or IV: 5 mg/kg/dose (Interval: 24 to 48 hours)	Yes	No	Avoid when GFR < 10 Avoid IM Use
Mannitol	IV: 0.25–2 gm/kg/dose (Interval: variable)	Yes	No	Maintain serum osmolality ≤ 320 mOsm/L
Furosemide	Neonate: IV, IM, PO: 0.5–2 mg/kg/dose (Interval: 12 to 24 hours) Infant/Child: IV, IM, PO: 1–2 mg/kg/dose (Maximum dose: 6 mg/kg) (Interval: 6 to 12 hours)	Yes	Possibly	Effective when GFR < 10 Oral bioavailability variable in neonates
Bumetanide	Neonate: IV, IM, PO: 0.01–0.05 mg/kg/dose (Interval: 24 to 48 hours) Infant/Child: IV, IM, PO: 0.015–0.1 mg/kg/dose (Interval: 6 to 24 hours)	Yes	Possibly	Effective when GFR < 10
Chlorothiazide	PO: 10–20 mg/kg/dose (Maximum dose: 2 gm/24 hr) (Interval: 8 to 12 hours)	Yes	No	Not effective when GFR < 10 Avoid parenteral use
Hydrochlorothiazide	PO: 0.5–1.5 mg/kg/dose (Maximum dose: 200 mg/24 hr) (Interval: 12 hours)	Yes	No	Not effective when GFR < 10
Metolazone	PO: 0.075–0.2 mg/kg/dose (Interval: 12 to 24 hours)	Yes	No	Potentially useful at low GFRs
Spironolactone	PO: 1.0–3.3 mg/kg/24 hours (Maximum: 200 mg/24 hours) (Interval: 6 to 12 hours)	Yes	Possibly	Allow 72 hours between dose adjustments Avoid when GFR < 20
Amiloride	No firmly established pediatric dose PO: Infants and small children (6–20 kg): 0.625 mg/kg/24 hours Adolescent: 5–20 mg/24 hours (Maximum: 40 mg/24 hours) (Interval: 12 to 24 hours)	Yes	No	Avoid when GFR < 20 Rarely used as a single agent
Triamterene	PO: 2–4 mg/kg/24 hours (Maximum: 300 mg/24 hours) (Interval: 12 to 24 hours)	Yes	Yes	Avoid when GFR < 20 Rarely used as a single agent

ABBREVIATIONS: PO = orally; IV = intravenously; IM = intramuscularly; and GFR = glomerular filtration rate (ml/min).
*Dosage adjustments may be necessary in patients with significant hepatic or renal insufficiency.

(pH greater than or equal to 7.60), which occurs after rapid transfusion with large volumes of blood products containing citrate or results from prolonged nasogastric aspiration of copious volumes of acidic gastric secretions.[66, 115] In adults with chronic obstructive lung disease and acute fluid retention, acetazolamide has been used to reduce hypoventilation-induced hypoxia.[156] Hypoventilation occurs secondary to the compensatory metabolic alkalosis that develops during acute CO_2 retention and vigorous loop diuretic therapy.[66, 156]

Ethacrynic Acid

With the development of furosemide and newer loop diuretics, ethacrynic acid has been used less frequently in children. The pharmacology and therapeutic applications of ethacrynic acid will be considered briefly. More detailed information can be found elsewhere.[24, 32, 126, 156, 158, 222, 257, 313]

Ethacrynic acid is absorbed well after oral administration. Like furosemide, ethacrynic acid is highly bound to plasma proteins.[156] Elimination of ethacrynic acid occurs primarily by renal tubular secretion and hepatic biotransformation. Approximately two thirds of a dose is excreted unchanged in the urine, whereas the remaining fraction appears to be metabolized by the liver to both active and inactive metabolites.[156, 300] Following oral administration to adults, the onset of diuresis and natriuresis occurs within 30 to 60 minutes.[32] Peak urine flow rates and sodium clearance occur within 2 to 4 hours, with a return to baseline values 6 to 8 hours after dosing.[32] When administered intravenously, the onset of action occurs within 10 to 20 minutes.[32] In adults, diuresis peaks within 1 to 2 hours and lasts approximately 3 to 6 hours, whereas in neonates, peak diuresis occurs within 1 hour, and the duration of the diuretic effect is prolonged to approximately 5 hours.[32, 333] Use of ethacrynic acid in children with a GFR of less than 10 ml per minute per 1.73 m^2 generally should be avoided.[272]

Unlike furosemide, ethacrynic acid does not inhibit carbonic anhydrase and thus has potentially less effect on bicarbonate excretion. Significant metabolic alkalosis, resulting at least in part from chloride depletion, occurs during therapy with either agent.[313] Adverse effects associated with ethacrynic acid are similar to other loop diuretics (see later).[57, 156] Gastrointestinal irritation has been associated with ethacrynic acid more frequently than with furosemide, however.[300] Also, reversible or permanent hearing loss has been observed in patients receiving ethacrynic acid.[57]

Furosemide

The pharmacology of furosemide has been studied more extensively than any other diuretic currently used in pediatrics. Observed alterations in the pharmacokinetics of furosemide in patients with renal failure, nephrotic syndrome, congestive heart failure, cirrhosis, and cystic fibrosis are summarized in Table 4. Changes in the pharmacokinetic parameters are variable but, in general, correlate with the severity of the disease process and the degree of concurrent hypoalbuminemia present in studied patients. Therefore, greater variation from normal can be expected in patients with severe disease or profound hypoalbuminemia.

The pharmacokinetics of furosemide in children less than 3 months of age are summarized in Table 5. The oral bioavailability of furosemide in neonates is reported to be approximately 25 to 50 per cent greater than in adults, but few patients have been studied, and this apparent difference needs further clarification.[187] In older children and adults, the oral bioavailability of furosemide averages 50 to 70 per cent.[64, 187, 300] When estimated by urinary recovery of furosemide, the apparent bioavailability is slightly less.[42, 300] Furosemide is absorbed more rapidly in fasted patients, but the extent of absorption is unaffected by coadministration of food.[64] Significant interindividual (20 to 84 per cent) and intraindividual (20 to 61 per cent)

Table 4. *Disease-Related Alterations in the Pharmacokinetics of Furosemide**

DISEASE	ORAL BIOAVAILABILITY	PLASMA PROTEIN BINDING	APPARENT VOLUME OF DISTRIBUTION	RENAL CLEARANCE	NONRENAL CLEARANCE	TOTAL CLEARANCE	ELIMINATION HALF-LIFE	DOSE-RESPONSE	REFERENCES
Renal failure	D	D	NC to SI	D	NC to D	D	D	D	33, 46, 219, 269
Nephrotic syndrome	D	D	NC to I	NC to SD	NC to I	I	NC to D	D	152, 214, 219
Congestive heart failure	NC	NC	NC to SD	SD	NC	NC to SD	NC to SI	SD to D	42, 44, 114, 239
Cirrhosis	NC	D	NC to I	NC to SD	NC to D	SD	NC to I	NC to D	3, 96, 288
Cystic fibrosis	?	?	NC to SI	NC	I	I	NC	I	8

ABBREVIATIONS: I = Increased; D = decreased; NC = no change; ? = unknown or indeterminate; and S = slight but not significant.

*Significant hypoalbuminemia associated with any of the disease states may result in reduced protein binding and an increased free fraction of furosemide in plasma. The degree of hepatic or renal failure correlates well with observed reductions in nonrenal and renal clearances, respectively. Observed differences between studies of patients with congestive heart failure may relate to the severity of patients at presentation. Disease severity is not always comparable between studies.

Table 5. *Pharmacokinetics of Furosemide in Neonates and Infants*

REFERENCE*	AGE	DOSE (mg/kg)	BIOAVAILABILITY (%)	$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	Vd (L/kg)	Cl (PLASMA) (ml/hr/kg)	Cl (RENAL) (ml/hr/kg)
Aranda et al, 1978	GA: 26–40 wks CA: 1–40 days	1.0–1.5 mg/kg (IV)	N/A	N/A	7.7 ± 1.0	0.829 ± 0.119	81.6 ± 15	N/A
Peterson et al, 1980	GA: 26–36 wks CA: 1–20 days	1.0 mg/kg (IV)	N/A	N/A	19.9 ± 3.0	0.239 ± 0.027	10.6 ± 2.1	N/A
Vert et al, 1982	GA: 27–34 wks CA: 2–69 days	0.29–1.48 mg/kg (IV)	N/A	0.26–6.50 (Mean = 1.79)	26.8 ± 12.2	0.204 ± 0.075	6.86 ± 5.08	N/A
	GA: 37–41 wks CA: 1–18 days	1.00–1.13 mg/kg (IV)	N/A	1.30–2.80	13.4 ± 8.6	0.523 ± 0.418	11.76 ± 9.32	N/A
Tuck et al, 1983	GA: 29–40 wks CA: 3–32 days	1.0 mg/kg (IV)	N/A	0.54 ± 0.12	9.5 ± 4.4	0.174 ± 0.028	15.3 ± 8.4	14.9 ± 7.7
Mirochnick et al, 1988	GA: 26.6 ± 2.9 wks PCA: 26.5–37 wks	1 mg/kg (IV) 2–3 mg/kg (ng)	84.3 (Range: 56–106)	N/A	1.8–67.3	First dose: 0.23 ± 0.04 Long term: 0.48 ± 0.14	N/A	1.62–73.8

ABBREVIATIONS: $t_{1/2\alpha}$ = Half-life of the distribution phase; $t_{1/2\beta}$ = elimination half-life; Vd = apparent volume of distribution; Cl = clearance; CA = gestational age; CA = chronologic age; PCA = postconceptual age; IV = intravenous administration; and N/A = not reported.

*Methodologic differences between studies that may have contributed to the observed variability in kinetic parameters are discussed in the referenced reports.

variations in bioavailability have been shown in healthy adults.[107] The bioavailability of furosemide may be decreased in adults with uremia or the nephrotic syndrome.[62, 219, 259] In adults with congestive heart failure (CHF), the extent of furosemide absorption was not different from normal, but the rate of absorption was slower, and the peak serum concentrations were lower than those observed in normal controls.[42, 114, 278] Although limited data are available, bioavailability appears unaffected by severe liver disease.[258]

Peak serum concentrations are achieved within 45 to 90 minutes after oral administration of furosemide to healthy adults.[209, 296] Plasma protein binding is extensive, averaging 95 to 98 per cent in healthy adults.[3, 219] Plasma protein binding is slightly lower in uremic and cirrhotic adults and in nephrotic children and adults.[3, 214, 219] Furosemide displaces bilirubin from albumin binding sites.[240, 307] Potentially significant displacement may occur at plasma furosemide concentrations attainable during clinical use, especially in critically ill premature neonates. A causal relationship between furosemide-induced bilirubin displacement and the development of kernicterus has not been shown, however.

Extensive protein binding limits glomerular filtration of furosemide. Elimination occurs primarily by proximal tubular secretion and hepatic biotransformation.[62] Furosemide undergoes conjugation, forming furosemide glucuronide, and oxidation, forming 2-amino-4-chloro-5-sulfamoylanthranilic acid, an acid metabolite that apparently retains modest diuretic activity.[14, 214] Both the glucuronide conjugate and the acid metabolite are polar and hence are rapidly excreted in the urine.[14] In normal adults and ill children, approximately 45 to 60 per cent of an administered dose is excreted unchanged in the urine.[115, 219, 258] The apparent volume of distribution of furosemide at steady state (Vd_{ss}) is remarkably consistent in healthy adults, varying from 0.07 to 0.18 liters per kg.[62] In adults with congestive heart failure, Vd_{ss} is relatively unchanged when compared with normal controls.[42, 114] As predicted from the decrease in protein binding, Vd_{ss} is increased in adults with the nephrotic syndrome.[219] Uremia has a minimal effect on Vd_{ss}, which becomes more significant with concurrent hypoalbuminemia.[219] In cirrhotic patients, Vd_{ss} is either unchanged or increased and seems to correlate directly with the serum albumin concentration.[3, 96, 258]

In general, reported values for the furosemide in neonates are substantially higher than observed values in adults.[13, 206, 285] The larger volume of distribution may result from several factors including slightly lower serum albumin concentrations, the presence of fetal albumin, relatively larger total body and extracellular water pools, and elevated concentrations of many endogenous compounds that compete for albumin binding sites. Changes in Vd_{ss} are significant in that if clearance remains the same, the elimination half-life will vary directly with Vd_{ss}. In premature neonates, Vd_{ss} is increased and both renal and nonrenal clearance of furosemide are significantly less than in older children and adults. Both factors combine to prolong the elimination half-life in these patients. In preterm neonates, the elimination half-life often exceeds 24 hours and may be as long as 46 hours, whereas in most term neonates, the reported values in individual patients are generally less than 12 hours.[13, 206, 285] As renal and hepatic functions mature, the clearance of furosemide increases and the elimination half-life is shortened.

In several studies of healthy adults, the mean plasma elimination half-life for furosemide was 0.7 to 1.1 hours.[3, 96, 158, 219, 288] The plasma elimination half-life was prolonged in adults with significant renal failure, but not significantly altered in most patients with cirrhosis or congestive heart failure unless concurrent renal insufficiency was present.[3, 114, 219, 289, 290, 258] The lag time between peak serum concentrations and peak urinary excretion of furosemide, however, is longer in patients with CHF. The renal clearance of furosemide is also significantly slower, resulting in a blunted and prolonged response.[44] In infants with congestive heart failure and pneumonia, renal clearance of furosemide was slower than in children with pneumonia alone.[213] The plasma elimination half-life of furosemide in adults with nephrotic syndrome is unchanged or slightly shortened.[158, 219]

The pharmacokinetics and pharmacodynamics of furosemide have been described in children with nephrotic syndrome.[105, 210–212] The oral bioavailability of furosemide in nephrotic and non-nephrotic children, estimated from 24-hour urinary recovery, averaged 56 ± 31 and 49 ± 15 per cent, respectively.[211] It should be noted that 2 of the 17 "nephrotic" children in this study had quantitative urinary protein excretion rates of less than 400 mg per 24 hours and that 5 of 17 had plasma albumin concentrations above 2.5 gm per dl.[211] The plasma elimination half-life following intravenous administration of furosemide to children with the nephrotic syndrome was 38.5 minutes compared with 28 minutes in a non-nephrotic control group.[105] The apparent volume of distribution was increased in the children with nephrotic syndrome (0.28 versus 0.19 liters per kg).[105] In adults, the greater apparent volume of distribution has been attributed to decreased plasma protein binding.[219] The plasma clearance of furosemide does not appear to differ between patients with and without nephrotic syndrome.[105] Urinary excretion of furosemide appeared to be initially greater in the children with the nephrotic syndrome, but after 3 hours, cumulative excretion was not significantly different between nephrotic children and healthy controls.[211] Urine volume and sodium excretion were significantly reduced in the children with the nephrotic syndrome, whereas the magnitude of potassium excretion was not different.[105] These findings support the clinical observation that children with nephrotic syndrome often appear to develop furosemide-resistant edema.[18, 101]

As is true of other loop diuretics, furosemide enhances excretion of water, sodium, potassium, chloride, calcium, magnesium, and phosphate. Following intravenous administration of furosemide to children beyond the neonatal period, onset of the diuresis occurs within 15 to 30 minutes, peaks within 1 to 2 hours, and dissipates during 4 to 6 hours.[73, 222] In neonates, the duration of the diuretic and saliuretic action appears to be variably prolonged.[317] Acutely, urinary flow and sodium excretion rates may increase as much as 10 to 35 times above baseline.[73, 221, 222, 224] Following extended use, hyponatremia, hypokalemia, and volume contraction may occur.[73] Hypochloremic metabolic alkalosis, similar to that observed during bumetanide therapy, is observed during vigorous furosemide treatment.[73] Enhanced urinary calcium loss resulting from chronic furosemide use in neonates may cause nephrocalcinosis and calcium nephrolithiasis.[77, 138] Following prolonged observation without specific therapy, furosemide-induced nephrocalcinosis appears to be partially to fully reversible.[77, 138] Also, secondary hyperparathyroidism and pathologic fractures have been documented in a few furosemide-treated infants with bronchopulmonary dysplasia.[253] Furosemide, like other loop diuretics, interferes with magnesium reabsorption. The incidence of diuretic-induced hypomagnesemia and the clinical significance of chronic furosemide therapy on magnesium homeostasis in children is unknown.

Adverse effects attributable to furosemide therapy are usually relatively mild and may include gastrointestinal irritation, diarrhea, weakness, fatigue, dizziness, muscle cramps, and various cutaneous eruptions.[87, 278] Rarely, cholestatic jaundice and cholelithiasis have been reported in neonates concurrently receiving parenteral nutrition.[51, 283, 311] Furosemide may induce hyperglycemia and has been associated with hyperosmolar nonketotic diabetes in adults.[87] Pancreatitis also has been reported in an adult receiving furosemide.[141] Anemia, thrombocytopenia, leukopenia, and neutropenia are rarely associated with furosemide therapy. Reversible interstitial nephritis has been associated with vigorous furosemide-induced diuresis in patients with the nephrotic syndrome.[172]

Tinnitus and cochlear injury occasionally accompany furosemide therapy. Pure

tone audiometry performed on 220 furosemide-treated patients revealed a 6.4 per cent incidence of hearing loss.[276] Animal studies and anecdotal data in infants suggest that concurrent administration of aminoglycoside antibiotics with furosemide may increase the risk of ototoxicity.[50, 171] Brain-stem auditory-evoked response testing of preterm neonates performed 30 to 60 minutes after administration of a single 1 mg per kg dose of furosemide did not reveal evidence of impaired response, but multiple doses and earlier time points were not evaluated.[26] Potentially, ototoxicity may be reduced by administration of furosemide as a slow infusion as opposed to a rapid bolus.[27] In animals, the diuretic effect during slow infusions appears to be prolonged and enhanced.[165]

Clinically significant interactions between furosemide and other medications are relatively unusual. Probenecid decreases renal tubular secretion and renal clearance of furosemide.[198] As expected, concurrent treatment with nonsteroidal anti-inflammatory agents may blunt the diuretic response to furosemide.[40] Concurrent administration of furosemide and other diuretics that act at different tubular sites may have additive effects on the excretion of sodium and water. Furosemide-induced potassium and magnesium depletion may decrease the therapeutic index for digoxin. Although the mechanism is unclear, chronic anticonvulsant therapy may decrease the response to furosemide.[3]

Furosemide has been used extensively in preterm neonates to treat various conditions including generalized edema, congestive heart failure with or without patent ductus arteriosus, respiratory distress syndrome, bronchopulmonary dysplasia, and fluid retention associated with acute renal insufficiency. Additionally, furosemide and acetazolamide have been used to decrease the rate of cerebrospinal fluid production in neonates with hydrocephalus.[244] Recently, several authors have reviewed the use and potential adverse effects of furosemide in these disorders.[15, 37, 39, 74, 111, 204]

Preterm neonates, because of immature renal function, altered furosemide pharmacokinetics, decreased plasma protein binding, and the frequent need for concomitant treatment with other nephrotoxins and ototoxins, are at increased risk to develop complications during prolonged furosemide therapy. Furosemide is not contraindicated but should be used with caution in neonates with total serum bilirubin concentrations above 10 mg per dl.[307] In critically ill neonates with hyperbilirubinemia, chronic administration of furosemide should be undertaken with great caution, especially if concurrent renal insufficiency exists or aminoglycoside antibiotics are used. Urinary calcium excretion should be closely monitored and, if persistently elevated, should suggest the possibility of calcium nephrolithiasis or nephrocalcinosis.

In older children, furosemide is widely used in the management of fluid retention secondary to acute and chronic renal insufficiency, glomerulonephritis or the nephrotic syndrome, and congestive heart failure.[73, 105, 211, 212, 216, 223] Furosemide has been recommended and widely used to treat hypertension in children.[249] Often, furosemide is coadministered with intravenous vasodilators to prevent fluid retention during the treatment of hypertensive emergencies. Furosemide may be useful when fluid retention contributes to the pathogenesis of the hypertension, but newer antihypertensive agents have replaced furosemide in the management of hypertension secondary to other causes.[250] Furosemide may be used as adjunctive therapy in children with elevated intracranial pressure.[122] Administration of relatively low doses of furosemide by continuous infusion prevents the antidiuretic effect otherwise observed in children treated with high-dose cyclophosphamide.[115] Other clinical situations in which furosemide has been useful include hepatic failure with ascites, cystic fibrosis with CHF secondary to pulmonary hypertension, and forced diuresis following certain childhood poisonings. Published data from adults and unpublished experience in children suggest that concurrent administration of dopamine and

furosemide early in the course of oliguric acute renal failure enhances urine output and sodium excretion.[109]

Bumetanide

Bumetanide and furosemide have significant structural and pharmacodynamic similarities. Although direct comparison of these agents with respect to the incidence, prevalence, and clinical significance of adverse effects in children has not been done, bumetanide therapy appears to offer only marginal theoretic advantages when compared with furosemide.

The pharmacology of bumetanide has been studied extensively in adults. More recently, similar data are becoming available for children. Bumetanide is absorbed rapidly, attaining maximum serum concentrations (T_{max}) approximately 60 to 90 minutes after oral administration to fasted healthy adults.[56, 161] In adults with congestive heart failure or moderate to severe renal failure, T_{max} occurred slightly later, suggesting that the rate of absorption may be slower in these patients.[56, 161] The numbers of patients in these studies were small and delayed absorption could not be statistically proven, however. Other investigators have shown that the absorption of bumetanide is prolonged in adults with congestive heart failure, resulting in lower peak serum concentrations and urinary excretion rates.[44] The bioavailability of bumetanide averages 65 to 90 per cent, is not altered significantly in adults with renal failure or congestive heart failure, and does not appear to be dose dependent over a fairly narrow range of doses.[23, 43, 56, 161, 178, 179] Rapid and complete absorption are observed following intramuscular administration of bumetanide to healthy adults.[126]

At plasma concentrations well above those achieved during routine therapeutic use, the in vitro binding of bumetanide to neonatal plasma proteins is consistently 96.6 to 97.5 per cent.[275, 294] Only when in vitro plasma concentrations exceed 100 μg per ml (approximately 200 to 1000 times the maximum plasma concentrations achieved during therapeutic use) does the unbound fraction begin to increase.[294] Hence, saturation of albumin-binding sites is unlikely at usual therapeutic doses. Bumetanide, like furosemide, is a potent displacer of bilirubin from albumin-binding sites.[275, 293] At presumed therapeutic plasma concentrations, bumetanide displaces less bilirubin in vitro than furosemide.[293] Plasma protein binding also may be reduced in uremic patients.[161]

Bumetanide is eliminated by renal excretion and hepatic biotransformation.[118, 237] Approximately 50 per cent of an intravenous dose is excreted unchanged in the urine, whereas the remainder undergoes oxidation or conjugation to form several metabolites.[118, 237] The metabolites are believed to be relatively inactive.[237]

In neonates or older patients with severe hypoalbuminemia, liver or renal disease, or CHF, the pharmacokinetics of bumetanide may be significantly altered. In healthy adults, the apparent Vd_{ss} volume of distribution of bumetanide is small, averaging 0.12 to 0.14 liters per kg.[56, 126, 161, 178] In preterm neonates and infants, the Vd_{ss} is increased to 0.28 to 0.38 liters per kg.[241, 316] Slight but statistically insignificant increases in Vd_{ss} have been observed in adults with CHF or renal failure without hypoalbuminemia.[56, 161] The apparent distribution volume of bumetanide is increased in hypoalbuminemic edematous adults, suggesting that bumetanide is distributed easily into the extracellular fluid.[23] As expected, renal and total body clearances of bumetanide are reduced significantly in renal failure, whereas nonrenal clearance is decreased in patients with cirrhosis.[161, 179] When a two-compartment model is used, the apparent terminal elimination half-life in healthy adults averages 45 to 90 minutes.[56, 161, 178] In patients with CHF, the renal clearance of bumetanide is decreased and, as a result, the elimination half-life is slightly prolonged.[56] As expected, the elimination half-life is significantly prolonged in patients with renal or hepatic diseases.[179]

Disease-related changes in the pharmacokinetics of bumetanide may result in altered diuretic response. Bumetanide enhances urinary excretion of water, sodium, potassium, chloride, phosphate, calcium, magnesium, and other divalent cations.[1, 86, 133, 297] Under normal circumstances, peak urine flow rates lag behind peak serum bumetanide concentrations by 20 to 30 minutes.[56, 161] Maximum rates of water, sodium, and potassium excretion occur during the first 30 minutes after intravenous administration of bumetanide as compared with 1.5 to 2.0 hours following oral administration.[179] The delay in achieving maximum water and electrolyte excretion following oral dosing correlates well with data describing the absorption half-life, T_{max}, and the lag time between peak plasma concentrations and peak urine flow rates.[56, 161] Most investigators have not found significant differences in the cumulative excretion of water and electrolytes following administration of equal doses of bumetanide by either the oral or intravenous routes.[161, 178] In healthy adults, the duration of diuretic effect appears to be approximately 3 to 4 hours after intravenous administration and 4 to 6 hours after oral dosing.[41, 118, 133, 250, 297] In patients with CHF receiving oral bumetanide, however, the rate of absorption is slowed, peak serum concentrations are lower and occur later, renal clearance is reduced, and the diuretic response appears to be decreased.[44, 56] In uremia, the oral bioavailability of bumetanide appears to be normal, whereas renal clearance is decreased in proportion to the degree of renal dysfunction.[179] The diuretic response in uremic patients is blunted because of a decrease in the number of functioning nephrons.

After acute administration of bumetanide, the fractional excretion of sodium may increase transiently to approximately 25 per cent. Following prolonged or vigorous bumetanide-induced diuresis, postural hypotension, hyponatremia, hypokalemia, hypochloremia, and hypochloremic metabolic alkalosis have been observed.[67, 86, 261] Also, hyperuricemia is frequently observed.[310] Adverse reactions to bumetanide are generally similar to those observed during furosemide therapy. Muscle cramps, gastrointestinal cramps, vertigo, headache, and cutaneous eruptions, including Stevens-Johnson syndrome, urticaria, and exfoliative dermatitis, have been reported infrequently.[86, 119, 261] In both clinical trials and animal studies, bumetanide appears to be less ototoxic than furosemide.[49, 261, 276] Although most studies have shown that bumetanide does not impair glucose tolerance, rare cases of hyperglycemia have been observed during therapy.[67, 86, 226]

Drug interactions involving bumetanide and other therapeutic agents are infrequent. Organic anions undergoing carrier-mediated secretion into the proximal tubule may competitively inhibit the rate of entry of bumetanide into the tubular fluid and thereby blunt the diuretic effect.[250] Nonsteroidal anti-inflammatory drugs also may blunt the natriuretic response to bumetanide.[40, 151] Metolazone further enhances urinary excretion of sodium and water in patients concurrently treated with bumetanide.[45, 112]

The use of bumetanide in pediatric therapeutics is increasing. Use in premature neonates with fluid overload and infants with CHF has been documented.[97, 293, 298, 314] Although less well documented, bumetanide has been used in children with acute and chronic renal failure, nephrotic syndrome, glomerulonephritis, and hypertension.

Numerous comparisons of the efficacy and toxicity of furosemide and bumetanide have been made.[1, 41, 44, 49, 67, 226, 261, 273, 276, 289, 297, 310] The observed diuretic and natriuretic responses following oral administration of 1 mg of bumetanide and 40 mg of furosemide are approximately equal.[44, 289] When the drugs are administered parenterally, a relatively larger dose of bumetanide may be required to maintain an equivalent diuretic effect.[1] Differences in oral bioavailability between furosemide and bumetanide (50 to 60 per cent versus 80 per cent) may partially explain this observation. With the exception of ototoxicity, adverse effects associated with furosemide and bumetanide occur with approximately equal frequency.[67, 119, 226, 261]

In patients receiving other drugs (e.g., aminoglycoside antibiotics) that potentially may injure the cochlea, bumetanide may be a safer alternative to furosemide.[50] At usual therapeutic doses, bumetanide interferes with bilirubin-albumin binding less than furosemide and hence may be useful when bilirubin displacement could be potentially harmful.[293] Clinical trials comparing the safety of furosemide and bumetanide in neonates have not been done, however.

Several newer loop diuretics are currently under investigation in this country or are available in other countries (torasemide, piretanide, muzolimine, and so forth). Little if any pediatric data have been published for these loop diuretics, and they will not be discussed further.

Thiazide Diuretics

The thiazide diuretics are a varied group of drugs that share the property of acting primarily on site III in the renal tubule. Following a discussion of the pharmacokinetics of individual thiazide diuretics used in children, therapeutic uses and adverse effects of this group of drugs will be jointly considered.

Chlorothiazide. Chlorothiazide is rapidly absorbed and eliminated unchanged in the urine. The absorption of chlorothiazide following oral administration is incomplete and dose dependent.[200, 238] In healthy adults, urinary chlorothiazide recovery fell from 56 to 33 per cent as the dose was increased from 50 to 250 mg.[200] Other investigators have confirmed these results.[185, 238] The 12-hour urinary recovery of chlorothiazide in preterm infants receiving chronic therapy (10 mg per kg per dose given twice daily) averaged 30 per cent of the administered dose.[156] Chlorothiazide has been shown to displace bilirubin from albumin binding sites, but the clinical significance of this observation is unknown.[214]

The onset of the diuretic effect generally occurs within 1 hour after administration of an oral dose of chlorothiazide.[202] In patients with normal renal function, the duration of action is generally 6 to 12 hours.[203] In a limited number of healthy adults, the peak plasma concentration of chlorothiazide was reached 1.5 to 3.0 hours after an oral dose.[238] The apparent elimination half-life averages 1.5 hours.[203] In preterm neonates with bronchopulmonary dysplasia, the mean elimination half-life following single doses of chlorothiazide was 5.2 hours.[156] Small amounts of chlorothiazide have been found in breast milk.[206]

Hydrochlorothiazide. Hydrochlorothiazide, unlike chlorothiazide, does not appear to undergo dose-dependent absorption.[21, 22] The bioavailability of hydrochlorothiazide following oral administration to fasted adults averages 60 to 80 per cent.[28, 29, 30, 277] When hydrochlorothiazide was administered to healthy adults following a standard meal, bioavailability was slightly enhanced.[30] Apparent peak serum concentrations were achieved after 1.5 to 4 hours and 1.5 to 6 hours in fasted and nonfasted patients, respectively.[30] The bioavailability of hydrochlorothiazide is variably reduced in patients with CHF.[21]

Hydrochlorothiazide is approximately 40 per cent bound to plasma proteins.[32] Following oral administration, the decline in plasma concentrations appears to be biphasic with a terminal elimination half-life in healthy adults ranging from 5.6 to 14.8 hours.[32] As expected, the elimination half-life of hydrochlorothiazide may be significantly prolonged in adults with renal insufficiency and CHF.[21, 197] The duration of hydrochlorothiazide-induced diuresis and natriuresis averages 7 to 12 hours, but may be longer in some patients.[30, 196, 239] In adults, significant incremental increases in the natriuretic and diuretic effects of hydrochlorothiazide appear to cease at doses between 12.5 and 50 mg.[32, 212] Hydrochlorothiazide, like chlorothiazide, is less effective as GFR falls. Both drugs should be avoided in children who have a GFR of 10 ml per minute or less.[272]

Chlorthalidone. Chlorthalidone is a phthalimidine derivative structurally distinct from chlorothiazide and hydrochlorothiazide. Despite these structural differ-

ences, chlorthalidone is pharmacodynamically similar to other diuretics in the thiazide group. Currently, chlorthalidone is not used as widely as other thiazides in pediatric patients in this country and will not be considered in detail here. The pharmacokinetics of chlorthalidone have been reviewed.[38] Chlorthalidone has a relatively prolonged elimination half-life and hence longer duration of action.[32] These properties permit a once-daily or alternate-day dosing schedule.[34]

Metolazone. Metolazone is a quinazolinone derivative with a mechanism of action similar to chlorothiazide and hydrochlorothiazide. Within the pediatric population, it has been used most often with furosemide to enhance the excretion of water and sodium in children with nephrotic syndrome. The bioavailability of metolazone in normal adults averages 60 to 80 per cent and may be reduced in patients with CHF.[189, 258] Metolazone appears to distribute widely into the tissue compartment.[258] Extensive binding to plasma proteins and erythrocytes has been observed.[189] Metolazone appears to be metabolized, but the extent to which this occurs is apparently small since most of the parent compound appears to be excreted unchanged in the urine.[258] The renal clearance of metolazone correlates with creatinine clearance; thus, in patients with reduced renal function, reductions in renal and total body clearance occur.[258] The estimated elimination half-life of metolazone from plasma is approximately 5 to 6 hours in normal adults, although a prolonged terminal elimination phase has been described.[258] Onset of the diuretic effect after oral administration of metolazone occurs within 1 hour and peaks at 2 to 3 hours.[188] In adults, the duration of the diuretic effect appears to persist for 12 to 24 hours.[188] The natriuretic effect of metolazone appears to be dose dependent up to 50 mg.[188]

In addition to inducing a moderate natriuresis and diuresis, the thiazide diuretics, like the more potent loop diuretics, cause significant increases in urinary excretion of potassium and magnesium.[188, 231] Hypokalemia and depletion of intracellular potassium stores often result from thiazide-induced kaliuresis.[21, 191, 257] Hypomagnesemia may contribute to refractory hypokalemia in adults treated with thiazide diuretics.[200] In adults, hypokalemia and hypomagnesemia may potentiate ventricular arrhythmias.[128] Contradictory experimental evidence *prohibits* concluding that a direct cause-and-effect relationship exists between thiazide-induced hypokalemia and arrhythmias.[90] The effect of thiazides on calcium excretion is more complex, although in sodium-restricted normovolemic patients, calcium excretion is reduced.[54] When sodium intake and urinary excretion are high, the hypocalciuric effect of thiazides may be blunted or lost.[61]

Adverse effects on glucose and lipid metabolism are known to occur in patients treated with thiazide diuretics. In hypertensive adults, several studies have shown a short-term increase in serum cholesterol following initiation of thiazide therapy, although this effect generally diminishes over time.[90] In one study, serum triglyceride concentrations were more consistently elevated during long-term thiazide treatment.[205] Low-density lipoproteins (LDL) were generally increased, whereas high-density lipoproteins (HDL) were unchanged.[205] Impaired glucose tolerance may develop during long-term thiazide treatment.[205] In adults, severe reversible nonketotic hyperglycemia has been attributed to metolazone and chlorthalidone.[67, 229] The effects of long-term thiazide therapy on lipid and carbohydrate metabolism in children are unknown.

Other reported adverse effects associated with thiazide therapy include hyperuricemia, hypersensitivity reactions, dermatitis, cholestasis, and, rarely, hypercalcemia.[152, 169, 203] Muscle cramps, dizziness, nausea, and vomiting have been reported.[169] Coma has been reported in several children given large doses or unintentional overdoses of chlorothiazide.[26, 256] Chlorothiazide has also been shown to displace bilirubin from albumin-binding sites, and therefore should be used with caution or avoided in neonates with significant hyperbilirubinemia.[307] Rarely, severe shaking chills and fever have accompanied administration of hydrochlorothiazide.[131]

The clinical use of thiazide diuretics in children with renal disease has been extensive. The addition of metolazone to the treatment regimen of nephrotic children with furosemide-resistant edema results in enhanced diuresis and natriuresis.[16, 101] Hyperuricemia (five of seven patients), metabolic alkalosis (two of seven patients), and a kaliuresis resulting in hypokalemia were observed in one study, however.[101] Both chlorothiazide and metolazone, used in combination with furosemide, have been shown to be equally effective in the treatment of nephrotic edema.[102] Thiazides have been used to treat nephrogenic diabetes insipidus (NDI) and acquired urinary concentrating defects.[65] This paradoxical effect likely results from sodium depletion and a slight decrease in GFR resulting in enhanced proximal sodium reabsorption and decreased distal delivery. Experimental evidence suggesting that medullary osmolality is increased, resulting in increased water reabsorption at sites distal to the proximal tubule, provides an alternate or possibly additive mechanism for thiazide-induced antidiuresis in children with NDI.[243] Combined therapy with indomethacin and a thiazide diuretic enhances the antidiuretic effect in children with postobstructive concentrating defect, suggesting that prostaglandins may play a role in the pathogenesis of this disorder.[65] In two children with congenital NDI, the combination of amiloride and hydrochlorothiazide reduced polyuria more effectively than hydrochlorothiazide alone and was as effective as hydrochlorothiazide plus tolmetin.[6]

Thiazide diuretics have been widely used in children to treat renal hypercalciuria.[146, 230] More recently, it has been suggested that thiazides reduce urinary calcium excretion in children with both absorptive and renal hypercalciuria.[223] As urinary calcium excretion falls, the net retention of calcium and phosphate is increased in thiazide-treated adults with severe hypercalciuria.[55] The hypocalciuric effect of thiazides may be diminished by failure to restrict dietary sodium intake during diuretic therapy.[223] In children with vitamin D–induced hypercalciuria, the addition of amiloride to hydrochlorothiazide appeared to have an additive hypocalciuric effect.[5]

Thiazide diuretics have been used to treat children with CHF and hypertension.[21, 79, 93, 184, 249, 250] Thiazides have been used to improve pulmonary function in neonates with respiratory distress syndrome, although in one comparative trial, chlorothiazide was shown to be less effective than furosemide.[110] Chlorothiazide combined with spironolactone improves pulmonary mechanics in infants with bronchopulmonary dysplasia, an effect that appears to be additive to theophylline.[147, 148] In a similar group of patients, however, other investigators have demonstrated that the diuresis induced by hydrochlorothiazide and spironolactone did not result in improved dynamic lung compliance or hemoglobin oxygen saturation.[73] Also, thiazides have been used to treat edema and ascites in patients with cirrhosis.

Doses of the various thiazide diuretics that have approximately equivalent natriuretic and diuretic effects have been estimated. In adults, 10 to 15 mg of metolazone was roughly equivalent to 50 mg of hydrochlorothiazide.[188] Chlorothiazide and hydrochlorothiazide have an equivalent dose ratio of roughly 10 to 1.[34, 194]

Spironolactone. Spironolactone was initially developed from progestational hormones and retains some minimal progesterone-like effects. Spironolactone has been used primarily to reduce the enhanced potassium excretion observed during therapy with thiazide or loop diuretics. Published pediatric pharmacokinetic and pharmacodynamic data for spironolactone are generally unavailable. Several important observations from studies performed in animals and adults merit consideration, however.

Under normal circumstances, the absorption of spironolactone is relatively rapid and complete.[38] In adults, administration of spironolactone with food has been shown to enhance its bioavailability significantly.[208] Spironolactone is metabolized to two active intermediate compounds, 7 α-thiomethylspironolactone and canre-

none.[149, 291] The intermediate compounds undergo further metabolism and are excreted primarily in the urine. Biliary excretion accounts for a smaller but significant fraction of the total body clearance. When spironolactone is administered as a sole agent, achievement of maximum efficacy after initiation of therapy or dose changes generally requires 3 days. The lag period results both from continued accumulation of metabolites and from delayed expression of postreceptor effects. Slower clearance of the active metabolites allows a 12-hour dosing interval in most patients.

Both spironolactone and canrenone are greater than 90 per cent bound to plasma proteins.[28] In drug-free adult volunteers, spironolactone reaches peak serum concentrations within 2 hours after oral dosing and is rapidly metabolized, decreasing from an apparent peak concentration of 185 ± 51 ng per ml at 1 hour to 6 ± 4 ng per ml at 8 hours.[201] The elimination half-life of spironolactone in plasma is 1.6 to 2.9 hours, whereas the elimination half-lives of its metabolites are longer.[202] Spironolactone and its metabolites accumulate in patients with renal failure; thus, the dosing interval must be adjusted as GFR falls. In general, spironolactone should not be used in children when the GFR decreases below 10 ml per minute.[272] Studies have not been performed in neonates to assess the effect of development on the bioavailability and clearance of spironolactone or canrenone.

Many of the adverse effects associated with spironolactone therapy are predictable from its structure and mechanism of action. Hyperkalemia occurs and may be life threatening, especially in patients with decreased renal function whose ability to excrete a potassium load is impaired. Concomitant administration of potassium supplements may contribute to the development of hyperkalemia. When spironolactone is used with thiazide and loop diuretics, hyponatremia, resulting from decreased distal sodium reabsorption, can occur. Gynecomastia, possibly secondary to enhanced metabolic clearance of testosterone and peripheral conversion of testosterone to estradiol, appears to be related to the dose and duration of spironolactone therapy.[228, 235] Spironolactone-induced gynecomastia is usually reversible on cessation of therapy. Other adverse effects include nausea, vomiting, abdominal pain or cramping, and mild azotemia. Rarely, agranulocytosis, eosinophilia, and thrombocytopenia have been reported in adults receiving spironolactone.[140, 301] Long-term treatment has been shown to decrease HDL cholesterol without affecting total or LDL cholesterol concentrations.[78] After 1 year of treatment with spironolactone, no difference in serum triglyceride or uric acid concentrations developed.[78] Limited data are available, but it appears that only small amounts of spironolactone and its metabolites are excreted in breast milk.[227]

Interactions between spironolactone and other commonly administered medications have been documented. Salicylates reportedly decrease tubular secretion of canrenone.[303] Spironolactone may cause a significant reduction in the total plasma clearance and volume of distribution of digoxin in adults, resulting in elevated serum digoxin concentrations.[290] More recent data in children ages 2 weeks to 3.5 years demonstrate that coadministration of spironolactone had no effect on serum digoxin levels.[157]

Clinically, spironolactone has been used effectively in premature infants, infants with bronchopulmonary dysplasia and CHF, children with hypertension, and in children with primary or secondary hyperaldosteronism and 11β-hydroxylase deficiency.[19, 27, 85, 96, 124, 144, 148, 194, 300] Spironolactone is a useful adjunct therapeutic agent in the treatment of familial male precocious puberty.[162] Mineral excretion in preterm infants treated with spironolactone (2 to 4 mg per kg per 24 hours) has been measured recently.[19] Hypercalciuria was observed in 25 per cent of the infants treated with spironolactone alone compared with 62 per cent of the furosemide-hydrochlorothiazide-spironolactone treated patients, 48 per cent of the hydrochlorothiazide-spironolactone treated patients, and 0 per cent of the control patients. Covariables associated with an increase in urinary calcium excretion were increased intake of calcium, sodium, and vitamin D, and increased urinary excretion of sodium and chloride. Excretion of magnesium was similar in all four groups. Mean sodium excretion was increased above control values in all three diuretic-treated groups.[19]

Amiloride and Triamterene. Like spironolactone, amiloride and triamterene have been used primarily to reduce potassium excretion in patients concurrently treated with thiazide or loop diuretics. Amiloride and triamterene have not been marketed for use in children, but have been used sporadically. Clinical observations in children treated with amiloride and triamterene will be discussed along with important data from studies completed in adults. Published pharmacokinetic and pharmacodynamic data for children are generally unavailable.

The oral bioavailability of amiloride in adults averages about 50 per cent (range: 30 to 90 per cent).[150, 176, 256, 305] In one study of healthy adults, apparent peak serum concentrations occurred 2 to 5 hours after a single oral dose of amiloride.[256] Apparent peak serum concentrations were delayed in adults with renal insufficiency, but not in patients with hepatic failure.[256] After an oral dose of amiloride, the onset of action usually occurs within 2 hours, and the peak diuretic effect is observed at 4 to 6 hours.[256] Amiloride is not believed to undergo biotransformation but is cleared primarily by renal excretion.[256, 305] The apparent volume of distribution of amiloride exceeds the total body water space.[176] Protein binding averaged 40 per cent at serum amiloride concentrations of 50 to 100 ng per ml.[256] In older studies of adult volunteers, the elimination half-life of amiloride varied from 6 to 9.5 hours.[150, 176] More recently, the terminal elimination half-life for amiloride has been shown to be substantially longer, averaging 20.8 hours in healthy adults.[256] The elimination half-life was slightly prolonged in patients with hepatitis and significantly prolonged in patients with chronic renal insufficiency, reaching 99 hours in one subject with a creatinine clearance of 22 ml per minute.[256] Although not well characterized, the duration of action of amiloride appears to be at least 10 hours and possibly as long as 24 hours.[176, 236, 256]

The apparent oral bioavailability of triamterene in fasted adults appears to be variable, ranging from 11.5 to 70 per cent.[120, 195, 217, 254] Triamterene is hydroxylated to form hydroxytriamterene, then rapidly conjugated to form an active sulfated metabolite, hydroxytriamterene sulfate.[120, 193, 254] Both hydroxytriamterene sulfate and triamterene are excreted in the urine, with a ratio of conjugate to parent drug of approximately 6 to 1.[254, 277] Under normal circumstances, triamterene is 55 to 65 per cent bound to plasma proteins, whereas hydroxytriamterene sulfate is approximately 90 per cent protein bound.[120, 155, 287] Apparent peak plasma concentrations of triamterene and hydroxytriamterene sulfate occurred at 1.23 and 1.34 hours, respectively, after administration of an oral dose to adult volunteers.[120] A reduction in the biotransformation of triamterene occurred in adults with cirrhosis, resulting in prolongation of the diuretic effect from 8 hours in healthy adults to 48 hours.[63, 287] As expected, renal insufficiency significantly reduces the clearance of hydroxytriamterene sulfate.[155] Because hydroxytriamterene sulfate retains diuretic activity, reductions in GFR are associated with a longer duration of diuretic activity despite the failure of triamterene to accumulate in serum.[155] Accordingly, dose adjustments must be made in patients with severe hepatic or renal dysfunction. Avoidance of both triamterene and amiloride in children with a GFR of less than 10 ml per minute has been recommended.[272]

Electrolyte excretion in children treated with amiloride and triamterene has not been extensively studied. In seven infants ages 6 to 47 days, oral administration of a single 20-mg dose of triamterene resulted in a significant increase in urinary excretion of sodium, and a slight but not statistically significant increase in urine flow rate.[295] A statistically significant reduction in potassium excretion was not demonstrated.[295] In adults, chronic administration of triamterene (200 mg per 24

hours) resulted in a significant increase in renal sodium clearance with a corresponding decrease in potassium clearance.[298] Additionally, calcium excretion was unaffected, whereas magnesium excretion increased significantly.[298] Other investigators report conflicting results (see discussion in Walker et al[297]). Controlled trials assessing the pharmacodynamics of amiloride in children have not been done. In adults, amiloride induces a mild natriuresis and antikaliuresis.[20] At lower doses, the natriuretic effect of amiloride appeared to last less than 24 hours, whereas at doses above 40 mg, the natriuresis was prolonged.[160] Amiloride induces a slight reduction in urinary calcium excretion, which appears to be additive to the reduction observed in adults and children treated with hydrochlorothiazide.[5, 168] The natriuretic and antikaliuretic effects of amiloride and triamterene are enhanced by concurrent therapy with thiazide or loop diuretics.

To some extent, the adverse effects of amiloride and triamterene overlap. Like spironolactone, both may cause hyperkalemia, especially in children with renal insufficiency. Concurrent administration of potassium supplements may contribute to the development of hyperkalemia. Triamterene and amiloride may cause nausea, vomiting, dizziness, and leg cramps. Laboratory abnormalities, including mild hyperuricemia and azotemia occasionally occur during therapy. Triamterene has been associated with several reports of urolithiasis in adults.[76, 157, 255] Rarely, photosensitive dermatitis and interstitial nephritis have been associated with triamterene use.[22, 81]

Few drug interactions between amiloride or triamterene and other agents are clinically important. Concurrent administration of ranitidine to healthy adults reduces the clearance of triamterene and hydroxytriamterene sulfate, resulting in a slight attenuation of the diuretic effect.[193] Cimetidine also has been shown to have a similar effect on the clearance of triamterene and hydroxytriamterene sulfate, although a statistically significant reduction in urine flow rate, natriuresis, or antikaliuresis could not be demonstrated.[188] Importantly, coadministration of hydrochlorothiazide and triamterene does not appear to affect the pharmacokinetics of either agent.[277] In healthy young adults, amiloride has been reported to increase renal clearance and decrease extrarenal clearance of digoxin, with the net effect of slightly decreasing the total body clearance of digoxin.[291] The positive inotropic effect of digoxin was slightly suppressed.[291]

Amiloride and triamterene are most often used to treat hypokalemia induced by thiazide or loop diuretics.[160, 181, 191] In children, hydrochlorothiazide and amiloride have been used to treat congenital nephrogenic diabetes insipidus and primary aldosteronism.[6, 99] Hypokalemia resulting from amphotericin B–related renal tubular injury has been successfully prevented by coadministration of amiloride.[231] Both triamterene and amiloride are used in adults to treat a wider variety of disorders including essential hypertension, hyperaldosteronism, ascites associated with cirrhosis, and edema associated with a variety of disorders.[63, 116, 176, 180, 181, 191, 286, 287]

SUMMARY

Selection of appropriate diuretic therapy in children is hampered by a lack of age-specific pharmacokinetic and pharmacodynamic data, especially in premature neonates. Well-designed clinical trials in neonates, infants, and younger children are necessary prerequisites to safer and more efficacious diuretic therapy.

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Review

Management of Sodium Abnormalities in Patients with CNS Disease

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Summary:

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Key Words: Hyponatremia—Hypernatremia—Antidiuretic hormone—Diabetes insipidus—Syndrome of inappropriate secretion of antidiuretic hormone—Natriuretic factors—Subarchanoid hemorrhage.

Sodium disturbances are surprisingly common in patients with CNS disease, reflecting the fact that the CNS plays an important role in the neuroendocrine regulation of sodium and water homeostasis. In addition, these patients are often subject to systemic disorders, trauma, surgery, chronic bedrest, and therapeutic maneuvers that can impact on sodium and water regulation. Therefore, when assessing an abnormal serum sodium concentration in patients with CNS disease, all these factors must be considered in developing an appropriate management strategy.

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Whereas an abnormal serum sodium concentration is often first noted with routine measurement of electrolytes, hyponatremia or hypernatremia may present with altered mental status, seizures, or dehydration. Appropriate management requires an understanding of the mechanisms that act to maintain sodium and water homeostasis. These mechanisms act to achieve two goals. The first is to maintain a tightly regulated concentration of solutes (osmolality) in the extracellular fluid (ECF). Sodium and its associated anions are the predominate ECF solutes, therefore, osmolality is usually reflected in the serum sodium concentration. Osmolality is controlled by tightly regulating the ECF water content. Since the cell membranes are freely permeable to water, the ECF osmolality controls the distribution of water between the intracellular and extracellular spaces and, therefore, cell size. Large deviations in ECF osmolality can result in cell shrinkage or swelling, as well as altered ~~intra~~inter cellular connections. These changes can dramatically alter cell function, especially in the CNS.

The second goal of the systems that regulate sodium and water homeostasis is to maintain normal intravascular volume. This is accomplished by controlling ECF sodium content. Since sodium is the major cation of the ECF and osmolality is maintained by regulating the water content, the ECF sodium content will determine its volume. Changes in ECF volume will produce secondary changes in intravascular volume.

Sodium disturbances in neurologic patients often result from abnormal central control of systemic water regulation (1). Recently, however, it has been recognized that sodium regulation is also disturbed in some patients with intracranial disease (2). This review will examine the mechanisms that regulate water and sodium homeostasis, discuss central disturbances commonly seen in patients with CNS disease, and present an approach to the evaluation and management of these ~~patients~~. disturbances.

REGULATION OF EXTRACELLULAR FLUID OSMOLALITY AND VOLUME

Sodium and volume are regulated by neural, humoral, and renal mechanisms that integrate information regarding ECF osmolality, intravascular volume, circulatory hemodynamics, and intake of sodium of water. These systems employ neural and humoral messengers to modify intake and excretion of sodium and water, and vascular tone. Whereas the regulation of sodium and water involve separate systems, they do not operate independently. Both respond to hemodynamic changes, and mediators from one system act to modulate the other.

Water Regulation

The body's water content is regulated by monitoring ECF osmolality, intravascular volume, and intravascular pressure. Under healthy conditions, osmolality is the major determinate of water balance and is maintained at ~285–295 mOsm (3). ECF hypo-osmolality represents an excess of solvent (water) relative to the number of osmotically active particles (solutes). This state is usually reached through an increase in the amount of water, but occasionally may result from a decrease

in the number of particles. Conversely, hyperosmolality is sensed by the body as a relative deficiency of water. The primary extracellular solutes are sodium, its anions (chloride and bicarbonate), glucose, and urea. Their contribution to ECF osmolality can be calculated with the following formula: [Na (mEq/L) × 2] + [glucose (mg%)/18] + [blood urea nitrogen (BUN, mg%)/2.8]. Mannitol and ethanol may contribute to osmolality in neurologic patients are not taken into account by this formula. When present, they produce a discrepancy between measured and calculated osmolality.

Changes in osmolality are monitored by specialized neurons (functionally defined as osmoreceptors) in the hypothalamus (4). When an osmotic gradient develops between the intracellular and extracellular compartments, water moves passively to maintain osmolal equilibrium. The osmoreceptors are capable of sensing these shifts. Changes in tonicity are communicated to the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. These neurons synthesize alcohol dehydrogenase (ADH) and transport it to the neurohypophysis (the posterior lobe of the pituitary) via their axons. Stimulation of this system by an increase in ECF osmolality of as little as 1% leads to release of ADH into the circulation (5). Maximal osmotic stimulation can produce plasma ADH concentrations of 10–15 pg/ml; concentrations fall to almost zero when osmolality is below ~280 mOsm/kg (6,7). Thus, the system is sensitive to changes in ECF tonicity that may result from changes in sodium or glucose concentration or administration of mannitol. Urea, on the other hand, will not produce a response since it crosses cell membranes and therefore does not produce an osmotic gradient or water shifts (Fig. 1).

The magnocellular neurons also respond to information regarding intravascular volume and pressure. Low- and high-pressure cardiac and vascular baroreceptors

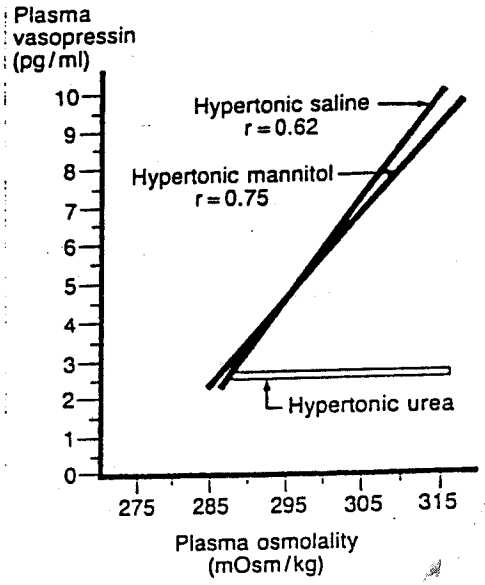

FIG. 1. Infusion of hypertonic saline or hypertonic mannitol solution increases plasma osmolality (horizontal axis) and leads to an increase in plasma vasopressin concentration (vertical axis). In contrast, hypertonic urea diffuses readily into the intracellular compartment and thus does not alter cell volume. Thus, there is a rise in plasma osmolality but no change in plasma vasopressin concentration. (Redrawn with permission from Robertson GL, Athar S, Shelton RL. In: Andreoli TE, Grantham JJ, Rector FC Jr, eds. *Disturbances in body fluid osmolality*. Baltimore: American Physiologic Society, 1977.)

sense blood pressure and volume. This information is transmitted via cranial nerves IX and X to relay stations in the brain stem (nucleus tractus solitarious) and finally to the hypothalamus (8). Whereas the system is insensitive to small changes in blood pressure or blood volume, input from baroreceptors indicating moderate-to-severe hypotension or hypovolemia can produce massive release of ADH (9). Baroreceptive stimuli can alter the slope and threshold of the ADH response to osmotic stimulation. Thus, in the setting of hypovolemia, higher levels of ADH are seen for a given osmolality. This is an attempt to preserve intravascular volume at the expense of hypo-osmolality.

Pain, stress, nausea, emesis, and hypoxia also stimulate ADH release (10). These inputs can produce high circulating levels of ADH in postoperative patients (11) and can result in hyponatremia lasting several days, especially if hyponatremic fluids are administered. Oropharyngeal stimulation appears to directly inhibit ADH release by a mechanism that is independent of changes in osmolality (12,13).

Circulating ADH acts on the kidneys (V_2 receptors) and blood vessels (V_1 receptors). ADH increases water permeability in the final portion of the distal tubule and collecting duct of nephrons. This results in water retention, a fall in ECF osmolality, and then a reduction in ADH secretion. ADH also acts to increase vascular resistance (14) contributing to the preservation of blood pressure during hypovolemia or hypotension. Despite maximal renal water conservation, water intake is essential to maintaining homeostasis. Thirst is controlled primarily by osmotic stimuli (3) but does not become an important stimulus until ADH levels have reached those that produce maximal renal water retention (15). However, thirst mechanisms are potent enough to allow an alert patient to maintain normal water balance during periods of inadequate release of ADH.

Sodium Regulation

Sodium regulation is directed toward the maintenance of adequate blood pressure and intravascular volume. These properties are monitored by a combination of high pressure (blood pressure) and low pressure (blood volume) baroreceptors located in the cardiac atria, pulmonary vasculature, aorta, and carotid and renal arteries (16). Hypothalamic centers integrate this information and utilize neural and humoral messengers to produce renal, vascular, and behavioral responses that act to preserve intravascular volume and blood pressure. In contrast to water regulation, there appear to be opposing systems that impact on sodium homeostasis. Two systems promote sodium retention and vasoconstriction: the renin-angiotensin-aldosterone system and the sympathetic nervous system. These are opposed by a third, less well-defined, natriuretic vasodilatory system, which may be mediated by atrial natriuretic factor (ANF or atriopeptin) and/or other natriuretic factors. In addition to antagonizing the physiologic effects of sodium-retaining hormones, ANF directly inhibits their release (17).

Renal baroreceptors located in the preglomerular arterioles respond to a decrease in blood pressure by stimulating secretion of renin. The sensitivity of these baroreceptors is regulated by distant as well as local factors. Sympathetic nervous

activity, transmitted via renal nerve, modulates renin release (18), as does the distal tubular sodium concentration, which is sensed by the macula densa region of the nephron (19). Renin stimulates the production of angiotensin II (via angiotensinogen and angiotensin I), which in turn is a powerful stimulator of aldosterone synthesis and secretion from the adrenal medulla. In addition, circulating angiotensin II induces drinking by stimulating receptors in the subfornical organ located in the third ventricle (20), and is a potent vasoconstrictor (21). Aldosterone acts in the distal tubule of the nephron to promote reabsorption of sodium in exchange for potassium and hydrogen ions. The actions of this system are summarized in Fig. 2.

The sympathetic nervous system also acts to promote sodium retention and vasoconstriction. It receives input from brain stem centers (22–24) about blood volume and arterial pressure, which is integrated with information on long-term sodium intake (25). Output from these centers is transmitted via the renal nerve and acts to modulate renin release as well as to directly regulate sodium reabsorption in the proximal tubule (26,27). Thus, neural mechanisms alter sodium excretion by both modifying the renin-angiotensin-aldosterone system and acting directly on the kidney.

The role of natriuretic factors may be to counteract the sodium-retaining vasoconstrictive systems by promoting sodium excretion and inducing vasorelaxation. The prototype, ANF, is released from the atria of the heart into the systemic circulation in response to increases in atrial pressure (28) (Fig. 3).

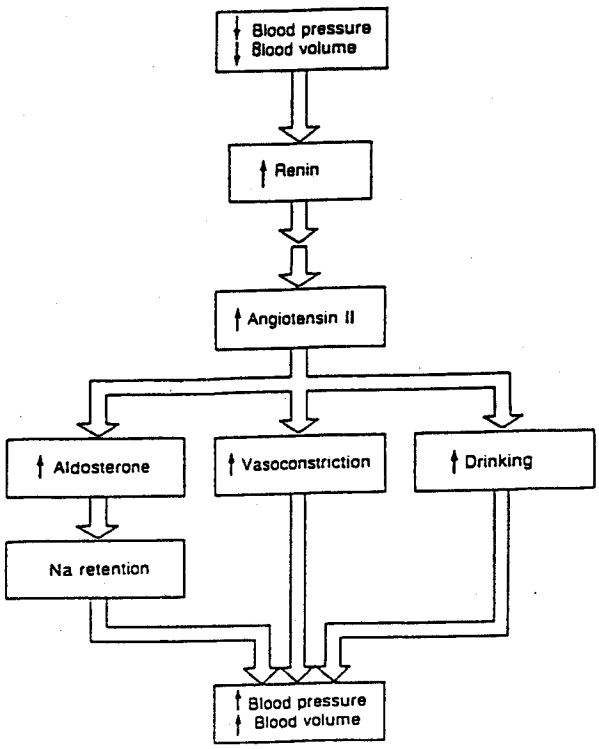

FIG. 2. Responses of the renin-angiotensin-aldosterone system to changes in blood pressure and volume. For details see text. (Reproduced with permission from Diringer MN. *Disburbances of sodium and water regulation. Critical Care Reports* 1:110–23, 1989.)

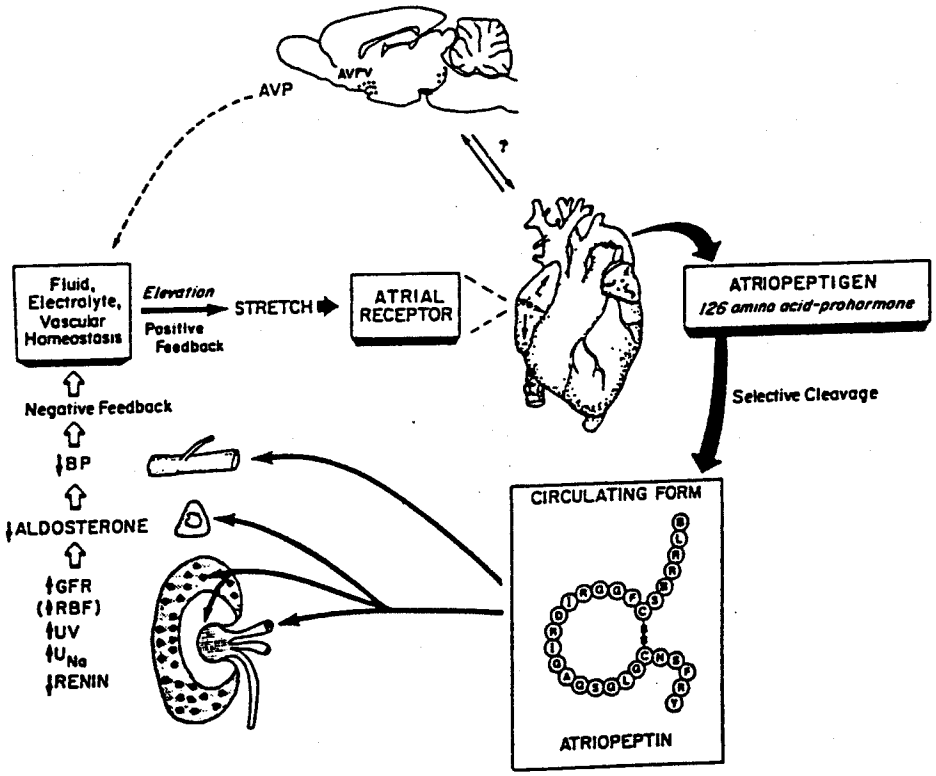

FIG. 3. The 126–amino acid prohormone atriopeptigen is stored in granules in atrial cardiocytes. Elevated intravascular volume results in release of atriopeptin (atrial natriuretic factor), which acts on kidney to increase glomerular filtration rate (GFR), renal blood flow (RBF), urine volume (UV), and sodium excretion (U_{NA}) and to decrease plasma renin activity. Natriuresis and diuresis are also facilitated by suppression of aldosterone and arginine vasopressin (AVP, antidiuretic hormone) release. Diminution of vascular volume provides a negative feedback that suppresses circulating levels of atriopeptin. BP, blood pressure; AVPV, anteroventral periventricular. (Reproduced with permission from Needleman P, Greenwald J. Atriopeptin: a cardiac hormone intimately involved in fluid, electrolyte, and blood-pressure homeostasis. *N Engl J Med* 1986;314:828–34.)

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Infusions have been shown to produce natriuresis and diuresis, relax vascular smooth muscle, and antagonize the release of ADH, renin, and aldosterone (29). ANF is also found in CNS centers that are involved in the regulation of cardiovascular, sodium, and volume homeostasis and may act as a neuromodulator in these centers (30). Central administration produces natriuresis and diuresis (31), inhibits angiotensin II–induced drinking (20), and inhibits ADH release (32). Thus, ANF acts both centrally and peripherally to promote sodium and volume loss directly and by antagonizing the opposing systems. There appear to be other central and peripheral natriuretic factor(s) that interfere with sodium transport by inhibiting sodium potassium adenosine triphosphatase (ATPase) and may play a role in regulating sodium homeostasis (33). Other potential regulators include brain natriuretic factor (34,35) and urodilatin, a natriuretic factor found in urine (36).

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HYPERNATREMIA

Pathophysiology and Manifestations

Hypernatremia results when there is a shift in the ratio of sodium to water that favors less water and/or more sodium. Extrarenal water loss due to sweating and diarrhea, renal loss of water through osmotic diuresis (diabetes mellitus, mannitol), lack of appropriate level of circulating ADH (central diabetes insipidus), or lack of a renal response to ADH (nephrogenic diabetes insipidus) can produce hypernatremia. However, hypernatremia will generally not develop when thirst mechanisms are intact and access to water is unrestricted. Primary hyperaldosteronism, Cushing's syndrome, and excessive sodium administration in hypertonic intravenous or oral solutions can result in hypernatremia through retention of sodium in excess of water.

A rise in ECF osmolality results in compensatory movement of water out of the cellular compartment with subsequent cell shrinkage. Although this has little effect on other organs, CNS function can be severely affected. However, within several hours the brain begins to adapt to this stress. The number of intracellular osmotically active particles is increased in order to draw in water and return cell size to normal. There are increases in intracellular sodium, potassium, and chloride (37), as well as the formation of idiogenic osmoles (38,39). However, it is interesting to note that this response may be limited to situations where hyperosmolality is caused by endogenous substances (sodium, glucose, urea) but not exogenous substances (mannitol, glycerol) (37,40,41). This phenomenon has important therapeutic implications. When the brain has been exposed to hypertonic conditions for several hours to days, it will be susceptible to cellular swelling from even isotonic solutions. Therefore, such patients should have their hyperosmolal state corrected very slowly, usually over 1–2 weeks.

In patients with CNS disease, hypernatremia usually results from the combination of insufficient release of ADH from the neurohypophysis and inadequate water intake due to disturbed thirst mechanisms (42) or limited access to water due to paresis, disorientation, or obtundation. Disturbed water regulation in adults is usually characterized by polyuria, thirst, polydipsia, and occasionally a preference for ice water (43). Children may present with vomiting, fever, and hypertonic dehydration (44).

The neurologic signs of hypernatremia include agitation, neuromuscular irritability, lethargy, coma, and seizures. Their severity is correlated with the degree and rapidity of onset of the hypernatremia. There may also be signs and symptoms characteristic of an underlying neurologic disorder. In rare cases, severe hypernatremia can result in brain shrinkage that is significant enough to produce mechanical disruption of blood vessels and hemorrhage (41).

Neurogenic Diabetes Insipidus

Neurogenic diabetes insipidus (DI) is characterized by excessive renal free water excretion due to a relative deficiency of circulating ADH. It is usually a manifestation of diseases that affect the optic chiasm or pituitary gland. Tumors

can produce chronic DI as they enlarge or, more frequently, following surgical resection (45). Pituitary adenomas and craniopharyngiomas are the most frequent tumors, however, pinealomas, dysgerminomas, epidermoids, meningiomas, metastases, and the histiocytoses can each present as a mass that can produce complete or partial DI. DI can occur with basilar inflammation from fungal or tuberculous meningitis, sarcoidosis, or syphilis. Vascular causes include expanding aneurysms, arteriovenous malformations, sinus thromboses, and intrathalamic hemorrhages. DI is common following head trauma and is frequently seen in brain death. Ethanol and phenytoin can produce DI by inhibiting the release of ADH (46). In addition, many cases of DI are idiopathic, usually occur in teenage boys, and are often permanent (47). Many of these patients have coexisting autoimmune disorders and circulating antibodies to ADH-secreting neurons (48).

Clinically, DI is characterized by hypotonic (osmolality <300 mOsm/kg or specific gravity <10.10) polyuria (>30 ml/kg/day) (49). Depending on the degree of impairment of ADH secretion, urine output can range from 3 to 20 L/per day. If capable, patients drink large volumes of water to compensate for losses. When water is denied them, if they become obtunded, or if the mass extends into the anterior hypothalamus and directly impairs thirst mechanisms, severe hypernatremia and hyperosmolality can develop.

DI may be the first clinical manifestation of a slowly developed CNS disturbance and present with polyuria and polydipsia. Alternatively, it may develop acutely as a secondary manifestation of cranial trauma or surgery. In most patients, the impairment of ADH release is incomplete. Clinically significant polyuria will not develop until ~75% of the ADH-secreting neurons are destroyed (50). Although some have postulated that there is a resetting of osmoreceptors, it is more likely that there is partial destruction of the osmostat (6,43). DI may also follow disruption of the axons of magnocellular neurons as they course through the median eminence or the nerve terminals in the neurohypophysis.

Surgical exploration of chiasmal tumors and head injury are often associated with DI. The disruption of ADH secretion is transient in 50–60% of cases. Polyuria develops in 12–24 h and normal osmoregulation returns in 3–5 days (51–53). Permanent DI develops in 30–40% of posttraumatic cases (54). In ~5–10% of patients, a triple response or DI with interphase is seen (Fig. 4) (55). This usually follows injury to the infundibular stalk due to severe head trauma or resection of large tumors. Initially, there is failure to release ADH. However, 2–5 days later there may be excessive release of ADH from degenerating cell bodies (52). The result is a period of high urine output from the initial absence of ADH release, then a period of water retention and hyponatremia due to the abrupt and unregulated release of large amounts of ADH from degenerating perikarya, followed by permanent DI. Persistent excessive water replacement or hormonal replacement with long-acting ADH preparations can complicate management of these patients and should be avoided (see below).

Evaluation and Management of Hypernatremia

When a patient presents with polyuria and already established hypernatremia, determining the etiology is relatively straightforward. The triad of hypernatremia,

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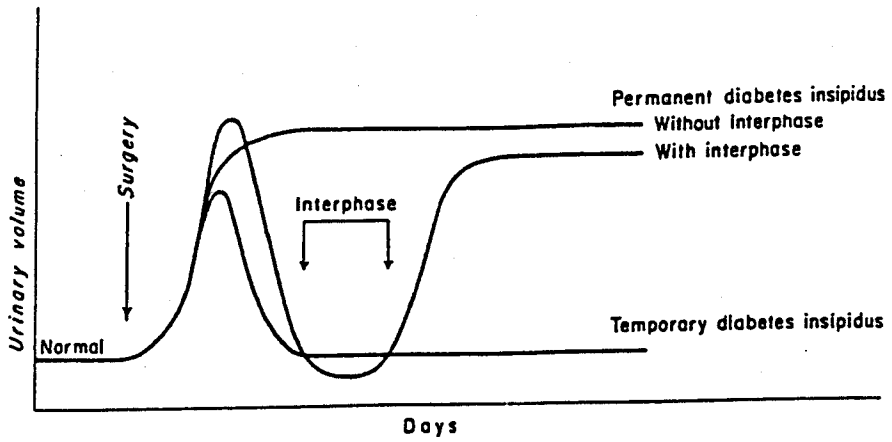

FIG. 4. Patterns of diabetes insipidus (DI) following pituitary surgery. Urine output may be elevated for a period of hours to days in temporary DI and remains elevated in permanent DI. In the case of permanent DI with interphase (triple response), urine output is initially elevated then falls below normal when there is massive unregulated release of antidiuretic hormone as magnocellular neurons degenerate. This is followed by permanent DI. (Reproduced with permission from Randall RV. Medical problems associated with pituitary operations. *Med Clin North Am* 1962;46:1037–43.)

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hypovolemia, and hypotonic urine indicates that the patient is unable to appropriately conserve water. The cause is either an impaired renal response to ADH (nephrogenic DI), insufficient release of ADH (neurogenic DI), or an osmotic diuresis. Nephrogenic DI can be congenital or acquired either through drug toxicity (lithium, demeclocycline, amphotericin B, gentamicin, glyburide, or furosemide) or renal disease. If appropriate, it can be distinguished from neurogenic DI by the lack of a response to administration of ADH (15). Osmotic diuresis may be due to administration of drugs such as mannitol and glycerol or a result of hyperglycemia that exceeds the renal threshold for conserving glucose.

Patients who have suffered head trauma or have undergone surgery for tumors located in or near the pituitary gland or hypothalamus are at risk for developing DI. Therefore, they require careful monitoring of fluid balance, urine specific gravity, and serum sodium concentration. Shortly after surgery or trauma, patients may develop a brisk urine output without a rise in serum sodium concentration. Given the potential for DI in these patients, the diuresis may represent the onset of inappropriate water loss. However, there are multiple potential causes of high urine output in these patients, therefore careful assessment is required. The diuresis may be an appropriate response to fluid administered during resuscitation from trauma or in the operating room. The high urine output could be a result of osmotic diuresis from hyperglycemia or administration of mannitol or glycerol. Diuretics may have been administered for treating increased intracranial pressure or the kidneys may have suffered a hypotensive insult. Therefore, there should be a careful assessment of previous administration of fluids and medications, blood pressure, body weight, and renal function. If any of these conditions are present, they should be corrected before diagnosing DI.

Once a diagnosis of neurogenic DI has been made, the treatment plan should

(1) Correct H_2O deficit as calculated
(2) maintenance fluids
(3) vasopressin if polyuria (> 300 cc/shift in adults generally)

reflect the acuity of the situation. Patients with chronic neurogenic DI usually require replacement therapy to control the polyuria and polydipsia so as not to interfere with daily activities. 1-Desamino-D-arginine vasopressin (dDAVP) is preferred because of its long duration of action and reduced pressor activity compared with vasopressin (56,57). It can be administered intranasally or by intravenous, intramuscular, or subcutaneous injections (57). Intranasal therapy usually begins with 2.5–10 μg at bedtime. The dose is increased by 2.5–5 μg every 1–2 days as needed (45). Many patients can be controlled with 2.5–15 μg of intranasal dDAVP twice daily (58). When administered by injection the same dose is used for the intravenous, intramuscular, and subcutaneous routes. Doses of 0.5–4.0 μg usually give an antidiuretic effect for 8–10 hours (57). careful

Treatment of acute DI requires ~~meticulous~~ management. Since the disturbance may have variable severity and duration, the use of easily controlled therapies is essential (59). Aggressive use of long-acting agents can produce severe hyponatremia and aggravate cerebral edema. This is particularly dangerous in a patient who may develop a triphasic response, especially if a long-acting agent is administered just prior to the phase characterized by massive unregulated release of ADH. Initial management of an alert patient with intact thirst mechanisms might be to allow the patient to regulate his or her own fluid intake. This may be all that is required if the disturbance is self-limited. Alternatively, intravenous fluids or aqueous vasopressin (see below) may be used if the polyuria and polydipsia is difficult to manage or the patient is not alert. If DI persists beyond a week, chronic therapy with long-acting agents should be instituted.

Patients who are obtunded or unable to sense thirst require meticulous monitoring of fluid balance, urine specific gravity, body weight, and serum sodium concentration. If urine volume is not excessive, replacement of urine output and insensible losses with intravenous fluids may be adequate. The choice of intravenous fluid depends on the serum sodium and intravascular volume. If the patient is volume contracted, normal saline should be used initially to replete the intravascular volume. Then the water deficit can be calculated as follows ~~(41)~~: Water deficit in liters = [0.6 × body weight (kg)] × (serum Na/140 − 1). Generally, half the losses should be replaced over 24 hours with hypotonic fluids (dextrose in water or 0.25% saline) and the remainder over 48 hours (45). If hypernatremia has not yet developed, then usually 0.5% or 0.25% saline is adequate replacement for urinary and insensible losses. Hormonal replacement with vasopressin in acute DI should be considered if urine output is >8 L/day. This procedure prevents the adverse consequences of polyuria that include washout of the concentrating ability of the renal medulla and loss of potassium, magnesium, and phosphate. Initial therapy should begin with aqueous vasopressin, which is rapidly absorbed from subcutaneous or intramuscular injections. Its peak action is in 1–2 hours and the duration of action is 4–8 hours. The usual starting dose is 2–5 U. The timing of subsequent doses is determined by urine volume, urine specific gravity, and serum sodium or osmolality. If the patient is allowed to develop hypotonic polyuria prior to each dose (urine volume >300 ml/h, specific gravity <1.005), this will confirm that DI persists in settings where the disturbance may be transient.

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An alternative is to employ a continuous intravenous infusion of vasopressin. This method is especially useful in patients who are hemodynamically unstable or have a fluctuating requirement for ADH replacement. The infusion can be made by diluting 1–2 U of aqueous vasopressin in 1 L of intravenous fluid (choice of fluid depends on plasma sodium concentration) and infusing the solution at a rate that equals the last hours' urine output plus 10%. This replacement of ADH and urinary losses, along with serial urine specific gravity and serum sodium assessments, achieves tight control over water balance. The infusion concentration or rate can be adjusted to achieve a desired serum osmolality and urine output. Another option is to begin a vasopressin infusion at 2.5 U/h, which is then adjusted to achieve normal urine output and serum sodium concentration. In this case additional fluids will be necessary for replacing urinary and insensible losses. Once the ADH requirement stabilizes, chronic therapy can be instituted.

HYPONATREMIA

Pathophysiology and Manifestations

Hyponatremia develops when there is an excess of ECF water relative to sodium. This can occur in states where there is an increase in body water content along with a lesser increase in sodium content, as in congestive heart failure and cirrhosis. The mechanism appears to be a reduction in effective arterial blood volume that stimulates release of ADH and aldosterone and increases sympathetic nervous system activity (60). Hyponatremia can also exist with an increase in water content and no change in sodium content. This situation occurs when there is nonosmotic release of ADH stimulated by pain, stress, and drugs; or in the syndrome of inappropriate secretion of ADH (SIADH). Hypovolemia and hypotension, regardless of sodium concentration, stimulate ADH secretion. In this situation, ADH release is an appropriate response to intravascular volume and blood pressure stimuli but inappropriate for osmotic regulation. ECF volume depletion from gastrointestinal and renal losses of sodium in excess of water can also produce hyponatremia. Renal loss may be due to diuretic excess (especially thiazides), mineralocorticoid or glucocorticoid deficiency, hypothyroidism, salt-losing nephritis, or possibly elevated levels of circulating natriuretic factors.

Postoperative patients are at relatively high risk for hyponatremia, which develops in ~4% of cases (61). They have multiple stimuli for ADH release including stress, nausea, volume contraction, and medications. Symptomatic hyponatremia resulting in permanent brain damage in healthy individuals has been reported to occur more frequently in women who receive hypotonic fluids during the postoperative period (62). — hyponatremia

ECF hypo-osmolality results in cellular swelling and brain edema (63–65). If this occurs rapidly it can lead to herniation and brain death. However, the acute increases in brain intracellular volume are modified over time (65) by reducing intracellular potassium (63). This results in a reduction of cell size back to normal. The process may be modified by estrogens and that might account for the predominance of permanent brain damage in premenopausal women (62).

Symptoms of hyponatremia result from cellular hypo-osmolality and include

muscle cramps, weakness, confusion, disorientation, seizures, and coma. Although there is a correlation between symptoms and degree of hyponatremia, the rapidity with which the hyponatremia develops is generally considered an important determinate of clinical symptoms (61,66–69). Some feel that the most important determinate is the interplay between increases in brain water and loss of brain electrolytes (64). Others feel that gender and age are the most important factors, since the vast majority of patients with permanent brain damage are premenopausal women (62).

SIADH is a major cause of hyponatremia in patients with CNS disease. Almost any CNS lesion can disrupt the regulation of release of ADH and lead to excessive water retention and dilutional hyponatremia. There have, however, been reports of centrally mediated renal sodium wasting (cerebral salt wasting) as a cause of hyponatremia (70–72). Although the existence of this syndrome remains controversial (73), negative sodium balance has been implicated in hyponatremia following subarachnoid hemorrhage (2,74–76).

Syndrome of Inappropriate Antidiuretic Hormone

SIADH is a disorder of osmoregulation (water regulation) without a primary disturbance of sodium regulation. The usual clinical presentation of SIADH is in one of three disease groups: carcinomas, pulmonary disorders, or CNS disorders. SIADH can be seen with almost any CNS disorders including head trauma, infections, tumors, cerebrovascular disease, as well as Guillain-Barré syndrome. Medications that can produce this syndrome include oral hypoglycemic agents, general anesthetics, chemotherapeutic agents, sedatives, opiates, and carbamazepine (77).

Several patterns of disturbed osmotic regulation of ADH release have been described in SIADH (6): erratic release of ADH independent of osmolality, failure to suppress ADH release at low osmolality but normal regulation at higher osmolalities, resetting of the osmostat, and impaired water excretion without detectable circulating ADH. The pathophysiology of the fluid and electrolyte abnormalities are basically the same for all forms of the syndrome (6). There is excessive water retention by the kidney producing a dilutional hyponatremia and ECF volume expansion. It is important to note, however, that ADH release alone will not result in hyponatremia unless there is continued intake of water (78). Since sodium regulation is unaffected, volume expansion results in increased urinary sodium excretion until intravascular volume returns to normal (79). This accounts for the "salt wasting" phase of SIADH. Once intravascular volume returns to normal, sodium excretion reflects sodium intake (69). While this phase has been associated with elevated levels of ANF (80–82), its role in the natriuresis remains unclear (81).

The diagnostic criteria for SIADH include hyponatremia with hypo-osmolal serum, inappropriately concentrated urine, continued sodium excretion (urinary sodium >25 mEq/L) and the exclusion of renal or endocrine disease (hypothyroidism or hypoadrenalism). There must also be an absence of stimuli that produce nonosmotic release of ADH such as hypovolemia, hypotension, pain, stress, and nausea.

Cerebral Salt Wasting

Early reports of patients with intracranial disease and hyponatremia emphasized the relationship to natriuresis and volume contraction (70,71,83). These reports suggested that excessive renal sodium excretion was the result of a centrally mediated process that was termed *cerebral salt wasting*. The patients were unresponsive to replacement with glucocorticoids or mineralocorticoids and could be corrected only by administration of large amounts of saline. Recent reports have described a similar picture (84,85). While the existence of this condition is a matter of debate, there appear to be some patients with CNS lesions who spontaneously develop hyponatremia and volume contraction when normal maintenance amounts of fluids and sodium are administered (72).

Hyponatremia following Subarachnoid Hemorrhage

Hyponatremia frequently develops following aneurysmal subarachnoid hemorrhage (SAH) (86,87); however, its etiology has not been clearly established. Initially SIADH was considered the cause of hyponatremia following SAH (88–90). However, this was questioned when it was found that hyponatremia was associated with intravascular volume contraction (91), a feature that is inconsistent with SIADH. Approximately 30–50% of SAH patients become volume contracted when given maintenance volumes of fluids, and hyponatremia is associated with a negative sodium balance (74,92,93). This distinction has important clinical implications. Patients with hyponatremia SAH treated with fluid restriction for presumed SIADH ~~have~~ had a much higher incidence of infarctions than those hyponatremic patients who ~~are~~ were not fluid restricted (76). Measurements of ANF (74,94–97), sodium balance, and plasma volume (74) have been unable to definitively establish the mechanism(s) responsible for hyponatremia and volume contraction following SAH. Interpretation of ADH levels has been difficult since elevated levels could result from volume contraction with or without a superimposed disturbance in osmotic regulation of ADH release. Hypervolemic therapy is now well accepted in the treatment of vasospasm. The impact of the treatment on hyponatremia and volume contraction has recently been studied. Prophylactic hypervolemic therapy was found to prevent volume contraction but not hyponatremia (98). In this series, euvolemic hypo-osmolal patients had inappropriately elevated levels of ADH, suggesting that SIADH does play a role in the development of hyponatremia in SAH.

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Evaluation and Management of Hyponatremia

Evaluation of a patient with hyponatremia should consider the clinical situation, state of sodium and water regulation, and possible confounding conditions. Historical data should be reviewed for determining if there is a possibility of heart failure, cirrhosis, renal disease, endocrinopathy, diuretic use, diarrhea, vomiting, recent surgery, or trauma. Oral intake and the quantity and type of recent intravenous fluid administration should be ascertained.

Comparison of measured and calculated serum osmolality will determine if the

hyponatremia results from the presence of additional osmoles in the blood such as mannitol and glucose. Determination of urinary osmolality is essential since it represents the end point of osmoregulation and reflects the level of plasma ADH, the ability of the kidney to respond to ADH, and the efficacy of renal concentrating and diluting mechanisms. Urine sodium content gives an indication of sodium excretion. It is best interpreted in relation to intravascular volume, which can be roughly estimated by considering heart rate, central venous pressure, pulmonary capillary wedge pressure, and orthostatic blood pressure changes. This information is usually sufficient for excluding cardiovascular, liver, renal, or endocrine causes of hyponatremia. If doubt remains, further tests may be indicated. Renal function can be assessed by determining creatinine clearance. Hypoaldosteronism is suggested by hyponatremia, hyperkalemia, and dehydration and could be confirmed by measuring circulating aldosterone. A morning cortisol level and free thyroxine index can help evaluate adrenal and thyroid functions that impact on sodium regulation.

An appreciation of the course of the change in sodium concentration is an important consideration in evaluating patients and planning their therapy. Most authors feel that the severity of symptoms, and thus the urgency of intervention, is related to the rate of the change in serum sodium (61,66–69). A patient with a sodium level of 120 mEq/L that has developed over several weeks will most often be asymptomatic and can be managed conservatively. On the other hand, the same sodium concentration that has developed over several hours can be life threatening and can require aggressive intervention. However, some feel that age and gender are the most important factors in predicting if ~~symptoms~~ brain damage will develop (62). The final determinate of the urgency of intervention should be the patient's neurologic status, as it reflects the severity of CNS involvement and thus the rapidity with which treatment is needed.

The management of symptomatic hyponatremia is controversial. The debate centers around which is potentially more harmful to the patient: the risk of CNS damage from the hyponatremia or the risk of CNS damage (central pontine myelinolysis) from rapid correction of the hyponatremia. Central pontine myelinolysis is a demyelinating syndrome, often restricted to the pons, originally described in alcoholic and malnourished patients (99). While the majority of patients with central pontine myelinolysis had normal serum sodium concentrations (100), there have been numerous reports associating the condition with hyponatremia and its treatment (101–106). What remains unclear is whether the disorder results from too rapid correction of hyponatremia (104,106–108), overcorrection of serum sodium concentration (109–111), hyperosmolality independent of hyponatremia (110), or associated factors such as hypoxia (101) or liver disease (101,112). On the other hand, hyponatremia producing severe neurologic symptoms (intractable seizures or coma) that is not treated promptly usually results in permanent damage (62,64). This is not surprising since progressive cerebral edema producing severe neurologic symptoms, if unchecked, can result in herniation. Therefore treatment should favor rapidly reversing a situation that has a high potential for permanent sequela. However, this approach does not preclude taking steps that would reduce the possibility of causing central pontine myelinolysis. A rational

approach to treating a symptomatic hyponatremic patient (100) would be raising the serum sodium concentration fairly rapidly (~1 mEq/L/h) to moderately hyponatremic levels (125–130 mEq/L) in order to rapidly reduce cerebral edema. Then the rate of correction should be slowed and overcorrection rigorously avoided.

Most cases of acute symptomatic hyponatremia that require rapid correction result from water excess, therefore, facilitating the excretion of water is the appropriate therapy. This is best achieved with the administration of loop diuretics (furosemide) and hypertonic saline. The diuretic produces a renal loss of free water that is replaced with a hypertonic solution (113). The use of osmotic diuretics to promote loss of free water in the urine has been advocated and may be as effective as loop diuretics (114,115). Administration of hypertonic saline alone will raise serum sodium levels, but the response is transient in SIADH because the infused sodium is rapidly excreted in the urine (116). The amount of sodium required to raise the serum sodium concentration to a desired level can be estimated from the formula: sodium required (mEq) = [rise in sodium concentration (mEq/L)] × ECF volume. The ECF volume is estimated by multiplying the body weight (in kilograms) by 0.6. However, this formula gives only a rough estimation since the sodium is being administered with water and there are ongoing sodium and water losses. The formula is useful however, for estimating the initial rate of the hypertonic saline infusion but not necessarily the total amount required.

The choice of the tonicity of the fluid administered is somewhat arbitrary. Concentrations of 3% or 5% sodium chloride have been traditionally used, but any hypertonic concentration can be employed. The rate of infusion should be adjusted based on frequent (initially hourly) determinations of serum sodium concentration. Care must be employed when administering hypertonic solutions. They carry a risk of hemolysis and therefore should be administered through a central venous catheter. Hypertonic solutions rapidly produce shifts of water into the ECF and vascular compartments that can precipitate fluid overload, especially in patients with poor cardiac or renal function. Monitoring of intravascular pressures and concurrent administration of diuretics should help control this problem.

Once an intermediate level of hyponatremia is achieved, fluid restriction can be substituted. This requires that total intake must be less than the combined renal and insensible losses and raise osmolality by only 1–2% per day (6). Some patients do not tolerate this level of fluid restriction or may require larger volumes of fluid (for administration of antibiotics or parenteral nutrition). In that setting continued administration of isotonic or hypertonic saline and diuretics may be necessary. Alternatively, medications that inhibit ADH release of its action on the kidneys can be administered (see below).

Often SIADH is self-limited in neurologic patients. Therefore, if tolerated, a period of fluid restriction may be definitive therapy. Periodically the restriction can be lifted and the response noted. If hyponatremia reappears, fluid restriction should be reinstituted or other measures employed. In chronic cases drugs may be useful. Phenytoin is reported to inhibit ADH release, however, it is usually not effective in treating SIADH (117). Lithium carbonate is useful because it inhibits the renal response to ADH. The recommended initial dose is 900–1,200 mg daily,

but the optimal dose is not known and it has potential for CNS, renal, and cardiac toxicity (77). Demeclocycline hydrochloride also inhibits the renal response to ADH. The recommended initial dose is 1,200 mg/day, which should be reduced to the lowest effective dose once an effect is seen (118). It usually takes 3–6 days for urine osmolality to fall and 1–2 weeks before polyuria becomes evident. At that point the patient must be allowed free access to water to prevent hypernatremia and volume contraction (77). In a trial comparing demeclocycline and lithium, demeclocycline was usually effective and had few adverse effects, whereas lithium was found not to be reliably effective and produced CNS toxic effects in a majority of patients (119).

The management of asymptomatic hyponatremia, irrespective of the severity, should be conservative. If the hyponatremia is associated with intravascular volume contraction and secondary release of ADH, treatment should consist of volume replacement with isotonic saline. Once the intravascular volume is normalized, the stimulus to ADH release will be eliminated. The patient will excrete the excess water, and the hyponatremia will be corrected. If the etiology is SIADH, then fluid restriction will slowly correct the hyponatremia or medications can be employed.

Rarely, patients who are believed to have SIADH do not respond to the usual therapy. If they clearly demonstrate continued excretion of large volumes of urine with a high sodium content, volume contraction, and worsening hyponatremia, they may be considered to have cerebral salt wasting (72). Initial management of these patients consists of correcting the volume contraction and hyponatremia with hypertonic saline. Once the patient is clearly euvolemic and normonatremic, a second trial of fluid restriction should be instituted. If the same pattern recurs, then they should be managed by continued administration of sufficient isotonic or hypertonic saline for maintaining an even fluid balance, normal sodium concentration, and stable body weight. This condition is rarely seen and is usually self-limited.

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Hyponatremia in SAH patients requires consideration. There appears to be a relationship between hyponatremia, negative sodium balance, and volume contraction (2,74,120). Fluid restriction is associated with an increased incidence of cerebral infarctions (76). Recently, because of the appreciation of the relationship between intravascular volume and cerebral vasospasm, the approach to management of SAH has shifted from an emphasis on fluid restriction to volume expansion, especially in patients with symptomatic vasospasm (92,121,122).

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Careful monitoring of fluid balance, intravascular pressures, and body weight are essential in patients with SAH. A recent series found that hypervolemic therapy prevented volume contraction but not hyponatremia and that there was inappropriate secretion of ADH (98). However, the hyponatremia was mild (125–132 mEq/L) and did not appear to impact on the clinical course of the patients. This finding may be due to the fact that free water intake was limited in these patients. Therefore, given the risk of vasospasm, it seems preferable that maintenance of intravascular volume take precedence over treatment of potential SIADH with fluid restriction. The use of isotonic fluids may prevent severe symptomatic hyponatremia. Should severe hyponatremia develop, treatment with hy-

pertonic saline may be useful. Diuretics may be of additional benefit but extreme care should be taken for avoiding volume contraction. In addition, it has been suggested that fludrocortisone is useful in reversing the negative sodium balance and volume contraction (123). Unfortunately, this agent has a slow onset and long duration of action and is therefore difficult to manage.

In summary, most sodium disturbances in patients with CNS lesions result from disturbed water regulation. Possible systemic and iatrogenic causes must be evaluated prior to treatment. Insufficient secretion of ADH leads to hypernatremia if fluid intake is inadequate and can be treated with either fluid or hormone replacement. Care must be exercised in patients with acute DI because of the potentially variable and transient nature of the disturbance. Hyponatremia usually results from inappropriate secretion of ADH and should be managed aggressively in symptomatic patients with loop diuretics and hypertonic saline. However, very rapid correction or overcorrection should be avoided. Patients with SAH and hyponatremia should not have fluids restricted because of the risk of exacerbating vasospasm but rather be treated with large volumes of isotonic saline.

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CURRENT CONCEPTS

JANE F. DESFORGES, M.D., *Editor*

EMERGENCY MANAGEMENT OF BLUNT TRAUMA IN CHILDREN

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DESPITE recent advances in prevention and treatment,[1] trauma remains the leading cause of death among North American children over the age of one year.[2] Blunt head injuries from motor vehicle collisions cause most of the deaths and injuries,[2-4] but penetrating injuries are increasingly prevalent in large cities.[5,6] Most preventable deaths are caused by acute respiratory failure due to airway obstruction or pneumothorax, unrecognized or inadequately treated intraabdominal bleeding, or secondary brain injury caused by an expanding intracranial hematoma, hypoxia, or shock.[7] The goal of emergency management is to detect and treat these and other immediate threats to life. This article is intended to guide practicing physicians through this important stage in the care of injured children. It discusses injuries caused by blunt physical forces, not penetrating injuries, drowning, burns, or poisoning.

ASSESSMENT

Definition and Scoring of Trauma

Multiple trauma has been defined as substantial injury to more than one organ system or life-threatening injury to a single system.[8] The recognized standards for describing injuries are the Abbreviated Injury Scale and its derivative, the Injury Severity Score,[9,10] which classify injuries according to anatomical site and severity. Neither is used clinically, however; instead, the Pediatric Trauma Score[11] (Table 1) and the Revised Trauma Score[12] (Table 2) are used in the field or the emergency department to predict the severity of injury. Children with a Pediatric Trauma Score ≤8 or a Revised Trauma Score ≤11 should be treated in a designated trauma center.[12] Regardless of their trauma scores, children who sustain a high-energy impact — in motor vehicle collisions or falls from heights, for example — should also be carefully assessed for possible life-threatening injuries.

Trauma Team

Most pediatric trauma centers have a team responsible for the initial care of children with major trauma. A specialist in general surgery (the team leader) and specialists in emergency medicine, anesthesiology, radiology, orthopedic surgery, and trauma nursing are often included. In some centers, emergency pediatricians respond first and are the leaders of the trauma teams.[13] Even hospitals without a caseload large enough to require a trauma team should have written protocols that define major trauma, criteria for activating the response to trauma, procedures for initial management, and criteria for transfer to a referral center.[14]

Transfer between Hospitals

Transfer to a trauma center should begin with a telephone consultation between the referring and receiving physicians. The condition of the patient should be fully stabilized (as outlined below) before transfer. Patients at risk for airway compromise, especially those with diminished consciousness, require endotracheal intubation before transfer, even if this means that paralyzing drugs must be given. Only rarely are surgical procedures such as laparotomy or the creation of cranial bur holes needed before transfer. The personnel accompanying the patient must be familiar with the equipment and working environment of the transfer vehicle and must be able to monitor the patient's condition accurately and perform any necessary procedures.

Anatomical and Physiologic Features

Because a child's head is large relative to the trunk, it is often the leading contact point on high-speed impact. The cranium is thinner and the brain less myelinated than in adults, and thus milder forces produce more severe injuries.[15,16] On the other hand, children, with open sutures, larger subarachnoid space and cisterns, and greater extracellular space in the brain, tolerate an expanding intracranial mass or brain swelling better. Since their body-surface area is large relative to their body-cell mass, children are more likely than adults to have hypothermia. The glottis lies in a more anterior and superior position in the pharynx, favoring orotracheal over nasotracheal intubation for airway control. The airway is narrowest at the cricoid level, so uncuffed endotracheal tubes are used until children reach the age of eight years.[17] The relative shortness of the trachea increases the risk of endobronchial intubation or accidental extubation. Because of age-related differences in size and physiologic norms, successful resuscitation requires equipment in a wide range of sizes and dosing according to weight and age.[15] The following relations are useful in establishing the norms. A child's weight in kilograms is approximately twice the age in years plus 8. Blood volume is approximately 80 ml per kilogram of body weight. The internal diameter of the endotracheal tube (in millimeters) should equal 4 plus one quarter of the age in years. Systolic blood pressure (the 5th percentile) is approximately 70 plus twice the age in years.

MANAGEMENT

Management requires an organized approach combining diagnosis and treatment. The recommended sequence is that first described by the Committee on

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Table 1. Pediatric Trauma Score.*

Variable	+2	+1	−1
Weight (kg)	>20	10–20	<10
Airway patency	Normal	Maintained	Unmaintained
Systolic blood pressure (mm Hg)	>90	50–90	<50
Neurologic status	Awake	Obtunded	Comatose
Open wound	None	Minor	Major
Skeletal trauma	None	Closed	Open or multiple

*A score of +2, +1, or −1 is given for each variable listed. The scores are then added (range, −6 to +12). A score ≤8 indicates potentially important trauma.

are four distinct phases: the primary survey, resuscitation, the secondary survey, and definitive care. During the primary survey and resuscitation, the patient's condition is stabilized by identifying and correcting immediate threats to life — inadequate gas exchange (the airway and breathing), and inadequate perfusion of vital organs (the circulation).[19] During the secondary survey all important injuries are identified by a thorough head-to-toe examination, and a plan of definitive treatment is developed.

Primary Survey and Resuscitation

The Airway and Cervical Spine

Airway obstruction is the most frequent source of ventilatory failure,[20] so airway patency should always receive the highest priority. Because of the relatively large tongue and narrow oropharynx, the mandibular block of tissue easily obstructs the airway in an unconscious child. Blood, vomitus, teeth, orthodontia, dirt, and other debris may also cause obstruction. Assess the airway by answering these questions: Can the patient phonate? Is air moving in and out? Is breathing labored or stridulous? Does the patient have cyanosis?

Establish an airway by positioning (lifting the chin or thrusting the jaw), suctioning, inserting an oropharyngeal airway or endotracheal tube, or all three. Whenever possible, administer 100 percent oxygen to the patient with a bag–valve–mask apparatus before attempting to intubate the trachea. Endotracheal intubation provides the most reliable airway. Early orotracheal intubation is indicated when the injured child is unable to maintain an adequate airway or breathe independently or is in uncompensated shock, or to facilitate hyperventilation when there is head injury with a Glasgow coma score ≤8.[21] As a last resort, needle (in children under 12 years old) or surgical (in those 12 or older) cricothyrotomy or tracheostomy may be required. Monitor the adequacy of oxygenation and ventilation by obtaining arterial blood gas measurements, or use noninvasive methods such as pulse oximetry and end-tidal carbon dioxide measurements.

Although injury to the cervical spine is uncommon in children who survive an injury,[22,23] the neck should be immobilized in all seriously injured children until spinal damage can be excluded. When intubation is indicated before the cervical spine has been fully evaluated, stabilize the neck manually during laryngoscopy.[17,19]

Table 2. Revised Trauma Score.*

Revised Trauma Score	Glasgow Coma Scale	Systolic Blood Pressure	Respiratory Rate
		mm Hg	*beats/min*
4	13–15	>89	10–29
3	9–12	76–89	>29
2	6–8	50–75	6–9
1	4–5	1–49	1–5
0	3	0	0

*A score of 0 to 4 is given for each of the three variables (Glasgow Coma Scale, blood pressure, and respiratory rate). The scores are then added (range, 0 to 12). A score ≤11 indicates potentially important trauma.

Breathing

After airway obstruction, pneumothorax and hemothorax are the most common causes of ventilatory failure.[24] Assess breathing by answering these questions: Is the chest expanding adequately and evenly? Is the trachea in the midline? Are the breath and heart sounds normal and bilaterally equal? Are the neck veins distended? Is the respiratory rate appropriate? Does the patient have cyanosis? Signs of respiratory distress include tachypnea, the use of accessory muscles, head bobbing, and flaring of alae nasi. Cyanosis is a late sign of respiratory failure.[17] Treat apnea or hypopnea immediately with 100 percent oxygen and ventilation with a bag–valve–mask apparatus, followed by endotracheal intubation.

Tension pneumothorax produces cyanosis, distended neck veins, mediastinal shift, and ipsilateral decreased breath sounds and hyperresonance. Diagnose tension pneumothorax clinically and treat it immediately, before obtaining a radiograph. First, relieve the tension by inserting an over-the-needle catheter into the second thoracic interspace in the midclavicular line. Then insert a chest tube at the nipple level in the anterior-to-midaxillary line.[19]

Circulation

Shock is a pathologic state characterized by tissue perfusion that is inadequate to meet metabolic demands.[17] The causes of shock in an injured child include internal or external bleeding, tension pneumothorax, pericardial tamponade, and injury to the brain stem or upper cervical spinal cord. Compensated shock occurs when there has been substantial blood loss but blood pressure has been maintained by reflex tachycardia and vasoconstriction. Blood pressure may not fall until the child has lost more than 25 percent of the volume of circulating blood.[15] Diagnose shock according to its clinical features: thirst, tachycardia, weak peripheral pulses, and poor peripheral perfusion. Hypotension, altered mental status, and the absence of peripheral pulses herald uncompensated shock and imminent cardiopulmonary arrest.

Begin the treatment of shock by inserting two large-bore intravenous cannulae. For initial resuscitation of

a small child, a 20- or 22-gauge cannula is usually adequate. Tibial intraosseous infusion provides quick access for rapid fluid resuscitation and the administration of drugs.[25] This technique is effective, is easy to learn, can be used in the field,[26] and is most applicable in children up to the age of six years. It is contraindicated in a fractured limb. Rapidly infuse isotonic crystalloid solution (normal saline or Ringer's lactate solution), using an initial bolus of 20 ml per kilogram of body weight over a period of 10 minutes. Repeat once if needed. Use packed red cells in boluses of 10 ml per kilogram, with normal saline, plasma, 5 percent albumin, or reconstituted whole blood in boluses of 20 ml per kilogram for additional volume replacement. Failing to switch to blood after two boluses of crystalloid solution can cause profound anemia due to hemodilution. Apply direct pressure to stop external bleeding, and splint obvious fractures. Pneumatic antishock garments have limited indications,[27,28] but they may temporarily preserve central blood pressure in patients near cardiac arrest from hypovolemia and can control bleeding in severe pelvic fractures before definitive surgical or orthopedic treatment.

Failure to reverse the signs of shock usually indicates ongoing bleeding and often the need for a laparotomy, especially if the abdomen is distended. Occasionally, another explanation will be found, such as spinal shock,[29] tension pneumothorax, cardiac injury, or cardiac tamponade. One or more of the elements of Beck's triad (increased venous pressure, hypotension, and distant or muffled heart sounds) and pulsus paradoxus can indicate cardiac tamponade,[30] which may be relieved temporarily by pericardiocentesis, followed by an urgent thoracotomy for definitive repair. In a child who has had shock the vital signs, urinary output, temperature, and arterial oxygen saturation should be monitored. Refractory shock may also require invasive monitoring of central venous and arterial pressure.

Completing the Primary Survey

Perform a brief neurologic examination, including measurement of pupillary size, response to light, and level of responsiveness (alert, responsive only to verbal or painful stimuli, or unresponsive). Remove any remaining clothing to inspect the entire body. Because small children are especially susceptible to hypothermia, insert a rectal probe for continuous monitoring of the temperature. Maintain normothermia, using overhead heaters, heating mattresses, blankets, warm intravenous solutions, and blood warmers as needed. Apply electrodes for continuous electrocardiographic monitoring. Perform a rectal examination to assess rectal tone and the location, size, and consistency of the prostate. Examine the stool for blood. In the absence of specific contraindications, insert a nasogastric or orogastric tube and a bladder catheter. The production of 1 to 2 ml of urine per kilogram per hour indicates adequate fluid resuscitation. If there are signs of urethral injury (inability to void, blood at the urethral meatus, perineal or scrotal bruising, or elevation of the prostate), do not insert a bladder catheter. Instead, obtain a retrograde urethrogram using fluoroscopy.[30] Perform a complete blood count, type and crossmatch, and measure amylase, electrolytes, glucose, urea, and creatinine. Order studies of arterial blood gases, coagulation, and liver enzymes as clinically indicated.

Obtain a brief history using the AMPLE mnemonic: allergies, medicines, past medical history, last meal, and events leading to the injury. Be alert to the possibility of child abuse, especially in infants. Ask the ambulance crew about the mechanism of injury, the child's response, treatment given, and the time since injury. Finally, keep the family informed, and allow a brief visit with the injured child as soon as possible.

Secondary Survey and Definitive Treatment

The secondary survey is a systematic physical examination of all body organs, supplemented by appropriate diagnostic imaging. Frequent repeated assessment of the vital signs and level of consciousness is essential at all times.

Examination

Inspect and palpate the face and scalp carefully for contusions, lacerations, and fractures. Battle's sign (bruising of the mastoid process), raccoon eyes, cerebrospinal fluid otorrhea or rhinorrhea, and hematotympanum indicate basal skull fracture. Examine the eyes for hemorrhage, visual acuity, and corneal reflexes. Inspect the teeth for fractures and avulsions. Document cortical function using the Glasgow Coma Scale (Table 3).[31] Several modifications of the scale have been suggested for children who do not yet talk,[32,33] although none have been validated. The most important indicator of intracranial bleeding and the need for immediate neurosurgical intervention is a decrease in the level of consciousness. This is best docu-

Table 3. Glasgow Coma Scale.

Variable	Score
Opening of the eyes	
Spontaneously	4
To speech	3
To pain	2
None	1
Best verbal response*	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Best motor response	
Spontaneous (obedience to commands)	6
Localization of pain	5
Withdrawal	4
Abnormal flexion to pain	3
Abnormal extension to pain	2
None	1

*The Children's Coma Scale, for use with children who do not yet talk, modifies the "best verbal response" section of the Glasgow Coma Scale as follows: smiles, is oriented to sound, follows objects, and interacts, 5 points; is consolable when crying and interacts inappropriately, 4; is inconsistently consolable and moans, 3; is inconsolable, irritable, and restless, 2; and makes no response, 1.

mented by a decrease in Glasgow coma score. Do not mistake intermittent flexor or extensor posturing for seizures. Abnormal posturing is an ominous sign suggesting a sharp rise in intracranial pressure.[8]

Inspect the neck for lacerations, bruises, and venous engorgement. Palpate the entire chest wall to detect tenderness, bone deformity, and crepitation. Listen to the breath and heart sounds for signs of pneumothorax or hemothorax and pericardial tamponade. Inspect the abdomen for a seat-belt bruise, which is often associated with intestinal, pancreatic, or lumbar-spine injuries.[34]

Palpate the abdomen gently for tenderness, and listen for bowel sounds. Frank peritonitis or substantial intraabdominal bleeding (defined as the requirement of >40 ml of whole blood or its equivalent per kilogram plus increasing abdominal girth) indicates a need for laparotomy.

Ask conscious patients about neck or back pain. Palpate the posterior neck for tenderness and irregularities suggesting injury to the cervical spine. Other signs of spinal-cord injury are priapism, hypotension with relative bradycardia, decreased motor power and sensation below the level of the lesion, and decreased anal-sphincter tone.[30] In the absence of spinal injury, logroll the patient to examine the back. If a spinal-cord injury is suspected, request immediate orthopedic or neurosurgical consultation (or both). Inspect the extremities for bruises, lacerations, and obvious deformities, and palpate for bony tenderness. Test for pelvic instability.

Diagnostic Imaging

After completing the physical examination, obtain lateral and anteroposterior cervical-spine and anteroposterior chest radiographs. Order radiographs of the skull, face, pelvis, thoracolumbar spine, and extremities and other views of the cervical spine only for specific clinical indications.[35] Although the value of skull radiographs in children with mild-to-moderate head trauma remains controversial,[36-38] children with severe head injury urgently require a CT scan to rule out a treatable intracranial hematoma.[39,40] In patients with stable vital signs, an abdominal CT scan with gastrointestinal and intravenous contrast dye is indicated when the results of the abdominal examination are equivocal or unreliable because of neurologic impairment. CT is also indicated to confirm the clinical diagnoses of liver, spleen, or kidney injuries, even though most of these can be safely treated without operation.[41,42] Continuous monitoring of vital functions, including the Glasgow coma score, and frequent reassessment of gas exchange and circulation are essential in the radiology suite.

Definitive Care

Prepare a preliminary list of documented and suspected injuries, and develop a plan of treatment with the appropriate consulting services. Evaluation and stabilization should be completed in the emergency department within one hour, by which time the patient should have been moved to the operating room or an inpatient unit. If necessary, arrange for expeditious transfer to a regional pediatric trauma center.

Special Considerations for Selected Organ Systems

Head

Children have relatively fewer intracranial-mass lesions but relatively more intracranial hypertension than adults.[16] The tendency to have diffuse brain swelling puts children at increased risk of secondary brain injury. All children with Glasgow coma scores ≤12 require special monitoring of their neurologic status. Those with scores ≤8 should be treated in an intensive care unit. Since little can be done to alter the extent of primary injury, treatment is directed at preventing secondary injury by attending to gas exchange and circulation and evacuating hematomas if they occur.[33] Keep brain-injured children well oxygenated and normotensive. Hyperventilation (partial pressure of arterial carbon dioxide, 3.3 to 4.0 kPa [25 to 30 mm Hg]) with adequate oxygenation is the primary method of reducing intracranial pressure. Therefore, intubate the trachea if the Glasgow coma score is ≤8 or if there are signs of brain-stem injury or posturing. Intravenous mannitol (0.5 g per kilogram) or furosemide (1 mg per kilogram) can be given in the absence of shock to reduce intracranial pressure rapidly when there is evidence of imminent herniation despite adequate hyperventilation.[43] Keep the head at an elevation of 30 degrees and straight with respect to the body to maximize cerebral venous drainage. Treat true seizures with anticonvulsant agents (0.1 mg of lorazepam per kilogram, followed by 10 to 20 mg of phenytoin per kilogram infused at a rate of 1 mg per kilogram per minute). Prophylactic phenytoin is recommended for severe head trauma.[44] Neither steroids nor "barbiturate coma" improves survival.[45,46]

Spine

The incidence of cervical spinal injury in children 1 to 15 years of age has been estimated at 18.2 per million,[22] as compared with an estimated 1850 pediatric brain injuries per million.[47] The case-fatality rate of cervical spinal injuries is 59 percent,[22] as compared with approximately 6 percent[4] for head injuries. Of all patients admitted to the hospital with cervical spinal injuries, only 4.8 percent are children.[22] These data suggest that cervical spinal damage is uncommon in children who survive injury, especially as compared with head injuries, but that the case-fatality rate for cervical spinal injuries is high. Children less than eight years old tend to sustain damage to the upper cervical spine (vertebrae C1 through C3), probably because of the effect of immature body proportions on the center of gravity.[48] As many as 50 to 60 percent of children with traumatic spinal-cord injury have no associated radiographic abnormalities.[49] Since most of these children have transient parasthesia, numbness, or paralysis after injury, evaluation of the cervical spine is not limited to obtaining radio-

graphs, but must include specific clinical assessment. Anteroposterior and lateral views are generally adequate to detect cervical spinal fractures[48]; additional views (open mouth, oblique, flexion, and extension) and magnetic resonance imaging may help delineate the full extent of injury, however.[50,51] Methylprednisolone (a bolus of 30 mg per kilogram, followed by 5.4 mg per kilogram per hour for 23 hours) was found to improve some measures of neurologic outcome in a comparison with placebo.[52] Although the clinical importance of these results remains open to question, the current practice among neurosurgeons at our institution is to use this regimen for confirmed spinal-cord injury.

Chest

Because the child's chest wall is very pliable, rib fractures are less common than in adults, and life-threatening intrathoracic injuries may occur without external signs.[24] The mediastinal structures shift more easily, so tension pneumothorax or hemothorax can cause both shock and respiratory failure. The most common chest injuries are pulmonary contusion, rib fracture, pneumothorax, and hemothorax, in that order.[24] Almost all resolve with supportive measures, and few require thoracotomy.

Treat simple pneumothorax and hemothorax with intercostal drainage. Massive hemothorax causes shock and dullness to percussion in addition to the signs of pneumothorax. Thoracotomy is indicated for massive or ongoing intrathoracic bleeding, which occasionally results from lacerations of the lung or intercostal vessels.

Direct injury to the larynx, trachea, or major bronchi may cause airway obstruction or massive air leak. Signs of a major airway injury include stridor, aphonia, hemoptysis, subcutaneous or mediastinal emphysema, large-volume air leak through a chest tube, or persistent pneumothorax despite one or two well-placed chest tubes. Such injuries require bronchoscopy and direct surgical repair.

Blunt cardiac injuries can cause arrhythmias and tamponade. Fortunately, they are rare.[53] The plain radiographic signs of injury to the thoracic aorta and its branches are the same in children as in adults (widened mediastinum, blurring of the aortic knob, left pleural cap, deviation of mediastinal structures, obliteration of the space between the aorta and left pulmonary artery, and fracture of the first or second rib or scapula).[54] An aortogram is diagnostic.

Thoracotomy in the emergency department is rarely indicated and almost never successful.[55] Consider it in penetrating chest trauma to relieve cardiac tamponade and control bleeding in a patient who cannot otherwise be resuscitated, and in blunt trauma with massive, clinically obvious intraabdominal bleeding to clamp the descending aorta before laparotomy.

Abdomen

Although less common than central nervous system and musculoskeletal injuries, blunt abdominal injuries are perhaps the second most frequent cause of preventable death after failure to control the airway. Liver, spleen, and kidney injuries are the most common but do not require operation when vital signs and the hematocrit are stable.[56] Bowel, pancreas, and bladder injuries are less common but can result in substantial morbidity if missed. The detection of abdominal injuries in children can be especially difficult, and the index of suspicion must be high. External signs may be few. An unconscious child is unable to indicate tenderness, and a conscious child may not cooperate. When the diagnosis is in doubt, an abdominal CT scan helps greatly in diagnosis, provided the vital signs are stable.[57] Most intraabdominal injuries that require laparotomy are recognized clinically because they produce peritonitis or shock requiring more than 40 ml of blood per kilogram and involve increasing abdominal girth. Although diagnostic peritoneal lavage is rarely performed in children, it may help if the patient is hemodynamically unstable and therefore unfit for CT or if the site of blood loss has not been detected. The surgeon who will operate should perform the diagnostic peritoneal lavage.

Limbs

Injuries to the limbs require attention not because they often threaten life but to make the patient comfortable and to avoid loss of function. Apply sterile dressings to all open wounds. Palpate all peripheral pulses and test motor power and sensation. Splint all clinically diagnosed fractures. When there is arterial insufficiency distal to a fracture, gently attempt to realign the limb and seek immediate orthopedic consultation.

Summary

Apart from the trend to nonoperative treatment of blunt abdominal injuries, based on accurate CT diagnosis, most of the recent and anticipated changes in pediatric trauma are organizational. They include resuscitation and triage before hospitalization, the use of designated trauma centers, resuscitation by trauma teams, noninvasive diagnosis and monitoring, comprehensive pediatric intensive care, the use of objective measures of outcome, and improved rehabilitation programs (Templeton JM: personal communication).

The treatment of individual cases is based on simple but well-established principles. The key steps in management are to recognize children with life-threatening injuries (on the basis of the mechanism of injury or a Pediatric Trauma Score ≤8 or a Revised Trauma Score ≤11), to support the function of vital organs by establishing and maintaining adequate respiratory gas exchange and circulation, and to identify all important injuries by thorough and ongoing assessment.

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REVIEW ARTICLE

CURRENT CONCEPTS

JANE F. DESFORGES, M.D., *Editor*

INITIAL TREATMENT OF PATIENTS WITH EXTENSIVE TRAUMA

DONALD TRUNKEY, M.D.

PATIENTS with life-threatening injuries make up approximately 10 to 15 percent of all patients hospitalized because of injuries.[1] Some authors have defined patients with extensive trauma as those with injury severity scores (ISSs) higher than 15 (for an explanation of the ISS see the Appendix).[2-4] That is an acceptable definition for purposes of triage, but in this discussion I shall define extensive trauma as indicated by an ISS above 25. Most patients in this category have multisystem trauma. Deforming and destructive injuries can be obvious, but the surgeon or physician who initially treats the patient must promptly conduct a systematic workup if all wounds, including life-threatening occult injuries, are to be treated in the best way possible. The principles of management in all cases of extensive trauma are simultaneous assessment and resuscitation, complete physical examination, diagnostic studies if the patient becomes hemodynamically stable, and lifesaving surgery.

Deaths due to trauma have a distinct pattern.[5] Approximately 50 percent of all such deaths occur at the scene of the accident. Another 30 percent occur within a few hours of injury. The remaining 20 percent of deaths occur within days or weeks of the injury as a result of sepsis and multiple-organ failure; frequently, delayed or incorrect diagnosis or inadequate treatment in the early period after the injury contributes to death. The 30 percent of patients who die within hours of hospitalization are those on whom the physician's or surgeon's treatment, combining timely and appropriate resuscitation with prompt, definitive surgical care, may have the greatest effect. Time works against the resuscitating physician, however, and most of the deaths among hospitalized patients with trauma occur within the first four hours. The majority of these patients either bleed to death or die from primary or secondary injuries to the central nervous system.

In order to reduce mortality the surgeon must promptly establish adequate ventilation and restore tissue perfusion, identify the sites of hemorrhage and stop it, diagnose and evacuate mass intracranial lesions, and treat cerebral edema. The first physician to treat a severely injured patient must begin resuscitation immediately and collect as much information as possible. In addition to the patient's symptoms, essential information includes the mechanism of injury and the presence of any preexisting medical conditions that may influence critical decisions. Gathering information, unfortunately, requires time, and the workup of the critically injured patient must often be rushed. In order to help physicians maximize their resuscitative efforts and avoid missing life-threatening injuries, various protocols for resuscitation have been developed, of which the Advanced Trauma Life Support (ATLS) course[6] is a model. In this discussion, I shall use the ATLS as a paradigm for assessment, resuscitation, and the establishment of priorities in treating the patient's injuries.

In the evaluation and treatment of actual life-threatening injuries, algorithms do not help in decision making. Humans do not think in a binary fashion. Instead, they use cluster analysis. This method can be exemplified by the workup of a patient who arrives in the emergency room obtunded after being ejected from a car, reacting only to pain, and with poor peripheral perfusion. Further examination reveals an unstable pelvic fracture, abdominal pain on deep palpation, and a deformity of the right thigh, presumably a closed femoral fracture. The surgeon must analyze this cluster of information, initiate resuscitation, and establish priorities immediately. The surgeon asks himself or herself: Does the patient have focal or lateralizing neurologic signs? Is the neurologic status changing? Is the poor peripheral perfusion due to blood loss in the chest, abdomen, or thigh? As resuscitation begins with high-flow oxygen and intravenous fluids, x-ray films of the chest and lateral films of the cervical spine are simultaneously obtained. Within the first five minutes of assessment and resuscitation, let us assume that the neurologic status improves slightly; let us further assume that the chest film shows no important blood loss but that the mediastinum is widened. Despite the infusion of 2 liters of balanced salt solution, the patient's shock is worsening.

Within these first few minutes the physician has established that the blood loss is not occurring within the chest; he or she suspects that the patient's neurologic deficits are probably due to hypoxia or hypovolemia, since there are no lateralizing signs and the neurologic status has improved with high-flow oxygen and intravenous fluids. The most likely sources of blood loss are the abdomen and the thigh. A traction splint is applied to the leg. Since the patient's blood pressure remains low, an immediate celiotomy is indicated. A widened mediastinum due to a contained

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rupture of the thoracic aorta is not a source of substantial blood loss. After celiotomy and control of intraabdominal hemorrhage, the patient will be taken to the radiology suite for an arteriogram of the aortic arch. If the arteriogram confirms aortic disruption, the patient can be returned to the operating room for operative repair followed by open reduction and internal fixation of the fractured femur.

This example highlights several points. Isolated injuries are not the rule. By obtaining as much information as possible in the shortest possible period of time, the surgeon can assign priorities to the life-threatening injuries and address each one in a definitive fashion.

Resuscitation

Resuscitation has two components: the primary survey and initial resuscitation, and the secondary survey and continuing resuscitation. All patients undergo the primary survey of airway, breathing, and circulation. Only patients who become hemodynamically stable will progress to the secondary survey, which focuses on a complete physical examination that directs further diagnostic studies. The great majority of patients who remain hemodynamically unstable require operative intervention immediately.

Primary Survey

The goals of the primary survey are, in order, to establish a patent airway and adequate ventilation, to maintain the circulation (including cardiac function and intravascular volume), and to assess the global neurologic status.

Ventilation

Patients with extensive trauma who are unconscious or in shock benefit from immediate endotracheal intubation.[7,8] To prevent injury to the spinal cord, the cervical spine must not be excessively flexed or extended during intubation. Oral endotracheal intubation is successful in the majority of injured patients. A few patients require nasotracheal intubation by an experienced physician. During intubation, firm compression of the cricoid cartilage against the cervical spine occludes the esophagus and reduces the risk of aspirating vomitus. On rare occasions, bleeding, deformity, or edema from maxillofacial injuries necessitates cricothyroidotomy or tracheostomy. Patients who are likely to require surgery to establish an airway include those with laryngeal fractures. The priorities with respect to the airway are to clear the upper airway, to administer high-flow oxygen initially with a bag mask, and to proceed immediately to endotracheal intubation in most cases and to surgery on the airway in a few.

Circulation

While an airway is being established, a quick assessment of the patient will determine the degree of shock present. Shock is a clinical diagnosis and should be readily apparent. The first step in its identification is to feel an extremity. If shock is present, the extremities will be cool and pale, lack venous filling, and have poor capillary refill. The pulse will be thready and mentation diminished. The status of the neck veins must be noted. A patient who is in shock with flat neck veins is assumed to have hypovolemic shock until proved otherwise. If the neck veins are distended, there are five possibilities: tension pneumothorax, pericardial tamponade, air embolism, myocardial contusion, and myocardial infarction. Myocardial contusion is a rare cause of cardiac failure in patients with trauma, but myocardial infarction from coronary occlusion is not uncommon in elderly persons. Tension pneumothorax should always come first in the physician's differential diagnosis of shock, since it is the easiest life-threatening injury to treat in the emergency department. A simple tube thoracostomy is the definitive method of management.

Air embolism[9,10] has come to be appreciated as an important complication in injured patients. It consists of air in the systemic circulation and is caused by a bronchopulmonary venous fistula. Air embolism occurs in 4 percent of all patients with major thoracic injuries. About a third of the time, air embolism is a result of blunt trauma, usually a laceration of the pulmonary parenchyma by a fractured rib. In about 65 percent of patients air embolism is a result of gunshot wounds or stab wounds. The surgeon must have high index of suspicion of air embolism whenever pulmonary injury has occurred. Any patient who has no obvious head injury but has focal or lateralizing neurologic signs may have air bubbles occluding the cerebral circulation. The observation of air in the retinal vessels on funduscopic examination will confirm the presence of cerebral air embolism. Any intubated patient on positive-pressure ventilation who has a sudden cardiovascular collapse should be presumed to have either tension pneumothorax or air embolism in the coronary circulation. Doppler monitoring of an artery can be a useful aid in detecting air embolism. The definitive treatment is immediate thoracotomy, clamping of the hilum of the injured lung to prevent further embolism, and expansion of the intravascular volume. Open cardiac massage, intravenous administration of epinephrine, and venting of the left side of the heart and the aorta with a needle to remove residual air may be required. The pulmonary injury is definitively treated by oversewing the laceration or resecting a lobe.

Pericardial tamponade is most commonly encountered in patients with penetrating injuries to the torso. Approximately 25 percent of all patients with cardiac injuries reach the emergency room alive. The diagnosis is often obvious. The patient has distended neck veins with poor peripheral perfusion; a few have pulsus paradoxus. Ultrasonography may establish the diagnosis in the very few patients with equivocal findings. Pericardiocentesis is occasionally useful as a diagnostic or therapeutic aid. The proper treatment is immediate thoracotomy, preferably in the operating

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room, although thoracotomy in the emergency room can be lifesaving.[11]

If the primary cause of shock is blood loss, the four steps to be taken are to gain access to the circulation, obtain a blood sample from the patient, determine where the volume loss is occurring, and give fluids for resuscitation. The fastest and most reliable way to gain access to the circulation is by a surgical cutdown on the saphenous vein at the ankle. Incision in this anatomically constant vein allows the physician to achieve access quickly with a large-diameter tube. Alternatively, the resuscitating physician can perform bilateral percutaneous femoral-vein cannulation with a large-bore catheter or an 8-French introducer, more commonly used for passing a pulmonary-artery catheter. Some experienced physicians prefer to gain access through the subclavian or internal jugular vein, but this approach is associated with a higher frequency of pneumothorax.

As soon as the first intravenous line has been established, base-line blood work should be undertaken; it should include the hematocrit, toxicologic screening, blood typing and crossmatching, and a screening battery of laboratory tests if the patient is elderly or has premorbid conditions. Blood gas determinations should be performed early in the course of resuscitation. Next, it must be determined where occult blood loss is occurring. Three sites of hidden blood loss are the pleural cavities (a possibility that can be eliminated by rapid chest radiography), the thigh, and the abdomen, including the retroperitoneum and pelvis. A fractured femur should be clinically obvious. Assessment of the abdomen on the basis of physical findings can be extremely misleading, however. Fifty percent of patients with substantial hemoperitoneum have no clinical signs.[12,13] Common sense dictates that if the patient's chest film is normal and the femur is not fractured, the patient who remains in shock must be suspected of having ongoing hemorrhage in the abdomen or pelvis. Most such patients require immediate celiotomy if death from hemorrhage is to be averted.

The fourth step for the resuscitating physician is to administer fluids for resuscitation, beginning with balanced salt solution and adding type-specific whole blood as soon as possible.[14,15] Type O blood should be given to the patient with exsanguination, whereas in the case of a stable patient it is prudent to wait for typed and crossmatched blood.

Although whole blood is preferable, it is difficult to obtain from modern blood banks; thus, the use of blood components is often imperative. In patients with limited blood loss, the infusion of balanced salt solution and packed red cells is all that is required. In those with extensive hemorrhage who require massive transfusion (more than one blood volume), administration of blood components must be guided by monitoring of specific defects, such as thrombocytopenia, hypofibrinogenemia, and factor V or factor VIII deficiency. The criteria for adequate resuscitation are simple and straightforward: keep atrial filling pressure at normal levels, give sufficient fluid to achieve adequate urinary output (0.5 ml per kilogram of body weight per hour in adults, 1.0 ml per kilogram per hour in children), and maintain peripheral perfusion. The only practical way to measure atrial filling pressure in the emergency room and immediately in the operating room is by monitoring central venous pressure. In elderly patients with extensive traumatic injuries, it may be prudent to place a pulmonary-artery catheter immediately, since it can be used to direct a sophisticated, multifactorial resuscitation effort in the operating room or in the intensive care unit. Resuscitation should be directed to achieve adequate delivery and consumption of oxygen. An important caveat is not to delay necessary therapeutic interventions to obtain noncritical diagnostic tests.

Neurologic Status

The next task during the primary survey is to assess neurologic status and to initiate diagnostic and therapeutic procedures. The six key factors assessed in a rapid neurologic evaluation are the level of consciousness, the size and reactivity of the pupils, eye movements and oculovestibular responses, skeletal-muscle motor responses, pattern of breathing, and peripheral sensory function.

A decreasing level of consciousness is the single most reliable indication that the patient has a serious head injury or secondary insult (usually hypoxic or hypotensive) to the brain. Consciousness has two components: awareness and arousal. Awareness is manifested by goal-directed or purposeful behavior. The use of language is an indication of functioning cerebral hemispheres. If the patient attempts to protect himself or herself from a painful insult, this also implies cortical function. Arousal is a crude function equivalent to simple wakefulness. Opening the eyes, either spontaneously or in response to stimuli, is indicative of arousal and is a brain-stem function. In coma both awareness and arousal are absent; eye opening does not occur, there is no comprehensible speech, and the extremities move neither on command nor appropriately in response to noxious stimuli.

The physician must assess all six components of neurologic status and make sure the four primary reflexes (ankle, knee, biceps, and triceps) are assessed, and he or she should repeat this examination at frequent intervals. In this way it is possible both to diagnose and to monitor the neurologic status in the emergency department. An improving neurologic status reassures the physician that resuscitation is improving cerebral blood flow. Neurologic deterioration is strong presumptive evidence of either a mass lesion or important neurologic injury. CT scanning of the head is the preferred technique for diagnosing head injury and should be performed as soon as possible.

The minimal diagnostic studies that should be undertaken when the patient is hemodynamically unstable after the primary survey are the chest film, lateral film of the cervical spine, and plain film of the pelvis.

Certain patients — for example, those with hematuria or severe deceleration injury — may require a single-film intravenous pyelogram to confirm the findings on bilateral nephrography. It must be emphasized that resuscitation should not cease during these films, and the resuscitating team must wear protective lead aprons. Optimally, the x-ray facilities will be close to the emergency room; if necessary, however, the basic x-ray films can all be obtained with a portable machine.

Secondary Survey

If the patient becomes hemodynamically stable during the initial phase of assessment and resuscitation, it is then appropriate to perform diagnostic studies as indicated to determine surgical priorities.

Diagnostic Studies

For patients with head injuries a CT scan is the diagnostic test of choice. Similarly, for maxillofacial injuries, CT scanning is superior to plain radiography but should be delayed until after the patient with injuries to the torso and head is stable. A plain anteroposterior chest film obtained while the patient is supine on the resuscitation stretcher is usually an adequate first step in the assessment of chest injuries. Increasingly, CT scanning is used to identify trauma to the torso. The diagnostic use of CT scanning may increase with the availability of newer, faster units. The arteriogram remains the gold standard for evaluating a widened mediastinum. Plain films of the abdomen add little; diagnostic peritoneal lavage is more useful in the patient whose condition is unstable, and CT scanning is more useful in the stable patient. Cystourethrography, pyelography, and diatrizoate meglumine (Gastrografin) upper intestinal series are helpful in the diagnosis of visceral injury. Cystourethrography should be considered before the insertion of a Foley catheter in patients with severe pelvic fractures, gross bleeding from the urethral meatus, or an abnormally located prostate.

Surgical Priorities

The priorities for surgical intervention are straightforward. A mass lesion in the cranial vault must always be treated immediately. Fortunately, mass lesions are infrequent and occur in less than 25 percent of all patients with closed head injuries. It is equally important for the surgeon to rule out secondary insult to the brain, such as hypoxia or hypovolemia, which can be just as devastating as a brain laceration. Hypoxia and hypovolemia account for neurologic deficits in up to 35 percent of patients with a diagnosis of closed head injury.[16] Injuries to the torso are next in line for surgical repair, but they can be treated at the same time as head injuries. As stated above, the surgeon can easily determine from a chest film whether there is hemorrhage into the chest. A patient in shock who has a normal chest film and no other obvious source of blood loss must have hemorrhage within the peritoneal cavity or the retroperitoneum. Such a patient requires immediate celiotomy to control the hemorrhage. If the chest film shows that the pleural cavity is filled with blood, the surgeon must determine whether the patient has a ruptured diaphragm with exsanguination from the abdomen into the chest cavity. A quick midline celiotomy or diagnostic peritoneal lavage can confirm this condition before the pleural cavity is opened to control hemorrhage.

Peripheral vascular injuries are assigned the third priority for surgery, and orthopedic injuries the fourth. Because of the benefits of early mobilization, it is best to undertake fixation of most orthopedic injuries of the extremities within the first 24 hours after the injury. A considerable reduction in mortality can be achieved by adhering to this principle.[17] Maxillofacial injuries receive the fifth priority. Operative treatment of facial fractures can often be delayed until the third or fourth day after the injury. Certain orthopedic injuries are also optimally treated after stabilization. An example would be an acetabular fracture, the repair of which often decompresses a pelvic hematoma.

In summary, the seriously injured patient with multiple injuries requires that rapid assessment be undertaken while he or she is being vigorously resuscitated. Within the first few minutes, the surgeon must gather enough information to set priorities for diagnostic studies to be performed if the patient becomes hemodynamically stable or to initiate surgical treatment if the patient remains hemodynamically unstable because of ongoing hemorrhage or has an intracranial mass lesion. Successful resuscitation and surgical treatment require a team approach to the care of injured patients. Comprehensive care for patients with trauma is most effective when a knowledgeable general surgeon coordinates the efforts of the team and when the hospital has been designated a trauma center as part of a regional trauma system.[3]

Appendix: The Injury Severity Score

The injury severity score[3] is based on the abbreviated injury score (AIS),[4] a score on a numerical scale ranging from 1 (indicating minor injury) to 6 (virtually unsurvivable injury). An AIS is assigned to each of six regions of the body: head or neck, face, chest, abdomen or pelvic contents, extremities, and body surface. The injury severity score is defined as the sum of the squares of the AISs for the three most severely injured body regions. The procedure can easily be seen in the following example:

Body Region	Injury	AIS	AIS^2
Head	Epidural hematoma	4	16
Face	Ear laceration	1	1
Chest	Rib fractures	2	4
Abdomen	Ruptured spleen	3	9
Extremities	Fractured femur	3	9

In this hypothetical case, the sum of the squares of the three highest AISs (those for the most severely injured body regions) is 16 + 9 + 9, or 34. The ISS is thus 34.

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TREATMENT OF TRAUMATIC BRAIN INJURY WITH MODERATE HYPOTHERMIA

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ABSTRACT

Background Traumatic brain injury initiates several metabolic processes that can exacerbate the injury. There is evidence that hypothermia may limit some of these deleterious metabolic responses.

Methods In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in 82 patients with severe closed head injuries (a score of 3 to 7 on the Glasgow Coma Scale). The patients assigned to hypothermia were cooled to 33°C a mean of 10 hours after injury, kept at 32 to 33°C for 24 hours, and then rewarmed. A specialist in physical medicine and rehabilitation who was unaware of the treatment assignments evaluated the patients 3, 6, and 12 months later with the use of the Glasgow Outcome Scale.

Results The demographic characteristics and causes and severity of injury were similar in the hypothermia and normothermia groups. At 12 months, 62 percent of the patients in the hypothermia group and 38 percent of those in the normothermia group had good outcomes (moderate, mild, or no disabilities). The adjusted risk ratio for a bad outcome in the hypothermia group was 0.5 (95 percent confidence interval, 0.2 to 1.2). Hypothermia did not improve the outcomes in the patients with coma scores of 3 or 4 on admission. Among the patients with scores of 5 to 7, hypothermia was associated with significantly improved outcomes at 3 and 6 months (adjusted risk ratio for a bad outcome, 0.2; 95 percent confidence interval, 0.1 to 0.9 at both intervals), although not at 12 months (risk ratio, 0.3; 95 percent confidence interval, 0.1 to 1.0).

Conclusions Treatment with moderate hypothermia for 24 hours in patients with severe traumatic brain injury and coma scores of 5 to 7 on admission hastened neurologic recovery and may have improved the outcome. (N Engl J Med 1997;336:540-6.)
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THE therapeutic use of hypothermia in a patient with traumatic brain injury was first reported in 1943.[1] However, since neither this report nor several subsequent reports provided comparative data on patients kept at normal temperatures, they failed to establish the efficacy of therapeutic hypothermia.[2-5] Moreover, the degree and duration of cooling and the interval between the injury and the initiation of treatment varied both within and among the studies.

In 1993, preliminary reports on three clinical trials of moderate hypothermia (a temperature of 32 or 33°C) in patients with traumatic brain injury were published, including our report on the first 40 patients in this study.[6-8] The largest trial included 46 patients. The studies differed slightly in terms of the duration of cooling (one day or two days) and when it was initiated (within hours after the injury or only after conventional therapy had failed to control intracranial pressure). In each study, there was a trend toward improved outcomes among the patients treated with hypothermia, as compared with those kept at a normal temperature. On the basis of these results, we continued our study. We also assessed the effects of hypothermia on post-traumatic cerebral physiology and ventricular cerebrospinal fluid concentrations of excitatory amino acids and interleukin-1β. This report describes the results in 82 patients, including the 40 patients described in our preliminary report.[8]

METHODS

From February 1991 through September 1994, 155 patients with closed head injuries who had a score of 3 to 7 on the Glasgow Coma Scale[9] were admitted to our trauma center. The Glasgow Coma Scale is based on patients' ability to open their eyes, speak, and use their arms or legs. Patients with a score of 7, for example, usually attempt to remove a painful stimulus with an arm but do not speak or open their eyes in response to the stimulus.

The predetermined entry criteria, in addition to a closed head injury and a Glasgow coma score of 3 to 7, were an age of 16 to 75 years, admission within six hours after the injury, and an inability to follow commands. Patients were excluded for the following reasons: clinical brain death (a score of 3 on the Glasgow Coma Scale and no brain-stem reflexes), prolonged hypoxia or hypotension, a gunshot wound, pregnancy, an undetermined time of injury, or normal findings on a computed tomographic (CT) scan of the head (class I according to the classification described by Marshall et al.[10]).

Eighty-two of the 155 patients met the entry criteria and were randomly assigned to hypothermia or normothermia within six hours after injury. Using a block-randomization scheme, we assigned patients with a Glasgow coma score of 3 or 4 to a treatment group separately from those with a score of 5 to 7 by choosing among equal numbers of sealed envelopes containing the group assignments. This procedure and the study protocol were approved by the University of Pittsburgh investigational review board. If family members were available within six hours after the injury, we obtained written informed consent before randomization. Otherwise, patients were enrolled in the study,

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and consent was obtained when family members arrived at the hospital.

Treatment Protocol

We began to cool the 40 patients assigned to the hypothermia group immediately after enrollment, using cooling blankets (Blanketrol II, Cincinnati Sub-Zero, Cincinnati) placed above and below the patient and nasogastric lavage with iced saline. Once the rectal temperature reached 33°C (a mean of 10 hours after the injury), it was kept between 32 and 33°C for 24 hours. During the next 12 hours, the patients were passively rewarmed to a temperature of 37 to 38.5°C, at a rate no greater than 1°C per hour, by a gradual adjustment of the blanket thermostat. In the 42 patients in the normothermia group, the temperature was kept between 37 and 38.5°C during the entire five-day monitoring period. The patients in the normothermia group who had rectal temperatures below 37°C at admission were passively rewarmed over a period of 12 hours. To prevent shivering, the patients in the hypothermia group received continuous infusions of a paralytic drug (vecuronium bromide, 10 mg per hour) and a narcotic agent (fentanyl citrate, 50 to 100 μg per hour) for the first 36 hours after the injury. The patients in the normothermia group received similar doses of these drugs during that time.

To determine how accurately rectal temperatures reflected brain temperatures, we compared the results of simultaneous rectal and brain measurements in the first 40 patients. Brain temperatures were measured directly with a microthermistor placed 2 cm from the tip of an external ventricular-drainage catheter (PMT, Chanhassen, Minn.). In 95 percent of over 4000 simultaneous measurements, rectal and brain temperatures did not vary by more than 0.5°C. We therefore used the rectal temperature as a reliable, easily measured indication of the brain temperature.

To monitor cerebral oxygen extraction, we determined the difference between arterial and jugular venous oxygen content every 4 hours for the first 24 hours and every 6 hours thereafter. A jugular venous catheter was inserted into the jugular bulb, and the oxygen content of blood samples obtained from this catheter was subtracted from the oxygen content of simultaneously obtained samples of radial arterial blood. Cerebral blood flow was measured every 12 hours for five days with the xenon-133 technique.[11]

The patients were treated according to the principles described in "Guidelines for the Management of Severe Head Injury."[12] We rapidly evacuated large subdural and epidural hematomas and hemorrhagic contusions. Intravascular volumes were maintained at nearly normal values by keeping central venous pressures between 6 and 15 cm of water. The cerebral perfusion pressure (the mean arterial pressure minus the intracranial pressure) was maintained at a level higher than 70 mm Hg at all times by keeping the mean arterial pressure at a level between 90 and 110 mm Hg and the intracranial pressure at a level below 20 mm Hg. A ventriculostomy catheter, with a closed column of cerebrospinal fluid coupled to a strain-gauge transducer, was inserted to provide continuous measurement of intracranial pressure. Ventricular cerebrospinal fluid was drained intermittently and bolus intravenous infusions of mannitol (25 to 50 g every three to four hours) were administered to reduce intracranial hypertension. If these measures were unsuccessful and follow-up CT scans showed no mass lesions that should be resected, pentobarbital was infused at a dose that resulted in the suppression of bursts on the electroencephalogram (60 to 120 mg per hour). Corticosteroids were not used. If the intracranial pressure remained high, we administered intravenous dopamine to increase the mean arterial pressure and maintain the cerebral perfusion pressure at a level above 70 mm Hg. Dopamine infusions were required in 22 patients in the hypothermia group and in 17 in the normothermia group. We used hypocapneic therapy (partial pressure of carbon dioxide, <33 mm Hg at 37°C) only to manage otherwise uncontrollable intracranial hypertension. All patients received phenytoin (300 mg per day) intravenously for seven days.

Cerebrospinal Fluid Analysis

We withdrew specimens of cerebrospinal fluid (3 to 4 ml) from the ventriculostomy catheter every 4 hours for the first 24 hours and every 6 hours for the next four days. Immediately before the samples were assayed, they were filtered to remove proteinaceous and particulate material. Aspartate and glutamate concentrations were measured by high-pressure liquid chromatography with the use of a fluorescence detector after precolumn derivation of amino acids with *o*-phthaldialdehyde.[13] Interleukin-1β was measured with a highly sensitive enzyme-linked immunosorbent assay (Cistron Biotechnology, Pine Brook, N.J.).

Assessment of Neurologic Outcome

A specialist in physical medicine and rehabilitation who was unaware of the patients' treatment assignments determined the neurologic outcome 3, 6, and 12 months after the injury. The neurologic outcome was scored according to the Glasgow Outcome Scale,[14] as follows: 1, death; 2, vegetative state — unable to interact with the environment; 3, severe disability — unable to live independently but able to follow commands; 4, moderate disability — capable of living independently but unable to return to work or school; and 5, mild or no disability — able to return to work or school.

Statistical Analysis

The base-line characteristics, complications, and outcomes in the two groups were compared with the use of chi-square tests, Fisher's exact tests, Wilcoxon rank-sum tests, or t-tests as appropriate. To compare values for pressure (intracranial pressure, cerebral perfusion pressure, and mean arterial pressure), cerebrospinal fluid neurochemical concentrations, and hematologic variables, we tested the differences in mean values with the use of generalized-linear-regression analysis. Because we performed multiple measurements of each variable in each patient and assumed that the values were correlated, we used a generalized linear model that adjusts for intraclass correlation.[15] An interim analysis of the outcomes at three and six months for the first 40 patients in the study, reported elsewhere, slightly reduces the power of this final analysis.[8]

Most of the demographic and clinical characteristics of the two groups were similar. On the basis of the CT class, the injuries were slightly less severe in the hypothermia group, but the difference was not statistically significant (Table 1). To adjust for a possible confounding effect of the CT class, we performed logistic-regression analyses with a dichotomous outcome variable (death, vegetative state, or severe disability vs. normal or moderate disability). The explanatory variables were treatment group, initial Glasgow coma score, and CT class.

RESULTS

Characteristics of the Patients

Most of the patients were men, and the most common cause of head injury was a motor vehicle accident (Table 1). The two groups did not differ significantly in terms of age; numbers of patients with abdominal or chest injuries or arm, leg, or pelvic fractures; or the initial Glasgow coma score, although a slightly higher percentage of patients in the normothermia group had a coma score of 5 to 7.

The mean stay in the trauma center was similar in the two groups: 38 days (range, 2 to 267) in the hypothermia group and 35 (range, 1 to 138) in the normothermia group. Eight patients in the hypothermia group and nine in the normothermia group died during this time. Among the surviving patients, 25 (78 percent) in the hypothermia group and 29

TABLE 1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF 82 PATIENTS WITH TRAUMATIC BRAIN INJURY ASSIGNED TO HYPOTHERMIA OR NORMOTHERMIA.*

CHARACTERISTIC	HYPOTHERMIA (N=40)	NORMOTHERMIA (N=42)
Age (yr)	31±12	35±15
	no. of patients (%)	
Male sex	36 (90)	33 (79)
Cause of injury		
Motor vehicle accident	30 (75)	25 (60)
Assault	2 (5)	1 (2)
Fall	4 (10)	14 (33)
Other	3 (8)	1 (2)
Unknown	1 (2)	1 (2)
Initial Glasgow coma score		
3 or 4	18 (45)	16 (38)
5–7	22 (55)	26 (62)
Pupillary abnormalities†	33 (82)	35 (83)
CT class‡		
I	1 (2)	1 (2)
II	15 (38)	9 (21)
III	10 (25)	8 (19)
IV	1 (2)	4 (10)
V	13 (32)	20 (48)
Abdominal injuries	4 (10)	6 (14)
Chest injuries	12 (30)	10 (24)
Pelvic or leg fractures	7 (18)	7 (17)
Arm fractures	6 (15)	4 (10)

*Plus–minus values are means ±SD. Percentages may not add to 100 because of rounding.

†Pupillary abnormalities were defined as abnormalities in size or the reaction to light in one or both pupils.

‡The CT class was determined according to the following classification: class I, no visible evidence of injury; class II, cisterns present, with a midline shift of ≤5 mm and no lesions >25 ml; class III, cisterns compressed or absent; class IV, a midline shift of >5 mm; and class V, a lesion requiring surgical evacuation.[14] All CT scans were reviewed by a neuroradiologist, and the CT classification was based on that review. The neuroradiologists interpreted the CT scans of two patients (one in each group) as normal (class I) after the neurosurgeon responsible for randomization had interpreted the scans as showing diffuse swelling (class II).

(88 percent) in the normothermia group were transferred to a head-injury rehabilitation hospital, where the average length of stay for each group was 69 days. The rates of incidence of delayed post-traumatic intracranial hematomas, infections, deep venous thrombosis, and pulmonary, renal, and cardiac complications were similar in the two groups.

Neurologic Outcome

Three months after injury, 15 (38 percent) of the patients in the hypothermia group had a score on the Glasgow Outcome Scale of 4 or 5, as compared with 7 patients (17 percent) in the normothermia group ($P=0.03$) (Table 2). At 12 months, 24 (62 percent) of the patients in the hypothermia group and 16 (38 percent) of those in the normothermia group had a score of 4 or 5 ($P=0.05$). The efficacy of hypothermia was related to the severity of the injury as indicated by the Glasgow coma score on admission. Patients with initial coma scores of 3 or 4 did not benefit from hypothermia, whereas those with scores of 5 to 7 did. Among these patients with higher scores, 16 (73 percent) in the hypothermia group and 9 (35 percent) in the normothermia group had a good outcome (a Glasgow outcome score of 4 or 5) at six months ($P=0.008$).

Logistic-regression analysis of the results in all patients revealed that the CT class and initial Glasgow coma score confounded the treatment effects ascribed to hypothermia (Table 3). When the logistic-regression analysis was adjusted to account for these two variables, the risk ratios were higher than the unadjusted ratios at 6 and 12 months. For the subgroup of patients with an initial Glasgow coma score of 5 to 7, the analysis adjusted for CT class also revealed that this variable may have confounded the treatment effect ascribed to hypothermia at 12 months. However, the unadjusted and adjusted risk ratios at three and six months did not change, and the 95 percent confidence intervals excluded 1 at both points in time. Thus, in the subgroup with an initial Glasgow coma score of 5 to 7, the significant improvement at three and six months in the patients treated with hypothermia could not be attributed to the slight difference between the groups in the CT-based classification of the severity of the injury.

Cerebral and Systemic Characteristics

During the first 36 hours after the injury (when the patients in the hypothermia group underwent cooling and rewarming), the hypothermia group had a lower mean intracranial pressure, cerebral blood flow, and heart rate and a higher mean cerebral perfusion pressure (Table 4). During the period after rewarming, the mean cerebral perfusion pressure was significantly lower in the hypothermia group than in the normothermia group, although it remained above 70 mm Hg. The mean intracranial pressure in the hypothermia group increased but did not significantly exceed that in the normothermia group.

Moderate hypothermia was not associated with significant changes in serum glucose, amylase, or creatinine concentrations or hematocrit values. The partial-thromboplastin times during the first 36 hours after the injury were slightly higher and the serum potassium concentrations were slightly lower in the hypothermia group, but these values were still within the normal range. Platelet counts and prothrombin times did not differ significantly between the two groups.

Cerebrospinal Fluid Analysis

Among the patients with an initial Glasgow coma score of 5 to 7, those in the hypothermia group had

TABLE 2. GLASGOW OUTCOME SCORES IN THE HYPOTHERMIA AND NORMOTHERMIA GROUPS AT 3, 6, AND 12 MONTHS.*

GLASGOW OUTCOME SCORE	AT 3 MONTHS		AT 6 MONTHS		AT 12 MONTHS	
	HYPOTHERMIA	NORMOTHERMIA	HYPOTHERMIA	NORMOTHERMIA	HYPOTHERMIA†	NORMOTHERMIA
	number of patients (percent)					
All patients						
1 (Death)	8 (20)	9 (21)	8 (20)	10 (24)	9 (23)	10 (24)
2 (Vegetative state)	6 (15)	11 (26)	3 (8)	7 (17)	3 (8)	8 (19)
3 (Severe disability)	11 (28)	15 (36)	7 (18)	11 (26)	3 (8)	8 (19)
4 (Moderate disability)	8 (20)	4 (10)	7 (18)	8 (19)	9 (23)	5 (12)
5 (Mild or no disability)	7 (18)	3 (7)	15 (38)	6 (14)	15 (38)	11 (26)
Total	40	42	40	42	39	42
P value‡	0.12		0.05		0.18	
Patients with coma score of 5 to 7						
1 (Death)	2 (9)	5 (19)	2 (9)	6 (23)	2 (9)	6 (23)
2 (Vegetative state)	2 (9)	7 (27)	1 (5)	3 (12)	1 (5)	4 (15)
3 (Severe disability)	6 (27)	9 (35)	3 (14)	8 (31)	3 (14)	6 (23)
4 (Moderate disability)	6 (27)	3 (12)	4 (18)	6 (23)	5 (23)	2 (8)
5 (Mild or no disability)	6 (27)	2 (8)	12 (55)	3 (12)	11 (50)	8 (31)
Total	22	26	22	26	22	26
P value‡	0.01		0.01		0.04	

*Percentages may not add to 100 because of rounding.

†One patient was lost to follow-up.

‡P values are for comparisons of all five outcomes in the hypothermia and normothermia groups.

TABLE 3. EFFECT OF HYPOTHERMIA ON THE GLASGOW OUTCOME SCORE AT 3, 6, AND 12 MONTHS.*

LOGISTIC-REGRESSION ANALYSIS	AT 3 MONTHS	AT 6 MONTHS	AT 12 MONTHS
	risk ratio (95% CI)		
All patients			
Unadjusted			
Hypothermia (yes vs. no)	0.3 (0.1–0.8)	0.4 (0.2–1.0)	0.4 (0.2–0.9)
Adjusted			
Hypothermia (yes vs. no)	0.3 (0.1–1.0)	0.5 (0.2–1.2)	0.5 (0.2–1.2)
CT class (as compared with next lower class)	1.4 (0.8–2.1)	1.7 (1.1–2.3)	1.4 (1.1–2.2)
Coma score (5 to 7 vs. 3 or 4)	0.3 (0.1–1.0)	0.4 (0.2–1.2)	0.7 (0.2–1.7)
Patients with coma score of 5 to 7			
Unadjusted			
Hypothermia (yes vs. no)	0.2 (0.1–0.7)	0.2 (0.1–0.7)	0.2 (0.1–0.8)
Adjusted			
Hypothermia (yes vs. no)	0.2 (0.1–0.9)	0.2 (0.1–0.9)	0.3 (0.1–1.0)
CT class (as compared with next lower class)	1.7 (0.9–3.3)	1.4 (0.9–2.5)	1.7 (0.9–2.5)

*The risk ratios derived in the logistic-regression analysis were for a Glasgow outcome score of 1, 2, or 3 (death, vegetative state, or severe disability, respectively), as compared with a score of 4 (moderate disability) or 5 (mild or no disability). CI denotes confidence interval.

TABLE 4. EFFECT OF HYPOTHERMIA ON SYSTEMIC AND INTRACRANIAL PHYSIOLOGIC CHARACTERISTICS IN THE HYPOTHERMIA AND NORMOTHERMIA GROUPS.

CHARACTERISTIC	HYPOTHERMIA		NORMOTHERMIA		P VALUE*
	NO. OF PATIENTS/ NO. OF OBSERVATIONS	MEAN VALUE	NO. OF PATIENTS/ NO. OF OBSERVATIONS	MEAN VALUE	
0–36 hours†					
Intracranial pressure (mm Hg)	40/813	15.4	41/853	19.7	0.01
Cerebral perfusion pressure (mm Hg)	40/756	82.4	41/778	77.4	0.05
Difference between arterial and jugular venous oxygen content (ml/dl)	40/260	5.1	40/252	4.6	0.11
Cerebral blood flow (ml/100 g of tissue/min)	30/62	28.8	29/55	35.7	0.05
Arterial pressure (mm Hg)	40/732	97.2	41/757	96.4	0.49
Heart rate (beats/min)	32/627	67.4	33/629	82.1	<0.001
37–60 hours					
Intracranial pressure (mm Hg)	40/676	19.2	37/577	17.4	0.10
Cerebral perfusion pressure (mm Hg)	40/604	73.5	37/516	84.1	<0.001
Difference between arterial and jugular venous oxygen content (ml/dl)	38/152	4.0	38/153	3.8	0.48
Cerebral blood flow (ml/100 g of tissue/min)	19/28	40.5	21/29	42.1	0.53
Arterial pressure (mm Hg)	40/599	92.6	37/516	101.4	<0.001
Heart rate (beats/min)	32/494	92.3	29/436	87.4	0.30

*P values are for differences between the values in the hypothermia group and those in the normothermia group; a generalized-linear-regression analysis was used to adjust for intraclass correlation.

†During this period, patients in the hypothermia group underwent cooling.

TABLE 5. VENTRICULAR CEREBROSPINAL FLUID CONCENTRATIONS OF ASPARTATE, GLUTAMATE, AND INTERLEUKIN-1β IN THE HYPOTHERMIA AND NORMOTHERMIA GROUPS.*

VARIABLE	HYPOTHERMIA		NORMOTHERMIA		P VALUE†
	NO. OF PATIENTS/NO. OF SAMPLES	MEAN (±SD) VALUE	NO. OF PATIENTS/NO. OF SAMPLES	MEAN (±SD) VALUE	
Patients with coma score of 3 or 4					
Aspartate (mg/dl)	3/19	0.02±0.016	3/17	0.013±0.02	0.50
Glutamate (mg/dl)	3/19	0.046±0.03	3/17	0.031±0.03	0.46
Interleukin-1β (pg/ml)	3/14	6.7±5.5	4/19	20.6±2.4	0.21
Patients with coma score of 5 to 7					
Aspartate (mg/dl)	8/46	0.025±0.02	6/37	0.036±0.03	0.45
Glutamate (mg/dl)	8/46	0.04±0.02	6/37	0.071±0.05	<0.001
Interleukin-1β (pg/ml)	9/45	3.1±3.5	3/21	21.5±3.9	0.03

*Mean values are for all specimens obtained in each group during the first 36 hours after injury (the period of cooling for patients in the hypothermia group). To convert the values for aspartate to micromoles per liter, multiply by 75.13; to convert the values for glutamate to micromoles per liter, multiply by 67.97; to convert the values for interleukin-1β to picomoles per liter, multiply by 0.059.

†P values are for the difference between the values in the hypothermia group and those in the normothermia group; a generalized-linear-regression analysis was used to adjust for intraclass correlation.

a significantly lower mean cerebrospinal fluid concentration of interleukin-1β and glutamate than did those in the normothermia group during the first 36 hours after injury (Table 5). In patients with the higher Glasgow coma scores, the mean interleukin-1β concentration remained significantly lower in the hypothermia group after rewarming (6.6 pg per milliliter [0.39 pmol per liter], vs. 41.4 pg per milliliter [2.44 pmol per liter] in the normothermia group; P=0.003).

DISCUSSION

Several clinical characteristics of severe traumatic brain injury influence patients' outcome. The most important characteristics are the patient's age, the initial Glasgow coma score, the presence or absence

of pupillary abnormalities, and to a lesser extent, CT-based classification of the severity of the injury.[10,16] In our study, the hypothermia and normothermia groups were similar with regard to these characteristics, but the Glasgow coma scores were slightly higher in the normothermia group and the CT class was slightly lower in the hypothermia group. The results of a logistic-regression analysis adjusted for the effects of these clinical characteristics suggest but do not establish conclusively that hypothermia improves the outcome for patients with a Glasgow coma score of less than 8. In the subgroup of patients with an initial Glasgow coma score of 5 to 7, however, hypothermia was associated with a significant improvement in the outcome three and six months after the injury, even after adjustment for the CT class.

In animals with global ischemia and traumatic brain injury, moderate hypothermia (a temperature of 32 to 34°C) reduces secondary brain injury and improves the behavioral outcome.[17-20] The specific effects of hypothermia include reducing cerebral ischemia, edema, and tissue injury and preserving the blood–brain barrier.[21-25] The mechanisms by which hypothermia limits secondary brain injury are ill defined. In uninjured primates, a reduction in the brain temperature from 37 to 22°C caused a linear decrease in cerebral metabolism and preserved high-energy phosphate stores.[26] In rats and primates with experimentally induced cerebral ischemia, however, reducing cerebral activity with inhalation anesthetics did not decrease brain-tissue injury.[27,28] In most of these studies, the cerebral effects of the anesthetics were measured according to the degree of suppression of electrical activity. However, anesthetics may depress only the rate of energy use associated with electrophysiologic activity, whereas hypothermia may reduce the rate of energy use associated with both electrophysiologic activity and the homeostatic functions required to maintain cellular integrity (basal metabolism).[29]

Alternatively, hypothermia may mitigate brain injury by reducing the extracellular concentrations of excitatory neurotransmitters, particularly glutamate.[30] We found that hypothermia significantly lowered ventricular cerebrospinal fluid glutamate concentrations in our patients with an initial Glasgow coma score of 5 to 7. The patients who had no benefit from hypothermia (those with a score of 3 or 4) had cerebrospinal fluid glutamate concentrations similar to those in the corresponding normothermia group. On the basis of these findings, we believe that glutamate is one potential mediator of hypothermia's beneficial effects.

Hypothermia may also reduce secondary brain injury by suppressing the post-traumatic inflammatory response. Extravasation of polymorphonuclear leukocytes in the injured area has been documented very early after several types of experimentally induced brain injury.[31,32] Hypothermia may reduce the infiltration of cells into the injured area by either preserving the blood–brain barrier[24] or reducing the amount of cytokines released. Interleukin-1β is one of several cytokines that appear in the ventricular cerebrospinal fluid soon after traumatic brain injury in humans.[33,34] Because it promotes the adhesion of leukocytes to endothelium and increases capillary endothelial permeability, interleukin-1β is undoubtedly important in initiating the post-traumatic inflammatory response.[35,36] We found that the mean ventricular cerebrospinal fluid concentration of interleukin-1β was significantly lower in the hypothermia group, both during cooling and after rewarming, than in the normothermia group. As with glutamate, this effect occurred only in the patients with an initial Glasgow coma score of 5 to 7.

Treatment with moderate hypothermia for 24 hours did not increase the incidence of complications in these critically ill patients. Although other investigators have documented a hypothermia-related increase in the incidence of infections (particularly pulmonary infection), coagulation disorders, and cardiac arrhythmias, these complications can be attributed to the use of temperatures below 30°C or a cooling period longer than 24 hours.[37,38] The partial-thromboplastin time, though not the prothrombin time, increased slightly during cooling in our patients treated with hypothermia, but we found no indication of clinically important hypothermia-induced coagulopathies[39] or bleeding.

We conclude that treatment with moderate hypothermia (a temperature of 32 or 33°C) for 24 hours, initiated soon after severe traumatic brain injury, significantly improved the outcomes at three and six months in patients without flaccidity or decerebrate rigidity (those with Glasgow coma scores of 5 to 7) on initial evaluation. Our results also suggest an improved outcome 12 months after the injury in this group of patients.

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Long term follow-up of children hospitalized with respiratory syncytial virus lower respiratory tract infection and randomly treated with ribavirin or placebo

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Purpose. **To determine the long term effects of ribavirin therapy in children hospitalized for respiratory syncytial virus (RSV) lower respiratory tract infection.**

Methods. **Fifty-four of 60 children in randomized trials of ribavirin therapy were enrolled in a prospective follow-up study. Subjects were examined annually and had age-appropriate pulmonary function tests; interim histories were obtained from families and personal physicians.**

Results. **Recurrent lower respiratory tract illness was reported at least once for 79% of the ribavirin and 73% of placebo group. In the first 5 years after RSV, 54% of the ribavirin group and 50% of the placebo group reported wheezing. There were no significant differences between the groups in annual rates, timing, or severity of recurrent lower respiratory tract illness. No significant differences in pulmonary function were detected by tests of oxygen saturation, peak expiratory flow and spirometry.**

Conclusions. **Children in the ribavirin treatment group did not have exacerbated respiratory symptoms compared with those in the control group, and their pulmonary function measurements were equal to those of the placebo-treated**

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group, suggesting no long term adverse effect or benefit of ribavirin therapy.

NTRODUCTION

Respiratory syncytial virus (RSV) is a significant pathogen for infants, especially those with prematurity or underlying cardiac or pulmonary disease.[1, 2] Ribavirin, a synthetic nucleoside delivered as small particle aerosol, was approved for treatment of RSV lower respiratory tract infection and licensed for use in the United States for hospitalized children in 1985. In six controlled, randomized studies ribavirin treatment meliorated the course of RSV illness by decreased iral shedding, improved oxygen saturation and improved clinical scores.[3–8] Although serious adverse vents were not associated with ribavirin treatment in hase III trials or post marketing surveys,[9] questions main regarding the long term effects of ribavirin erapy in infancy.

This report presents results of a long term follow-up udy of children enrolled in randomized controlled als of ribavirin in Rochester, NY. The study was tiated in 1983 to determine the long term effects of avirin therapy for respiratory syncytial virus lower spiratory tract infection. Sixty children participated randomized controlled trials of ribavirin or placebo atment of RSV between 1982 and 1985, and 54 of se (ribavirin, 28; placebo, 26) participated in a long m follow-up study that ended in 1993.

Earlier epidemiologic and follow-up studies of RSV ection[10–14] consistently noted higher rates of recurt wheezing and lower pulmonary function scores in dren who had RSV or viral lower respiratory tract ction in infancy than in children without a history wer respiratory tract illness. The study design for wing children in the ribavirin trials was similar to r RSV follow-up studies,[10, 12, 14] consisting of peri- physical examinations and family and physician rts of respiratory and allergic symptoms and to- o smoke exposure. Pulmonary function was aseed by oxygen saturation values and, when children were old enough to cooperate, by peak expiratory flow rates and spirometry.

TABLE 1. Study population and participation

	Ribavirin	Placebo
lation		
rolled in RSV/ribavirin treatment studies 1982–1985	30	30
Died soon after ribavirin trial	2	1
Moved away soon after ribavirin trial	0	3
gible and enrolled in follow-up study	28	26
v-up study measures completed		
SaO_2, LRTI reports, peak flow, spirometry nd challenge	12	15
SaO_2, LRTI reports, peak flow and pirometry	8	5
SaO_2, LRTI reports, peak flow tests	3	3
SaO_2, LRTI reports	5	3
	28	26

k expiratory volume; SaO_2, arterial oxygen saturation.

POPULATION

Sixty children hospitalized with RSV lower respiratory tract infection were enrolled in trials conducted in Rochester during the winters of 1982 through 1985. Three children with severe cardiopulmonary conditions died within 1 year of their RSV infection from complications of their underlying disease, and 3 children moved out of the region soon after discharge from the hospital. The remaining 54 children enrolled in the follow-up study (Table 1).

The three children who moved away and did not enroll and four children who were seen only in the first year of the study have been traced. All are alive and healthy, although one child has cerebral palsy as a result of her premature birth.

METHODS

Parents of children in the randomized trials gave written consent for regular follow-up visits and pulmonary function tests. Children were seen every 1 to 2 years by members of the study team and followed routinely by their personal physicians.

At study visits parents were interviewed about respiratory illnesses or allergy symptoms in their children and about household smoking, and children had oximetry measurements. Beginning at 4 to 5 years of age the children were measured for height and taught to provide peak expiratory flow measurements. Spirometry tests before and after exercise challenge were performed at 7 to 10 years of age. All observations and data were recorded on standard forms. Pertinent characteristics of study participants are summarized in Table 2.

Subsequent lower respiratory tract illness. Recurrent lower respiratory tract illnesses (LRTI) included physician-diagnosed episodes of wheezing, asthma or reactive airway disease, pneumonia, croup, bronchiolitis, and bronchitis. After each study visit we requested from the private pediatricians reports of any respiratory or allergic symptoms in the period since the child was last seen for a study visit. Even when

TABLE 2. Characteristics at enrollment

Characteristics	Ribavirin	Placebo
Age in mo at RSV infection	2.4	4.1
% boys	70	50
No. with:		
Prematurity (<36 wk gestation)	4	3
Premature with BPD	2	2
Cardiac disease	3	5
Wheezing before RSV infection	2	0
% with exposure to household tobacco smoke	61	76
(mother smoke)	50	64
% with family history of allergy	21	31

BPD, bronchopulmonary dysplasia.

ceived ribavirin were no more likely to have RLRTI in ≥2 years of follow-up than those who had received placebo (ribavirin, 58%; placebo, 65%). The proportion of children in each group who reported any RLRTI in 2-year intervals of follow-up is shown in Figure 1, and there are no statistically significant differences between the two groups for any time interval or over the entire period of follow-up.

No differences between the two groups in severity of lower respiratory illness were noted. Thirty-five percent of the ribavirin group and 27% of the placebo group had physician-documented wheezing in two or more annual intervals of follow-up. Eight children (four ribavirin and four placebo) were readmitted to the hospital with lower respiratory tract symptoms, most often asthma, over a period of 8 years after RSV infection.

Tobacco smoke exposure. Children in both groups were exposed to high rates of environmental tobacco smoke (Table 2), and in the first 3 years 69% of children with smoke exposure had lower respiratory tract illness compared with 42% of children in smoke-free homes.

Pulmonary function. *Oxygen saturation values.* Children treated with ribavirin had significantly greater improvement in their oxygen saturation during their acute RSV illness, but no differences existed between the groups at any of the follow-up intervals, and none of the children had arterial oxygen saturation values <95% after the first year of follow-up.

Peak expiratory flow measures. Peak expiratory flow values obtained at 4 to 6 years of age (mean age, 5.7 years) are shown in Table 4. No significant differences existed between the two groups. The ribavirin-treated children were slightly younger and shorter at the time of the peak flow tests, and more were boys (80% *vs.* 46%). The peak expiratory flow rates are close to the predicted values for height for the placebo group and slightly higher than predicted for the ribavirin group.

Spirometry. Forty children, 20 from each group, were able to complete evaluable spirometry examinations. The most recent spirometry test was selected for analysis because test results from older children proved more complete and interpretable (Table 4). No statistically significant differences are seen between the 2 groups on any pulmonary function measure.

TABLE 3. Recurrent lower respiratory tract illness

	%	
	Ribavirin	Placebo
No RLRTI	21	23
≥1 episode of RLRTI	79	77
Any LRT in first 5 years	71	65
Wheeze in first 5 yr	54	50
First LRTI ≥6 yr post-RSV	15	16
First wheeze ≥6 yr post-RSV	15	12
Hospitalized with RLRTI	14	15

TABLE 4. Pulmonary function measurements for all subjects*

	Ribavirin	Placebo	All	
Peak expiratory flow rates				
No.	20	26	46	
Mean age (yr)	5.4	5.8	5.7	
Mean height (cm)	110	114	112	p = .086
Mean % predicted	113	102*	106	*p = .173
Spirometry				
No.	20	20	40	
Mean age (yr)	9.3	9.8	9.6	
Mean height (cm)	134	136	135	p = .498
Mean SaO_2	98.3	98.3	98.3	
Mean % predicted FVC	98.3	99.6	98.9	
Mean % predicted FEV_1	96.4	94.4	95.4	
Mean % predicted FEF_{25-75}	88.6	83.6	86.1	

* Comparisons between groups by Student's *t* test.

SaO_2, arterial oxygen saturation; FVC, forced vital capacity; FEV_1, forced expiratory volume at 1 s; FEF_{25-75}, forced expiratory flow.

Airway reactivity. Of the 27 children in the comparison groups who completed postexercise spirometry testing, none had >25% decrease in spirometry values or were considered to have reactive airways. Two children from the placebo group had 10 to 20% decreases after exercise. Both had a history of RLRTI and had been diagnosed with asthma.

Growth. At 8 to 11 years of age children in the ribavirin group had normal growth and development, with height percentiles averaging between the 40th and 60th percentile. Children in the placebo group were taller than average (50th to 75th percentile) (P = 0.263). Differences between the mean percentiles for weight were also marked (ribavirin, 45 to 65 percentile; placebo, 50 to 80 percentile), but not statistically significant (P = 0.144).

Underlying diseases. Because both treatment groups included children with preexisting cardiopulmonary conditions, we performed a separate analysis that eliminated those who had a cardiac or pulmonary condition affecting pulmonary function, including those diagnosed as having asthma before RSV infection. When children with underlying diseases were removed, the average values for pulmonary function tests and for rates of RLRTI did not change for either the ribavirin or the placebo group, and there were still no significant differences between the two treatment groups.

DISCUSSION

Careful long term follow-up of 54 children did not detect any long term adverse effects or benefits that might be ascribed to rapid and effective treatment of RSV infection in infancy. There were no significant differences in rates, severity or timing of recurrent LRTI in the two groups or on measures of pulmonary function.

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Adverse reactions to trimethoprim-sulfamethoxazole among children with human immunodeficiency virus infection

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Background. **The clinical course of HIV infection is frequently different among infants and children from that in adults. In adults among the most common sources of morbidity related to therapy are adverse drug reactions, notably to trimethoprim-sulfamethoxazole. Although there are case reports of serious adverse reactions to trimethoprim-sulfamethoxazole among infants and children with HIV infection, the precise rate and clinical characteristics of these adverse reactions among HIV-infected children are unknown.**

Methods. **We reviewed the clinical records of all children referred to a regional HIV clinic in a 6-year period. Therapy and suspected adverse drug reactions to therapy were reviewed by one of the investigators not involved in patient care. Adverse drug reactions were identified and characterized according to previously established criteria.**

Results. **During this time 78 children were referred for assessment of possible HIV infection, 45 of whom were ultimately determined to have the infection. Twenty-five were treated with tri-**

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Compliance = 1/Elastance

Resistance = $\frac{\Delta P}{\dot{V}}$ (flow)

$E = IR$ $\quad E/I = R$

$R = \frac{\Delta P}{\dot{V}}$ $\quad$ ΔP is lg for certain flow then resistance is high.

$R = \frac{4}{2}$ $\quad$ $R = \frac{4}{1}$

> Resistance - less flow for same ΔP.

Compliance = $\frac{\Delta V}{\Delta P}$

for given ΔV - if ΔP is larger then C is lower

∴ Compliance is lower (stiffer)

Low compliance - stiffer

High " - more elastic.

↑ Viscoelastic forces — time constants.

P/V loopes - wider ↑ Resistance

Δ in ~~exp~~ insp/exp.

For Obstruction

spirometry { FEV_1 → ↓ and. $\frac{FEV_1}{FVC}$ ratio will ↓ - reported as # - i.e. 1.6

FVC → ↓ or nl (~~if FVC~~ residual volume ↑↑ if FVC ↓ in obstructive dx)

reported in %'es. >80% is relatively nl

70-60% in mod

60-50% mod → sever

50-34% severe

<34% very severe

for FVC - same table as above applies but is predictive of restrictive dx

Anemia

George B. Segel, MD*

The questions below should help focus the reading of this article.

1. What are the clinical and laboratory findings in transient erythroblastopenia of childhood?

2. What are the causes of microcytic/hypochromic anemias?

3. How does iron deficiency anemia differ from β-thalassemia trait?

The evaluation of anemia in pediatric practice involves a number of choices and considerations for the clinician. The pediatrician must decide first which patients should be evaluated, when the evaluation will be done, and which hematologic studies are needed. Are a hemoglobin and packed RBC volume (hematocrit) sufficient or should additional studies including a blood smear, reticulocyte percentage, and RBC indices also be obtained? When the laboratory data are reported, do they reflect age-adjusted standards for their assessment? If the clinical findings and laboratory reports suggest that the patient is anemic, the pediatrician must then establish a definitive diagnosis and provide a specific treatment plan, if required.

A practical approach to the assessment of potential anemia should encompass the following topics: (1) the clinical features that suggest that the patient is anemic (signs and symptoms), (2) criteria for establishing whether or not the patient is actually anemic (normal values), (3) recommendations for screening patients who are otherwise asymptomatic (issues of screening), (4) a method for narrowing the differential diagnostic possibilities (approach to anemia), (5) a description of the laboratory tests needed to arrive at a specific diagnosis with the least discomfort and cost to the patient, and (6) specific treatment or general management for the patient's problem. The first four topics correspond to the discussion that follows. The diagnostic laboratory tests and the management of the anemias are considered in the descriptions of each of the specific disorders.

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HISTORY, SYMPTOMS, AND SIGNS OF ANEMIA

Laboratory assessment of hemoglobin and hematocrit is initiated either because the clinical features of anemia are present or because a screening program has suggested an abnormality. The clinical features of anemia may be evident from the patient's medical history or from results of the physical examination. Small children offer few specific complaints, but parents may describe pallor, excessive sleepiness, tiredness, irritability, or inappropriate behavior. Older children may have shortness of breath, decrease in exercise tolerance, palpitations, syncopy, or orthopnea. Pallor, tachycardia, or signs of cardiac failure are rare but may be evident when the child is examined.

A dietary history of excess milk intake between 6 months and 2 years of age strongly suggests iron deficiency as the cause of anemia. Hematochezia (red blood in the stool) or melena (tarry stools) indicates blood loss and, if chronic, could account for iron deficiency in a patient of any age. A family history of cholecystectomy for stones at a young age or splenectomy may reflect a hereditary hemolytic disorder such as hereditary spherocytosis, and a family origin from the Mediterranean area heightens the possibility of a thalassemia syndrome. The acute onset of anemia after exposure to an oxidant drug strongly suggests glucose-6-phosphate dehydrogenase (G6PD) deficiency leading to hemolysis, which is prevalent in Mediterranean, black and Middle Eastern peoples. The hemoglobinopathies, particularly sickle cell disease and sickle thalassemia, are most prevalent in black populations. The presence of concurrent disease such as chronic inflammation (for example, juvenile rheumatoid arthritis) or chronic renal or hepatic disease may underlie the anemia. The sociologic history also is important because lead intoxication occurs primarily in inner-city areas with older dwellings where lead is present in the paint and plaster. Lead intoxication should be considered if there is a history of pica or in patients living in inner cities.

EDUCATIONAL OBJECTIVE

6. The pediatrician should be able to evaluate a 3-year-old child with anemia, differentiating among iron deficiency anemia, sickle cell anemia, other hemaglobinopathy, anemia of chronic blood loss, and lead poisoning, and develop an appropriate plan for management (Topics, 88/89).

Tortuosity and narrowing of fundal vessels or "cork screw" vasculature of the conjunctiva, which may indicate a severe sickle syndrome, may be identified by physical examination. Glossitis and decreased vibration and position senses suggest a lack of vitamin B_{12}, which is a rare disorder in children. Substantial enlargement of lymph nodes may indicate a neoplastic process, and expansion of the diploe of the bones creating frontal bossing and maxillary overgrowth indicate chronic hemolysis, which is seen in patients with thalassemia syndromes. An enlarged spleen may result from an immune hemolytic anemia or hereditary spherocytosis. Skeletal abnormalities may be seen in persons with Fanconi anemia or the Diamond-Blackfan syndrome, and pigmentation at mucosal-epidermal junctions in older children may be associated with chronic lead poisoning.

WHAT ARE "NORMAL" VALUES FOR HEMOGLOBIN AND HEMATOCRIT?

The results of the hemoglobin and hematocrit measurements (Table 1) should be interpreted in light of their

TABLE 1. Normal Hemoglobin and Hematocrit Values*

Age	Hemoglobin (g/dL)	Hematocrit (%)
Newborn	16.8 (13.7–20.1)	55 (45–65)
2 wk	16.5 (13.0–20.0)	50 (42–66)
3 mo	12.0 (9.5–14.5)	36 (31–41)
6 mo–6 yr	12.0 (10.5–14.0)	37 (33–42)
7–12 yr	13.0 (11.0–16.0)	38 (34–40)
Adult		
Women	14 (12.0–16.0)	42 (37–47)
Men	16 (14.0–18.0)	47 (42–52)

* Results are mean values with ranges in parentheses. From Behrman RE and Vaughan VC (eds).[27]

variation with the patient's age, sex (particularly after puberty), cardiopulmonary status, residence (altitude), and more rarely hemoglobin-oxygen affinity. For example, a hemoglobin value of 13 g/dL is normal for a child 6 months to 12 years of age but is below the normal range for a newborn infant or for a postpubertal boy. The normal values for persons without cardiopulmonary disease do not apply to patients with cyanotic congenital heart disease or chronic pulmonary disease which result in chronic arterial desaturation and secondary "normal" polycythemia. The issue is occasionally more complex if the patient's values are within the normal range for age, sex, and other factors but a documented decrease in hemoglobin and hematocrit values within this normal range has occurred.

ISSUES OF SCREENING

Routine or "screening" values may permit earlier detection of changes when the clinical situation warrants a subsequent measurement. However, the timing of routine hematologic screening in infants and children varies greatly among pediatricians. The hemoglobin and hematocrit values normally decrease during the first 1½ to 2 months of life, and full-term infants may have a nadir in hemoglobin concentration of 10.5 to 11 g/dL, whereas the nadir for premature infants may be 9 to 10 g/dL. For those infants with neonatal anemia resulting from isoimmunization, bleeding, infection, prematurity, or other factors, early follow-up is required because the hemoglobin and hematocrit concentrations decrease to even lower levels. During this time the hematologic values should be closely monitored along with the physical status of the infant. Transfusion should be avoided if the cardiovascular status is stable and the hemoglobin concentration remains greater than 6 g/dL. If the infant requires transfusion, the physiologic nadir of marrow activity may be delayed and be more severe. Consequently, continued monitoring of the hemoglobin and hematocrit concentrations is necessary. There is a particular risk for those newborns with hemolysis and efficient livers who do not require exchange transfusion. The hyperbilirubinemia that warrants careful follow-up does not develop, and a progressive anemia may be overlooked.

A number of pediatric practitioners obtain routine hemoglobin and hematocrit screening tests between 6 and 14 months of age. Such testing yields two important pieces of information. First, in addition to the history, it allows early assessment of a common problem, that is, dietary iron deficiency. Second, it provides a baseline value for future comparison if anemia develops later. The cost-effectiveness of such screening is difficult to assess because of the multiple methods for obtaining hemoglobin and hematocrit values and the difficulty in quantifying the advantage of early diagnosis for the number of patients benefited. However, the cost of a "spun" hematocrit in a pediatrician's office is minimal. A more complete blood cell count including a reticulocyte percentage, blood smear, and RBC indices can be obtained if the initial hematocrit value is low.

APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF ANEMIA

Anemias may be classified on the basis of the size and appearance of the RBCs on the peripheral blood smear. This choice reflects a practical utility in using erythrocyte morphologic features to narrow the diagnostic possibilities. This algorithm helps to limit the hematologic laboratory tests which are ordered and hence potentially reduces the cost of the evaluation. In this scheme there are three major morphologic categories (Fig 1). These include (1) RBCs that are microcytic and hypochromic, (2) those that are normocytic and normochromic, and (3) those that are macrocytic. If the central pallor of the RBC exceeds one third of the diameter of the total cell as observed on a Wright-Giemsa-stained blood smear, the cells are likely hypochromic and, hence, microcytic. It is difficult to find the small lymphocyte nucleus that usually is compared to the RBC diameter for assessment of RBC size. Thus, it is often easier t establish that the majority of cells are hypochromic and use the electronically determined volume from the cell counter to assess RBC volume. If the cells are hypochromic and microcytic, there are five major diagnostic possibilities as shown in Fig 1.

Hypochromic and Microcytic Anemias (Table 2)

Iron Deficiency

Iron deficiency is the most prevalent of hematologic disorders in childhood and affects approximately 5% to 10% of infants.[1] However, iron deficiency is not a complete diagnosis. The iron lack may be due to dietary insufficiency, iron loss from bleeding or, rarely, chronic intravascular hemolysis, and urinary loss. The possibility of bleeding is more ominous in internal medicine where treatment of iron deficiency without an etiologic diagnosis can mask a gastrointestinal malignancy. In pediatrics, our administration of "trials of iron" may be defensible in infants younger than 2 years of age when dietary iron deficiency is most common and carcinoma of the cecum and colon

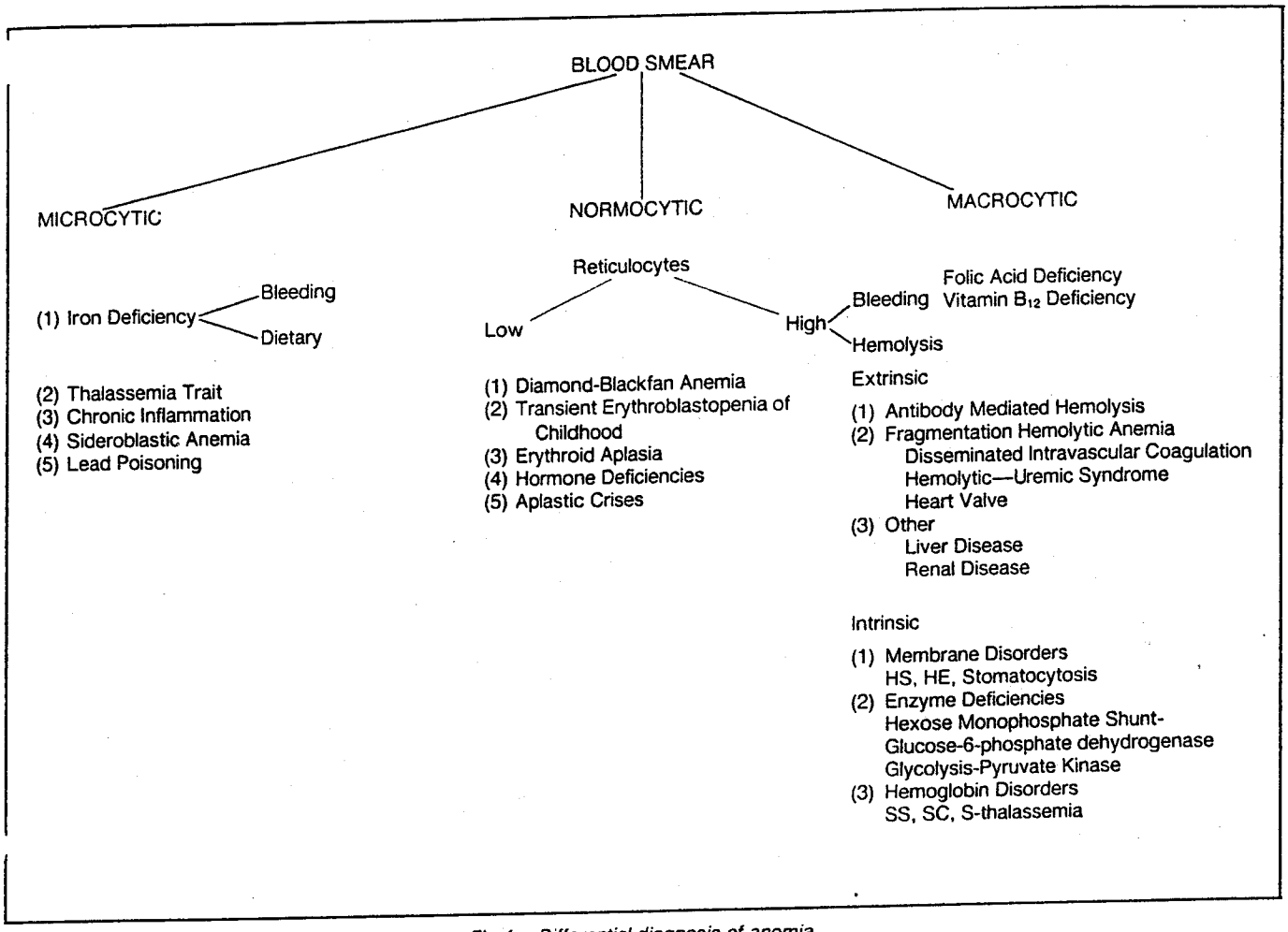

Fig 1. Differential diagnosis of anemia.

nonexistent. A dietary history of excessive and/or exclusive intake of unfortified milk suggests dietary iron lack as the cause for the anemia. Furthermore, bleeding from the gastrointestinal tract in infants may result from gastrointestinal intolerance to large amounts of fresh cow milk. Additional evaluation for gastrointestinal blood loss should be considered in all children who have a normal dietary history. There are a variety of disorders including ulcer disease, gastrointestinal duplication, Meckel diverticulum, inflammatory bowel disease, intestinal polyps, and others that may cause bleeding at any age. These diagnoses will be overlooked unless "trials of iron" are administered thoughtfully. Adequate follow-up is necessary for patients treated with iron, and failure of response or recurrent anemia should warrant a more extensive evaluation to establish bleeding, a thalassemia syndrome, chronic inflammatory disease, or some other problem to explain a hypochromic and microcytic anemia.

In children older than 2 years of age, dietary iron deficiency is less likely the cause of iron deficiency anemia, and there is less justification for iron administration without further evaluation. In an older child with a hypochromic microcytic anemia, the major considerations are bleeding and thalassemia trait (see below). Note that the child's surname may not reflect the ethnic background because the mother rather than the father may be of Mediterranean origin. In the older child, the diagnosis of iron lack should be substantiated with measurements of serum iron, total iron-binding capacity, and ferritin. If results of these studies indicate a diagnosis of iron deficiency, a vigorous search for a bleeding site is indicated. The most common location for bleeding is the gastrointestinal tract. Rarely, occult bleeding may occur into the lungs in idiopathic pulmonary hemosiderosis or Goodpasture syndrome or into a variety of tumors. In patients with chronic intravascular hemolysis secondary iron deficiency may also develop when the capacity of the hemoglobin-binding proteins of the blood is exceeded. Free hemoglobin is deposited in renal tubular cells and the iron is subsequently lost in the urine. These are unusual conditions and should not prevent consideration of the major issue of gastrointestinal bleeding.

As long as the underlying nature of the iron deficiency is considered (dietary *v* bleeding), iron therapy can be administered. Adequate treatment requires elemental iron, 6 mg/kg/d. This is given until the hemoglobin concentration reaches the normal range and then continued for an additional 2 months to replete the iron stores. Black stools are observed

TABLE 2. Laboratory Evaluation of Hypochromic and Microcytic Anemias*

Diagnosis	Laboratory Test	Expected Result
Iron deficiency	Serum ferritin	Low <25 μg/L
	Serum iron and total iron-binding capacity	Low/high
	% iron saturation	Low <15%
	Bone marrow iron stores	Absent
	Stool for occult blood	Positive (if gastrointestinal bleeding)
	Urine for blood, hemoglobin or hemosiderin	Present (if renal loss)
	Ratio of MCV/RBC[26]	>13
β-Thalassemia trait	Blood film	Basophilic stippling
	Hemoglobin electrophoresis	Increased A_2 or F hemoglobin
	Biosynthetic β/α-globin chain ratio	<1
	Ratio of MCV/RBC	<13
	Family studies	Hb/Hct decreased Blood film Anisocysotis Poikilocytosis Basophilic stippling MCV <70 fL/cell
α-Thalassemia trait	No routine specific test	Normal A_2 hemoglobin
	Family studies	Hb/Hct normal or slightly decreased Blood film Anisocytosis Poikilocytosis MCV <70 fL/cell
	Biosynthetic β/α-globin chain ratio	>1
	Specific genetic probe analysis	Absent genes
Chronic inflammation	Nonspecific tests	
	ESR	Increased
	Acute phase reactants C-reactive protein Fibrinogen Haptoglobin	Increased
	Serum ferritin	Increased
	Serum iron + total iron-binding capacity	Low/low
	% iron saturation	Low
	Bone marrow iron stores	Increased
	Bone marrow sideroblasts	Decreased
Sideroblastic anemia	Serum ferritin	Increased
	Serum iron + total iron-binding capacity	Normal to increased/normal
	% iron saturation	High
	Bone marrow iron stores	Increased
	Bone marrow sideroblasts	Increased + "ringed" sideroblasts
Lead poisoning	Blood film	Basophilic stippling
	Erythrocyte protoporphyrin	Increased
	Blood lead	Increased

* Abbreviations: MCV, mean corpuscular volume; Hb, hemoglobin; Hct, hematocrit.

soon after the initiation of iron therapy and serve as an index of compliance with the iron administration.

β-Thalassemia

β-Thalassemia trait is the primary differential diagnostic possibility in patients suspected of having iron deficiency. A diagnosis of thalassemia trait eliminates the need for iron therapy and mandates a genetic evaluation. The gene is carried by approximately 4% of persons of Mediterranean heritage.[2] It is obligatory to evaluate both parents of a child with β-thalassemia trait to establish whether only one or both are affected. Appropriate genetic counseling is indicated either to reassure the parents that future pregnancies are at no risk or to establish clearly the 25% risk for a severe thalassemia syndrome in each subsequent pregnancy if both parents are carriers of the gene.

β-Thalassemia trait implies diminished or absent expression of the β-hemoglobin genes and a decreased β to α biosynthetic globin chain ratio[3] (Table 3). The heterozygous state results in mild anemia, hypochromia (central pallor >⅓ the diameter of the RBC), and microcytosis (mean corpuscular volume [MCV] usually <70 fL per cell). A hemoglobin electrophoresis usually shows an elevation in the percentage of A_2 ($\alpha_2\delta_2$), virtually always >4% or F (α_2,τ_2) hemoglobin.

The severity of the anemia in homozygous β-thalassemia will depend on the β-globin synthesis from the respective parental genes. The genetic defect from each parent may be complete and result in a β^o-thalassemia or partial and produce a β^+-thalassemia. The most severe case results from inheriting two B^o genes wherein no β-globin would be produced. This results in severe anemia during the second half of the first year of life when fetal hemoglobin ($\alpha_2\tau_2$) production normally diminishes and hemoglobin A ($\alpha_2\beta_2$) cannot be produced. There is an almost certain requirement for transfusion therapy with all of the potential complications, including iron overload, hepatitis, and more rarely AIDS, resulting from long term receipt of blood products. A milder condition may result from the inheritance of two β^+ genes. Such

patients usually have an anemia intermediate between β^o-thalassemia major and thalassemia trait and may not require transfusion.

α-Thalassemia

A hypochromic microcytic anemia may result also from a failure of the production of α-globin chains needed for formation of hemoglobins F ($\alpha_2\tau_2$) and A ($\alpha_2\beta_2$). The α-thalassemias are inherited in a more complex fashion resulting from the interaction of four α-globin genes (Fig 2). The severity of the clinical syndrome depends on the number of genes expressed.[4] Absence of all four genes occurs in Asian populations and results in the production of hemoglobin Barts (τ_4 with no α chains) leading to hydrops fetalis and fetal death. The absence of three α-globin genes (one normal gene present) produces a moderately severe chronic hemolytic anemia called hemoglobin H (β_4) disease. The pathophysiology of this syndrome is related to the precipitation of the unpaired β chains in the RBCs, resulting in a Heinz body-type hemolytic anemia in addition to the decrease in overall hemoglobin production resulting from impaired α chain synthesis.

In α-thalassemia trait, there are two absent genes (two normal genes present), and the patient has a hypochromic microcytic blood smear, not unlike β-thalassemia trait but with a normal A_2 hemoglobin on electrophoresis. Anemia is not usually present with this disorder. The condition is common in both the Asian and black populations. However, two defective genes in blacks do not occur on the same chromosome, and thus only the normal and α-thalassemia trait (two gene deletion) phenotypes are seen (Fig 2). Hemoglobins Barts and H and hydrops fetalis do not occur.

α-Thalassemia trait is suspected in patients of the appropriate ethnic background who have hypochromic microcytic RBCs without iron deficiency and with a normal hemoglobin A_2 by electrophoresis. There are more sophisticated techniques to establish this diagnosis by determining the rates of synthesis of α and β chains[3] (Table 3) and, more recently, direct molecular probe analysis of the genes themselves,[4] which in most cases are absent rather than defective in expression (Fig 2).

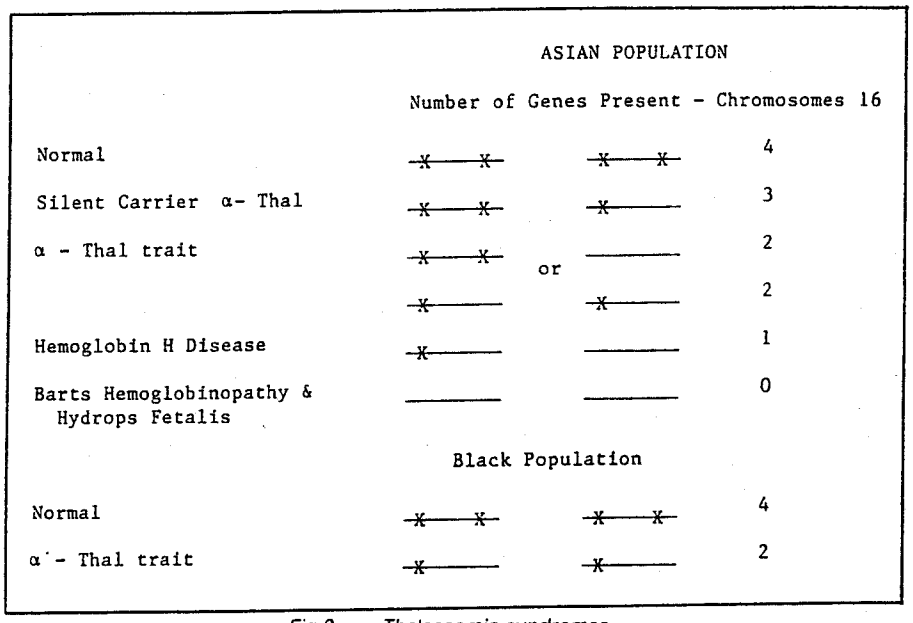

Fig 2. α-Thalassemia syndromes.

Chronic Inflammatory Disease and Sideroblastic Anemias

Anemias associated with chronic inflammatory disease such as juvenile rheumatoid arthritis may be normochromic or hypochromic in nature.[5] The mechanism of the anemia in these circumstances involves failure of mobilization of iron from major storage sites (histiocytes), through the transferrin system to the developing RBCs, and an insensitivity of erythroid precursors to erythropoetin. The transferrin concentration as reflected by the serum iron-binding capacity is low, as is the serum iron concentration.

In contrast are the "sideroblastic" anemias seen more commonly in later life. In the sideroblastic anemias, the iron traverses the transferrin system and appears in the developing erythroblast, but it cannot be inserted into the tetrapyrrol precursor to produce heme. This results in iron accumulation in the mitochondria of the cells. When a bone marrow preparation is stained with prussian blue to demonstrate iron, heavy blue staining is seen in the mitochondria of the developing erythroblasts. These RBC precursors are termed sideroblasts, hence sideroblastic anemia. This often is a preneoplastic condition in older patients, culminating in leukemia.

TABLE 3. Biosynthetic β/α-Globin Chain Ratio*

Disorder	Value
Normal	1.0 ± 0.2
β-Thalassemia trait	0.5 ± 0.2
Thalassemia major	0.1 ± 0.1
Silent carrier α-thalassemia	1.1 ± 0.1
α-Thalassemia trait	1.3 ± 0.2
Hemoglobin H disease	2.6 ± 1.0

* From Nathan.[3] These ratios are determined by measuring the incorporation of ^{14}C-leucine into the α- and β-globin chains of hemoglobin in reticulocytes. ^{14}C-leucine normally is incorporated about equally into each chain reflecting their equal rate of synthesis. Normal β/α ratio is 1:1. If B chain synthesis is impaired as in β-thalassemia trait, the ratio is <1. If α chain synthesis is impaired as in α-thalassemia trait, the ratio is >1.

Lead Poisoning

Lead poisoning is an important consideration in patients with a hypochromic microcytic anemia, particularly if it is associated with coarse basophilic stippling of the RBCs. Lead is an environmental toxin that has no known physiologic function. Blood lead levels greater than 15 to 18 μg/dL produce an increase in the free erythrocyte protoporphyrin concentration.[6] This reflects an inhibition

of critical synthetic enzymes, such as ferrochelatase and aminolevulinic acid dehydratase, necessary for the production of hemoglobin. The inhibition of these enzymes results in an elevated erythrocyte protoporphyrin concentration which can be detected fluorometrically.

The threshold for erythrocyte protoporphyrin elevation occurs well within the "acceptable" range for blood lead concentration observed in urban children.[6] Thus, lead may be an important toxin even at blood levels that are reported as normal. A critical issue in lead intoxication is the potential for lead exposure through ingestion of contaminated paint and plaster or breathing contaminated dust in inner-city areas. Children in these areas may have anemia thought initially to result from iron deficiency. The contributory role of lead in the pathogenesis of the anemia is difficult to assess because dietary iron deficiency is also often present. The evaluation of inner-city children with or without a hypochromic anemia is warranted. The assessment of the possibility of a significant lead burden with prompt evaluation could prevent debilitating neurologic complications from CNS lead toxicity. The treatment for lead poisoning involves, most importantly, elimination of the environmental exposure. Appropriate chelation therapy with dimercaprol and EDTA may be necessary, depending on the patient's clinical condition and lead burden.[7]

TABLE 4. Laboratory Evaluation of Normocytic Anemias*

Diagnosis	Laboratory Test	Expected Result
Anemias with low reticulocyte percentage		
Diamond-Blackfan anemia	Bone marrow examination	Decreased erythroid precursors
	Fetal hemoglobin and i antigen	± Increased
	Mean corpuscular volume	± Macrocytosis
Transient erythroblastopenia of childhood	Bone marrow examination	Decreased erythroid precursors
Erythroid aplasia	Bone marrow examination	Decreased erythroid precursors
	Chest x-ray or CT scan	± Enlarged thymus
	Immunologic studies	Antibodies against erythroid precursors
Hormone deficiencies	Hormone assays	Decreased thyroid, glucocorticoid, testosterone, or growth hormones
Aplastic crises	History	Underlying hemolytic disease
	Bone marrow examination	Decreased erythroid precursors
	Serology and/or viral culture	Parvovirus
Anemias with high reticulocyte percentage		
Extrinsic		
Antibody mediated	Blood film	Spherocytes
	Antiglobulin (Coombs) test	Positive
	Complement consumption assay	Positive (used if Coombs test is negative)
	Tests for underlying disease	See Table 5
Fragmentation hemolytic anemia	Blood film	Fragmented RBC
	Tests for underlying disease	See Table 6
Intrinsic		
Membrane disorders	Blood film	Characteristic RBC: spherocytes, stomatocytes, elliptocytes
	Incubated osmotic fragility	Increased fragility if spherocytes present
	Autohemolysis	Increased and corrected by glucose
	Membrane protein-structural analysis (investigational)	Abnormal, eg, decreased spectrin in spherocytosis
Hemoglobin disorders	Blood film	Irreversibly sickled cells in severe sickle syndromes: SS, SC, or S-thalassemia
		Targeting in CC, also in SS, SC, and S-thalassemia
	Hemoglobin electrophoresis or Isoelectric focusing	Abnormal
		Hemoglobin(s) present
Enzyme disorders		
Glucose-6-phosphate dehydrogenase deficiency	Screening tests	Positive
	Enzyme assay	Low activity
Pyruvate kinase and other glycolytic defects	Enzyme assay	Low activity
		High K_M (some)

Normochromic and Normocytic Anemias (Table 4)

Normochromic anemias may result from increased destruction of RBCs, ie, hemolytic anemia, or failure of RBC production. Clinically, these conditions are defined by the "reticulocyte count." This measurement indicates the percentage of RBCs with residual RNA material reflecting their young condition. The normal reticulocyte percentage is approximately 1.0, which represents approximately 50,000 reticulocytes per microliter of blood. The absolute count is more relevant in assessing the bone marrow response to anemia which should reach six to eight times the resting level. Thus, for an anemic child with a hematocrit value of 15%, an RBC count of 1.5 million and a reticulocyte percentage of 4, the absolute number of reticulocytes is 60,000/μL which is an inadequate response for the degree of anemia.

Low Reticulocyte Count

The finding of a low reticulocyte percentage in an anemic patient indicates that there is an inadequate bone marrow response to the low hemoglobin and hematocrit values.

Low numbers of reticulocytes may reflect a selective aregenerative anemia or general bone marrow failure associated with granulocytopenia and/or thrombocytopenia. Thus, it is critical to rule out bicytopenia or tricytopenia which imply a totally different differential diagnosis including infiltrative diseases of the marrow and aplastic anemia. The following conditions are limited to those with selective erythroid failure with normal granulopoiesis and thrombopoiesis.

Diamond-Blackfan Syndrome

Patients with Diamond-Blackfan syndrome usually have progressive severe anemia during the first year of life. The reticulocyte percentage in their blood is characteristically near zero, indicating the aregenerative nature of the anemia. Examination of the bone marrow reveals a paucity or absence of erythroid precursors in more than 90% of the patients. At the time of diagnosis, there may be evidence of fetal erythroid proliferation with an increase in the hemoglobin F concentration, an increase in the expression of the i antigen, and macrocytosis. Approximately one third of the patients exhibit some associated congenital anomaly such as short stature, abnormal faces with cleft palate or eye abnormalities, abnormalities of the thumb, congenital heart disease, or mental retardation.

The pathogenesis of this disorder is not entirely clear, but the erythroid failure appears to result, in part, from decreased numbers of bone marrow progenitors (CFUe and BFUe) and peripheral blood BFUe. More recent data indicate that these progenitors may be relatively insensitive to erythropoietin.[8] A familial occurrence of the disorder has been reported, but the mode of inheritance is unclear, reflecting either a dominant pattern with incomplete penetrance or, in some cases, recessive inheritance. Although this disorder is not common (approximately 300 cases have been reported),[9] it is critical that it be recognized early to ensure the best response to therapy. The anemia in the Diamond-Blackfan syndrome is progressive and will require repeated transfusions if untreated. However, most patients will show improvement in their reticulocyte response and hematocrit concentrations when given glucocorticoids such as prednisone. The drug is administered initially at 2 mg/kg/d. This is continued until the hemoglobin and hematocrit values are normal. The dose of prednisone is then tapered to provide the minimum necessary for maintenance of acceptable hematologic values. To minimize the side effects from the glucocorticoids, an every-other-day regimen is preferred. Many of these patients will require prolonged prednisone therapy. Some, perhaps 15% to 20%, will remit spontaneously during the course of the disease with complete loss of their glucocorticoid requirement.

Transient Erythroblastopenia of Childhood

Transient erythroblastopenia of childhood and Diamond-Blackfan anemia are the most notable differential diagnostic possibilities in children with reticulocytopenic, normochromic anemias. Transient erythroblastopenia of childhood is an uncommon disease of unknown etiology (more than 150 cases reported)[9] that results in acquired erythroid bone marrow failure. The patients are usually older with a mean age of 1½ to 2 years as compared to those with Diamond-Blackfan anemia, who are usually less than 1 year of age. They have a normochromic normocytic anemia with a low absolute reticulocyte count. The other formed elements of the blood are normal. In contrast to patients with Diamond-Blackfan anemia, these patients do not have congenital anomalies or short stature. Furthermore, no evidence for toxic, immune, or specific viral causes has been demonstrated. In particular, the parvovirus, which may be responsible for aplastic crises in patients with chronic hemolytic anemias, is not associated with transient erythroblastopenia of childhood.

Aplastic crises in chronic anemias such as spherocytosis, ellipocytosis, and sickle cell disease may mimic the clinical features of transient erythroblastopenia of childhood and should be considered in the differential diagnosis. There is no specific diagnostic test for transient erythroblastopenia of childhood, but the bone marrow has a paucity of erythroid precursors (unless the patient is already recovering), and no evidence for an underlying hemolytic anemia can be found.

Treatment involves observation unless the hemoglobin and hematocrit levels decrease to symptomatic levels, at which time the judicious use of packed RBC transfusions is indicated. The disease usually persists a few weeks to several months, resolves spontaneously, and almost never recurs.[10,11]

Erythroid Aplasia

Erythroid aplasia is a rare condition primarily seen in the adult population which results from antibodies directed at the RBC precursors. Approximately one half of these patients have a thymoma. The treatment of this disease involves removal of the primary thymic tumor or glucocorticoid therapy if no tumor is present.

Hormone Deficiencies

A number of endocrine disorders may produce anemia. In hypothyroidism the anemia usually is normochromic and normocytic (occasionally slightly microcytic) and may be associated with irregularly shaped, spiculated RBCs seen on the peripheral blood smear. Glucocorticoid, testosterone, and growth hormone deficiencies also may result in normochromic anemia.

Aplastic Crises (Owren Crisis)

Erythroid aplastic crises are characterized by a relative failure of RBC production. Such crises occur in patients with hemolytic anemia during viral illness, particularly those due to parvovirus infection.[12] Parvovirus also has been implicated in the genesis of Fifth disease and a syndrome of rash and arthritis in adults. The condition is particularly important in patients with a high reticulocyte percentage and increased RBC turnover. Normal RBC survival is approximately 120 days. If no RBCs are produced for ten days in a normal person, there is little effect on the

hemoglobin and hematocrit values. In contrast, if the patient has a hemolytic anemia such as hereditary spherocytosis, or sickle cell anemia and an RBC life span of 20 days, a marked decrease in hemoglobin and hematocrit concentrations may be observed. Aplastic crises may be life threatening to the patient with chronic hemolysis and must be considered when these patients are evaluated for febrile illnesses.

High Reticulocyte Count

The clinical definition of hemolysis is the presence of an elevated reticulocyte count in the absence of bleeding. The second part of this definition is critical because occult bleeding can result in clinical findings identical with hemolysis. The subsequent conditions under the heading of "High Reticulocyte Count" are discussed with the assumption that the patient is not bleeding or suffering from an aplastic crisis that might obscure the reticulocytosis.

Conditions Extrinsic to the RBC (Acquired)

The conditions extrinsic to the RBC that cause hemolysis are usually acquired rather than inherited. These can be divided into two major categories, each of which encompass a number of problems: (1) antibody-mediated hemolysis and (2) fragmentation hemolysis.

Antibody-Mediated Hemolysis. Antibody-mediated or immune hemolysis is an unusual problem but may be associated with a number of pathologic conditions (Table 5). The involved antibody frequently is IgG or "warm"-type and less frequently IgM or "cold"-type antibody. The hemolysis secondary to cold antibodies results from complement fixation and complement-mediated lysis and is dependent upon the temperature at which the antibody is active, ie, the "thermal amplitude" of the antibody. Antibody-mediated RBC destruction may be autoimmune in nature and idiopathic. It also may be related to a viral syndrome (eg, infectious mononucleosis) or drug or reflect an underlying collagen vascular disease, lymphoma, or other disorder.

TABLE 5. Antibody-Mediated Hemolysis

- Autoimmune—warm antibody
  - Idiopathic
  - Secondary
    - Collagen-vascular (eg, lupus erythematosis)
    - Lymphoma
    - Hypogammaglobulinemia
    - Viral (Epstein-Barr virus, human immunodeficiency virus)
    - Drug related (eg, methyldopa, quinine, penicillin)
- Autoimmune—cold antibody
  - Idiopathic, lymphoma, *Mycoplasma* infection
- Isoimmune
  - Incompatible transfusion
  - Hemolytic disease of newborn

The clinical severity of antibody-mediated hemolysis varies greatly. The patient may have no anemia and only mild reticulocytosis or profound anemia requiring transfusions. The peripheral blood smear is normochromic but there are characteristically a large number of spherocytes present. These represent cells that have lost membrane in relationship to their volume and appear dense and round. The Coombs test is diagnostic in most of these patients. Coombs reagent is an antihuman γ-globulin (or complement) that reacts with the antibody or complement on the RBC surface to agglutinate the cells. This test is sensitive enough to detect approximately 200 molecules of IgG per cell compared with a normal level of less than 50.[13] There are rare instances of immune hemolysis that occur below the Coombs-detectable density of antibody but can be detected by a special complement consumption assay.[13] The intensity of the Coombs test result does not necessarily reflect the severity of the immune hemolysis in an individual patient, although a diminution in the degree of Coombs' positivity usually accompanies resolution of the disease.

Treatment for autoimmune hemolytic anemia secondary to warm antibody involves the use of glucocorticoids such as prednisone at a dosage of 2 mg/kg/d. The patient should be maintained on this dosage until the hemoglobin, hematocrit, and reticulocyte percentage approach normal levels, and then the prednisone dosage should be tapered. Most patients respond promptly to this treatment, but in some relapsing or chronic hemolysis will develop which may be related to an underlying disorder such as lupus erythematosus or lymphoma. For those rare patients in whom prednisone is ineffective, a number of other treatments have been used with varying success. These include splenectomy, immunosuppressive drugs, intravenous γ-globulin, and plasmapheresis.

Fragmentation Hemolysis. Microangiopathic damage to RBCs results from mechanical injury as the cells traverse a damaged microvascular bed. The anemia is normochromic but the RBCs are markedly misshapen. The characteristic cell is a "schistocyte" or fragmented RBC which may take a number of shapes or forms. Such cells are seen in patients in whom fibrin has been deposited in the vasculature by intravascular coagulation and in patients with renovascular disease such as the hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, or giant hemangiomata (Kasabach-Merritt syndrome) (Table 6). Similar clinical findings may be seen with larger vessel disease as in poorly epithelialized replacement heart valves.

The treatment of the disorder should be directed toward the underlying condition, and the prognosis is dependent upon how well that condition can be treated. Transfused RBCs will, of course, suffer the same fate as those endogenously produced, limiting the effectiveness of transfusion therapy. Examination of the blood smear in these conditions is critical because it provides the clue that the hemolysis results from RBC fragmentation.

Other. Hemolysis may complicate other conditions that generate soluble factors in plasma that are toxic to the RBC membrane. In patients with liver disease, there may be an alteration of the ratio of cholesterol to phospholipid concentrations in the plasma which results in changes in the composition of the RBC mem-

TABLE 6. Fragmentation Hemolysis

Microangiopathic (small vessel disease)
Disseminated intravascular coagulation
Hemolytic—uremic syndrome
Thrombotic thrombocytopenic purpura
Renovascular disease (eg, hypertensive)
Giant hemangiomata
Other
Cardiac prosthesis
Burns

brane, shortening the RBC life span. Liver disease may be associated with at least two somewhat different morphologic findings on the peripheral blood smear, one characterized by large numbers of target cells and the other by spiculated cells.[14]

Anemia may complicate renal disease for several reasons including decreased RBC production and shortening of the RBC life span. The RBCs usually appear normal but may be scalloped or misshapen. The changes seen in microangiopathic hemolytic anemia are seen if the underlying cause of renal failure is related to hypertension or the hemolytic uremic syndrome.

Conditions Intrinsic to the RBC (Inherited)

The RBC is constructed of three primary components: the membrane, a variety of enzymes to support RBC metabolism, and hemoglobin. A number of inherited abnormalities are related to each of these components, and clues often are available from blood smear findings.

Membrane Disorders. The major RBC membrane disorders include hereditary spherocytosis, hereditary ellipocytosis, and hereditary stomatocytosis. The most common of these is hereditary spherocytosis with a prevalence of approximately one in 5,000. The spheroid RBCs result from a deficiency of spectrin, one of the structural proteins of the RBC membrane.[15] Hereditary spherocytosis usually is inherited as an autosomal dominant condition, and a family history is found in approximately 75% to 80% of the patients. It is particularly helpful to ask the parents of a patient about episodes of anemia (aplastic crises), splenectomy, cholelithiasis, or cholecystitis or unexplained jaundice in their own medical history. It is not uncommon to make the diagnosis of hereditary spherocytosis in a child and detect the same condition in one of the parents who has been asymptomatic. Clinically, the patient may have a history of episodic pallor or jaundice or incidental splenomegaly. It is a simple matter to obtain a blood cell count and smear from each of the parents and examine their abdomens at the time the patient is seen.

The blood smear is normochromic with many spherocytes (usually greater than 10%). Polychromatophilia representing young reticulocytes often can be seen. There is no easily obtained, definitive diagnostic test, although positive results of an incubated osmotic fragility test support the diagnosis of hereditary spherocytosis. However, results of an osmotic fragility test will be abnormal if there are spherocytes present from any cause, eg, immune hemolytic anemia. For these reasons, all of the clinical findings and blood smear findings are critical in establishing the diagnosis of hereditary spherocytosis. The evaluation of the patient should include a Coombs test to ensure that splenomegaly, reticulocytosis, and peripheral spherocytosis are not secondary to antibody on the RBC surface.

The spherocytes in hereditary spherocytosis are destroyed almost exclusively in the spleen; thus, splenectomy provides a cure for the hemolysis associated with this disorder. There is some controversy as to whether all patients with hereditary spherocytosis should have their spleens removed. The severity of the disease varies greatly, and hence the management should be tailored to the individual patient. It has been our practice not to remove the spleens of those patients who are growing normally and have normal hemoglobin and hematocrit values and a reticulocyte percentage less than 10. Their management includes folic acid supplementation and periodic reevaluation. We alter this recommendation if the patients experience repeated aplastic crises, have extraordinary splenomegaly, or deteriorate in their clinical course. For those patients with more severe anemia and reticulocytosis we try to delay splenectomy until the age of 5 or 6 years. It is not advisable to remove the spleen from children younger than 2 years of age because of the marked risk of sepsis from encapsulated bacterial organisms.[16]

Hereditary ellipocytosis (ovalocytosis) also is a disorder with dominant inheritance. The clinical findings are variable, and the patients may be totally asymptomatic and have a normal hemoglobin value and reticulocyte percentage or have a moderately severe hemolytic anemia. The blood smear is normochromic but there are numerous oval shaped RBCs seen. The osmotic fragility test is normal unless spherocytes are present also. Splenectomy has been helpful in those patients who are severely affected.

Hereditary stomatocytosis likely represents a family of disorders.[17] The RBCs of some of these patients appear to have excess water ("hydrocytes"), whereas others appear to be dehydrated ("xerocytes"). The inheritance of this disorder varies and may be autosomal recessive or autosomal dominant. Splenectomy has been of variable benefit[18] and is particularly unsatisfactory if the hemolysis is not corrected, because severe thrombocytosis may develop in association with the persistent postsplenectomy hemolysis.

Enzyme Deficiencies. RBCs contain two major enzymatic pathways for the metabolism of glucose. Deficiencies of enzymes in each of the pathways may occur. The most common defect, G6PD is a sex-linked condition that involves a deficiency of the major enzyme of the hexosemonophosphate shunt. Absence of this enzyme results in a decrease in the oxidative protective mechanism for the sulfhydryl groups of the membrane and hemoglobin. This disorder is common worldwide and is present in 10% (A-minus variety) of the American black male population. This variety of the enzyme is unstable and is

present in relatively normal amounts in reticulocytes but disappears rapidly as the cell matures. Fortunately, hemolysis occurs in the A-variety only with a severe oxidative insult. Normal dosages of aspirin or sulfonamides usually do not cause problems. However, antimalarial agents such as primaquine cause a syndrome of rapid RBC hemolysis, reticulocytosis, and hemoglobinuria which can be life threatening. This disorder is seen also in persons from the Mediterranean area and the Middle East. Such individuals may have deficiency of the enzyme in their entire population of RBCs which makes the disorder potentially more severe.

The peripheral blood smear in these patients is normochromic and for the most part normocytic. There may be minor changes in RBC morphology, but they are not diagnostic. A variety of screening tests are available to detect the deficiency of G6PD or of reduced glutathione, but the definitive test is a G6PD assay which can be performed in most clinical laboratories. Other defects of the hexose-monophosphate shunt such as 6-phosphogluconate dehydrogenase deficiency, glutathione reductase deficiency, and γ-glutamyl cysteine synthetase deficiency have been described but are rare.

Defects in the RBC glycolytic pathway, the other major glucose-metabolizing pathway, are rare. The most common of these is erythrocyte pyruvate kinase deficiency which results in diminished energy production (adenosine triphosphate) by the RBC. Most of these disorders are inherited in a recessive fashion and may result in striking hemolytic anemia when they are present.

Hemoglobin Disorders. The primary consideration among the hemoglobinopathies is given to sickle hemoglobin and the sickle cell syndromes. The sickle gene is carried by approximately 8% of the black population and may be as high as 2% in Mediterranean populations. Sickle cell syndromes are recessive disorders and persons with sickle cell trait are usually asymptomatic. Rarely, the trait condition may be complicated by renal papillary necrosis and hematuria, but other vasoocclusive complications occur only with severe hypoxic or hypotensive stress.

Of primary clinical concern are the severe sickle syndromes that include homozygous sickle cell anemia (SS disease), sickle thalassemia, sickle hemoglobin C disease (SC disease), and some rare variants such as SD and S-O-Arab. Although the anemia in these conditions is classified as normochromic, there are features of the peripheral blood smear that raise the suspicion of one or another of these diseases. The most important clue for the clinician is the presence of irreversibly sickled cells. These may have the usual sickled crescent shape or be eliptoid cells containing a dense concentration of hemoglobin (dense elliptocytes). Their presence is highly suggestive of a severe sickle syndrome, and irreversibly sickled cells are not seen in persons with sickle cell trait. Other features may suggest one or another of these syndromes. For example, the presence of microcytosis and hypochromia suggests sickle-thalassemia (or occasionally SS disease with concomitant iron deficiency). A large number of "target cells" in conjunction with irreversibly sickled cells may indicate SC disease, although target cells are seen in SS disease as well.

The clinical features of the sickle syndromes are related to (1) chronic hemolytic anemia, (2) intravascular sickling, and (3) a susceptibility to infection with encapsulated organisms. Sickle hemoglobin containing RBCs have a shortened RBC life span, and thus hemolytic anemia is characteristic of the disease. The hematocrit in SS disease usually is between 20% and 25% with a reticulocyte percentage of 15% to 20%. The anemia is complicated by episodic intravascular sickling which results in vasoocclusive crises. These episodes may be related to abnormal adherence of sickle hemoglobin containing cells to endothelium[19,20] and to the concentration of sickle hemoglobin within the cell.[21] The frequency of painful, vasoocclusive crises is not predicted by the severity of the anemia or the abnormalities found in the blood smear.

The susceptibility to infection with encapsulated organisms appears related to a number of factors which include relative hypofunction of the spleen[22] and potential immunologic dysfunction.[23]

The treatment of severe sickle syndromes remains symptomatic and supportive. Folic acid is administered at 1 mg/d to prevent a superimposed folic acid deficiency. Penicillin, 125 mg twice per day, should be administered prophylactically because of the susceptibility to encapsulated organisms (particularly pneumococcus), and the pneumococcal, meningococcal, and *Haemophilus* influenzal vaccines should be given at 2 years of age. Painful crises are treated primarily with fluid therapy and analgesia. If the crises are prolonged or particularly severe, a partial exchange transfusion may be used. Specific drug therapy has not been universally accepted, although there are investigational agents that may prove useful. One such agent, cetiedel, produces slight swelling of the RBCs with reduction of the concentration of the sickle hemoglobin. This treatment shortened the duration of crises in one controlled study.[24] Occasional patients who have repeated intractable crises, CNS symptoms, leg ulcers may require prolonged transfusion therapy and adjunctive treatment with desferol to decrease the rate of iron accumulation.

The sickle syndromes were reviewed in detail by Pearson[25] and are not considered here further.

Macrocytic Anemias (Table 7)

Macrocytosis may be observed in patients with a marked reticulocytosis, aplastic anemia, and dyserythropoetic anemias without association with a megaloblastic bone marrow. Reticulocytes are normally larger than mature RBCs, and extreme reticulocytosis can increase the mean cell volume. Furthermore, the MCV varies with the age of the patient,[9] and we consider RBCs macrocytic if the MCV exceeds 2 SD above the mean or, for older children and adults, 100 fL per cell. The megaloblastic anemias, particularly folic acid and vitamin B_{12} deficiency, produce a megaloblastic bone marrow and peripheral macrocytosis. The characteristic RBCs on the blood smear are macroovalocytes, and there often are

TABLE 7. Laboratory Evaluation of Macrocytic Anemias

Diagnosis	Laboratory Test	Expected Result
Vitamin B_{12} deficiency	Blood film	Macroovalocytes, Howell-Jolly bodies; nucleated RBC and hypersegmented granulocytes
	Serum vitamin B_{12}	Low <100 pg/mL
	Bone marrow examination	Megaloblastic erythroid and granulocyte precursors
Folic acid deficiency	Blood film	Same as above
	Serum folate	Low <3 ng/mL
	RBC folate	Low <160 ng/mL
	Bone marrow examination	Same as above

nucleated RBCs and Howell-Jolly bodies (nuclear remnants) present. The characteristic finding in a megaloblastic bone marrow is the dissociation in the maturation of the nucleus as compared to the cytoplasm. Developing erythroblasts are observed with large reticulated nuclei when substantial amounts of hemoglobin are present in the cytoplasm. Normal RBCs at this maturational stage would have markedly condensed nuclei which are ready for extrusion.

Folic Acid Deficiency

The body stores of folic acid are small in comparison to the daily requirement, and dietary deficiency may result in a megaloblastic bone marrow with anemia, granulocytopenia, and thrombocytopenia. The syndrome of megaloblastic anemia of infancy is seen infrequently today with current formula and nutritional supplementation. This syndrome used to occur during the first 1½ years of life and apparently resulted from a combination of dietary insufficiency, rapid growth, and concurrent illness. An increased requirement for folic acid is present during pregnancy and in patients with chronic hemolytic anemias. Thus, folic acid most commonly is administered to prevent a more profound anemia in patients with hereditary spherocytosis, sickle cell disease, and other chronic hemolytic problems. The usual administered dosage is 1 mg/d.

Rarely, folic acid deficiency may complicate malabsorption syndromes, drug therapy (eg, diphenylhydantoin and trimethoprim), or alcoholism. The diagnosis may be established by measurement of the serum folic acid concentration. It is possible for the serum folic acid level to be low when the RBC folic acid level is normal, but such patients should not yet manifest a macrocytic anemia. The diagnosis of folic acid-induced megaloblastic anemia can be established if the morphologic features of megaloblastic anemia, an MCV greater than 100 fL per cell, hypersegmented granulocytes on the peripheral blood smear, and a low serum folate level are present. It is critical to rule out concomitant vitamin B_{12} deficiency because the administration of therapeutic amounts of folic acid will correct the hematologic findings of vitamin B_{12} deficiency but will not treat the neurologic findings. It is safer to administer physiologic quantities of folic acid, 50 to 100 μg/d, and monitor the reticulocyte percentage. If a diagnosis of folic acid deficiency is correct, a reticulocytosis, proportional to the degree of anemia, will occur on the fifth through eighth day of treatment. Maintenance therapy of 1 mg/d can then be provided.

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency also can result in a pancytopenia with macrocytosis, hypersegmented granulocytes, and bizarre misshapen RBCs on the blood smear. In children, vitamin B_{12} deficiency is rare but may result from a number of causes that include true pernicious anemia, congenital absence of intrinsic factor, and ileal disease. The clinical findings may include not only anemia, granulocytopenia, and thrombocytopenia but also gastrointestinal complaints and neurologic manifestations which may become irreversible if not treated with specific therapy. The diagnosis can be confirmed by measurement of the serum vitamin B_{12} concentration which is normally between 200 and 900 pg/mL. In patients with pernicious anemia, a gastric analysis will reveal little gastric juice and a pH greater than 5 even after stimulation with a secretagogue. Almost all patients with pernicious anemia will have antibodies to parietal cells and about two thirds will have antibodies to intrinsic factor. Treatment of vitamin B_{12} deficiency requires lifetime parenteral administration of the vitamin. The initial treatment is 500 μg/d, vitamin B_{12} for ten days to restore the tissue levels, and then 500 μg every 2 months. The anemia associated with vitamin B_{12} deficiency usually will resolve 1 to 2 months after initiating parenteral therapy.

SUMMARY

The differential diagnosis of anemia is made easier by classifying RBC morphology as (1) hypochromic and microcytic, (2) normochromic and normocytic, and (3) macrocytic. This limits the number of diagnostic considerations and, hence, limits the laboratory evaluation. There are relatively few considerations if the RBCs are hypochromic and microcytic, including iron deficiency and the thalassemia syndromes. If the RBCs are normochromic, the reticulocyte percentage indicates whether the bone marrow is providing an appropriate response for the degree of anemia. There also are few possibilities if the reticulocyte percentage is low, ie, Diamond-Blackfan syndrome and transient erythroblastopenia of childhood. In the absence of bleeding, a brisk reticulocyte response indicates hemolysis due either to an intrinsic (congenital) or to extrinsic (acquired) RBC defect. The patient's history and physical examination findings may provide additional clues, and RBC features such as irreversibly sickled cells or spherocytes may indicate a specific diagnosis. Finally, the macrocytic anemias are suggested when the MCV exceeds 100 fL per cell and there are macroovalocytes on the blood smear. Such findings warrant further exploration of vitamin B_{12} and folic acid deficiency syndromes.

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Self-Evaluation Quiz

4. A 2-year-old apparently healthy boy is pale and has an hematocrit of 24%. There is no history of chronic illness, blood loss, or unusual diet. Each of the following would be consistent with a diagnosis of transient erythroblastopenia of childhood, *except*:

A. Reticulocytopenia.
B. Normochromic RBCs.
C. Congenital anomalies.
D. Normal WBC count and differential.
E. Bone marrow examination shows decreased erythroid precursors.

5. Each of the following is a cause of microcytic/hypochromic anemias, *except*:

A. Iron deficiency.
B. Thalassemia trait.
C. Chronic inflammation.
D. Folic acid deficiency.
E. Lead poisoning.

6. A 1-year-old girl has a hemoglobin concentration of 9 g/dL. Her father is of Greek descent. Which of the following would suggest that she has β-thalassemia trait rather than iron deficiency?

A. History of large intake of fresh cow milk.
B. Guaiac-positive stools.
C. Blood smear shows hypochromic and microcytic RBCs.
D. Low serum iron concentration.
E. Normal serum ferritin concentration.

Glomerulus - free filter $\bar{x}$ proteins + immunoglobulins
unbound diuretics filter → tubule

Prox tubule conv - lots of surface area for reabs of H_2O, lytes, glucose, AA, etc.
lots of mitochondria → ATP for active transport.

straight - less surface area, fewer mitochondria

Reabs: glucose + other sugars
↳ coupled to Na 1:1) active mechanism [mannitol has a system for active reabsorption ∴ → osmotic diuresis]

Na+ - 60-70% reabsorbed in prox tubule.

out Na^+ → ← H^+ in out

Na^+ → $SO_4^{=}$ $PO_4^{=}$ AA's organic A's ←

Na^+ ↔ ATPase ↔ K^+

H_2O - 70-80% of reabsorption here ∝ osmotic gradient

K^+
- reabsorption proportional to Na+ + H_2O reabsorption
- K^+ secretion in straight + distal convoluted tubule
- reabs is passive, balance dependent on K^+ load and urine flow rate, acid/base balance, GFR, etc. (related to Na^+ reabsorption)

Ca^{++} - bound Ca^{++} ∝ filtered @ glomerulus.
- ion Ca^{++} freely filtered (if Alb nl = 55-60% of total serum Ca^{++})
- of filtered (i.e. ion Ca^{++}) 50-70% reabs in prox tubule
- reabsorption via passive + active methods
  - active via Ca^{++}-Mg^{++} ATPase (this hypothesized ± in distal tubule) → via electrochemical gradient
  - hi concentrations of diuretics inhibit this pump.

loop of Henle - fewer mitochondria - passive processes dominate.
important in ability to produce concentrated urine

Na, K, Cl together

descending limb: H_2O reabsorbed + conc of Na, Cl, urea ↑.

thin ascending limb: relatively impermeable to H_2O, but Na^+ + Cl^- reabsorbed

net: nearly isoosmotic before reaching distal conv. tubule.

Distal Tubule - lots of mitochondria + Na/K ATPase → for Na reabs.
- relatively impermeable to H_2O

20-25% of filtered Ca^{++} reabs here - active + passive
50-60% " Mg " .

distal convoluted:
++ mitochondria
hypotonic filtrate when enters
little H_2O reabsorption
Na^+ actively reabsorbed throughout this section
K^+ secreted in the most distal portion (near collecting duct)
↑10% Ca^{++} remaining @ this point
if parathormone, thiazide diuretics, ↑ PO_4, ↑ distal HCO_3 → ↑ Ca^{++} reabsorption here

distal straight

Collecting Duct
principal + intercalated cells
ADH → H_2O reabs
Aldost active here: Na^+ in + K^+ out via Na/K ATP pump
ANP → inhibition of Na^+ reabsorption

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

$$R_{resist} = \frac{\Delta P}{\dot{V}_{(flow)}}$$

$\dot{V}$ is proportional to r^4

$$P_{RS} = P_{EL} + P_{res}$$

$$P_{elastic} = 1/_{comp} \times Volume$$

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

	NH_3	Anion gap	↓ gluc
Organic Acidurias	+/- ↑	+ acidosis	+/-
Amino			~l
Urea Cycle Defect	↑↑		~l

<u>Fatty acid decarboxylation defects</u>

VLCFA - peroxisomal deficiency
SCAD
MCAD

hypoglycemia $\bar{5}$ ketonuria
presentation infancy → mos → yrs.

Give 100-200 cc/kg + $NaHCO_3$ in fluids.
K acetate if Na ↑
1/4NS + 40 mEq $NaHCO_3^-$/Liter ≈ 1/2NS Na with
may want to avoid bolus $NaHCO_3^-$ if ~~o~~ intubated.
run @ <u>maint</u>. Bolus ± <u>isotonic</u> fluids prn.

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

Amicar = ε amino caproic acid
inhibits plasminogen → plasmin –
so enhances clot formation.

Bld volume 75 cc/kg adult ~70/kg
premies ~80 cc/kg

↓ cc/kg t'fs by ~15%
PRBC's ATP/mannitol/citrate

Vit K II VII IX, X, C+S
made by liver V, VII, IX + X I, II, XI

cryo = 1-2 u/10 kg

chest out/lungs in

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

Anion gap.

$Na - (HCO_3^- + Cl^-)$ nl = 8-16 mEq/L

↑ anion gap ī nl Cl^- → excess acid production (ex disorders of organic + AA metabolism)

nl gap ī ↑ Cl^- = HCO_3^- loss (ex: intestinal + renal transport disorders)

gap reflective of unmeasured anions i.e. lactate, ketones + other organic acids

IEM

metabolic acidosis

organic acidurias

galactosemia + E coli sepsis

Hyperammonemia

NH_3 = intermediate of nitrogen catabolism

Hypoglycemia

? +/- met. acidosis

+ hepatomegaly + + ketones → fatty acid oxidation defects

+ hepatomegaly → glycogen storage diseases

DKA

3.5 mEq/kg depletion on average.

insensible loss A's 1 mg 100cc/kg/degree cent/

↑ Aldost 2° dehydration ~~precipitates~~ loss K^+ to preserve Na^+

Goals: ↓ acidosis + ketone bodies; restore euvolemia

fluids

10 ≈ 15% dehydrated

so if 10 kg nly + now 8kg = 20% dehydrated so −2000cc net down

+ 100cc/kg/day maint = 1000/day need 4000cc over next 48°

$750 Airway Shuttle $12 228-3000

200 Thurs

~~330-0790~~ 421-9828

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

Induc
isotonic fluid
pulse ox volume ↑

? mg/kg lidocaine IV ≈ intub for asthmatics +/or
to prevent airway spasm

asthmatic
raised + fentanyl or ketamine ↓ airway complications
tachypnea is often sign of failure in asthma.
Paralytic - ≈ very last moment or immediately p̄ intubation
avoid steroid analog steroids if steroid dependent
↳ steroid myopathies.

Ketamine
sympathetic
mildly ↑ HR + ↓ contractility
succ for head injuries
recurarization 30-60 sec
higher dose → quicker onset ± longer duration

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

controlled mandatory ventilation
1 time % based on this # of
breaths vs SIMV rate

Rocuronium 0.6 1.2 mg/kg for intubation for rapid onset.
+ head trauma
Pentothal for head trauma
short acting, ↓ cerebral metabolic rate/O_2 consumption
↓ cerebral blood flow. Immediate onset.
2-3/kg ↓ SVR, cardiac depressant
Lidocaine 1mg/kg - head trauma

+/- versed
NMB succ or MN/~~atracurium~~ - short acting
↓ will delay neuro exam because longer acting @ higher doses.

Histamine release: Atracurium ~~Cisatracurium~~

? upper + lower alm limit - ? always equals minute ventilation ? yes
? insp rise time - % 5-7%
? settings for insp time + insp rise time
? accelerating / decelerating insp flow vs constant pressure/during insp flow.
vc/vs/pcips
volume support/ insp support = PIP - PEEP
PRVC = PC + ventilation guarantee or volume control c̄ pressure limitation
PC only - be wary of tidal volume.

ing
psolly
use
pressure
↑ + stays same
↑ insp period
ds.

? can you control I:E in volume control - dial in
? In PS ? PIP = PS + PEEP ?
? how does vent regulate to pt pressure Δ/compliance Δ. ↑ rate, ↑ pressure?

CVM vs BPM on SIMV + PS/~~PS~~ (PC/VC)

flow trigger b/c for ikm Tony

acct for TV lost in system. NO
? I time based on cmv in simv
? where is flow trigger on tubing

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

lost to circuit:
Inf circuit:
lose 1cc volume for each cm H_2O of peak pressure
adult lose 2cc per...
intermed lose ~1.6cc per...

UA obstruction
Tracheitis
Staph

can BVM ventilate if acute obst.
NG to vent. belly
allow to breathe on own as much as possible

Post obstructive pulm edema
i.e. ~~p~~ T+A - esp if done for sleep apnea & obstructive breathing.
SX - lots of secretions/bld, etc
can BVM - but beware of pushing secretions into airway.
make sure can BVM ventilate ~~a~~ NMB

MAP = area under curve on pressure curve
so ↑ PC can get higher MAP ↑ lower PIP's.

PRVC = decelerating flow ↑ constant pressure

I time .75-1 sec is basic.
Pause is incl in I time - separate setting

↑ oxygenation
- ↑ FIO_2
- ↑ PEEP
- ↑ PIP
- ↑ I time

↑ ventilation
- ↑ rate
- ↑ TV
- ↑ PIP
- ↑ expiratory time

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

Asthma

early dyspnea → hyperventilation & often ↓ or nl pCO2. May get acidotic b/c ↑ lactate from resp muscle work or kidneys' attempts @ buffering & ↑ acid production.

Vent - want slow rate for long E time, relatively low tidal volumes

1:E 1:2 or 1:3 (then can calc I time from)

often ∅ PEEP - they have plenty on own & don't need to overdistend more.

HeliOx avail 70/30 O_2 or 60/40 O_2 max

does work for UA obst b/c helium is denser + tends to get thru turbulent airway flows + sinks to alveoli. But, can only deliver 30-40% O_2.

For asthma ∅ proven effective b/c problem is distal airway/airflow obst so not necessarily turbulent flow so denser molecule that carries O_2 is ∅ helpful.

Steroids study 1mg/kg/day
2-4mg/kg/day
6-8 mg/kg/day

higher doses better than 1mg/kg/day ∅ sig diff bet 2-4 and 6-8 but ↑ risk HTN, ↑ glucose + GI bleeds in highest dose category.

Any neuromuscular pt want them to have WOB from beginning

Ascites - may need ↑ pressure/volumes to compensate for ↑ abd pressure

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

80
-60 500

mediators IL 6 + IL 8 TNF
neutrophils → ~~release~~ destroy elastin properties of alveoli
O_2 diffuses much slower than CO_2
$\dot{V}/\dot{Q}$ mismatch probably most

Inverse Ratio Ventilation
1:1 or even 2:1 - have fluid ready for volume release, as ↓ SVR
as PAP's ↑
preserves MAP yet ↓ PAP (longer I time)

N1 A-a gradient ~ 5-10 / < 50

$P_B - P_{H_2O}$

A-a [760 - 47] (.FIO2) - $\frac{PaCO_2}{.8}$ - PaO_2
(equal)

Permissive hypercapnea ($\bar{p}$ CMV + IRV has failed)

↳ PLV
↳ HFOV
↳ ECMO

usually back to nl PFT's

COST CONTAINMENT IN CARDIAC SURGERY

ESSENTIAL NEW TECHNIQUES AND IMPLICATIONS FOR THE 90'S

Post fossa Tumors

Astrocytoma - resection only
chemo/radiation only if incomplete resection
excellent prog. 25yr survival > 95%

Medulloblastoma chem +/or radiation regardless of resection

Glioma - resection only

Comps
- CSF drainage
blocked aqueduct, etc
→ VP shunt in majority post op
- pseudomeningocele around incision site
- mutism
9% post fossa
13% vermicere area
latent period first
CN problems/palsies
swallowing diff
emotional lability
often whining/moaning
diff voiding
Most fully resolve
mutism last to correct
50% w. 1 mo 2 wks
all within 4 mos
@ fluent levels
dentato thalamic pathway ?
etiology unclear

THE UNIVERSITY OF TEXAS AT ARLINGTON

SCHOOL OF NURSING

September 18, 2006

Karen Corlett, RN, MSN, CPNP
Children's Medical Center, Dallas
1935 Motor St.
Dallas, TX 75235

Dear Ms. Corlett:

I am pleased to offer your appointment as an Clinical Instructor without compensation, September 1, 2006 through August 31, 2007. This appointment will be subject to an annual review.

Please indicate your willingness to accept the appointment by signing this letter and returning it along with a copy of your current CV. For your convenience, a self-address postage-paid envelope is enclosed.

We appreciate your efforts in working with our students and faculty and supporting the mission of the University of Texas at Arlington and the School of Nursing. Your involvement adds to the quality and strengths of our program.

Sincerely,

Elizabeth Poster

Elizabeth C. Poster, PhD, RN, FAAN
Dean

I accept the Clinical Instructor position with The University of Texas at Arlington School of Nursing.

Signed: Karen Corlett Date: 9/25/06

Please include information about you that we could include in our Nursing E-News on our website.

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THE UNIVERSITY OF TEXAS AT ARLINGTON

SCHOOL OF NURSING

November 8, 2006

Karen Corlett, BNS, MSN, PNP
Children's Medical Center of Dallas
Intensive Care Unit
1935 Motor Street
Dallas, TX 75235

Dear Ms. Corlett:

I would like to take this opportunity to thank you for sharing your information with the PNP and ACPNP students during the 2006-2007 academic year. Your presentation was outstanding. The feedback from the nurse practitioner students was highly complimentary. The other faculty members listening to you also felt you did an excellent job. We all really appreciate your taking time from your busy schedule.

I hope we can call upon you again to share your knowledge and expertise.

Sincerely,

Judy LeFlore

Judy Leflore, PhD, RNC, NNP, CPNP, ACPNP
Director of Pediatric Nurse Practitioner Program
University of Texas at Arlington School of Nursing
411. S. Nedderman Drive
Arlington, TX 76019
(817) 272-2776
jleflore@uta.edu

N. 5441 Pediatric Acute Care

Class Schedule Fall 2006

Class Hours 9AM-5PM

September 8, 2006		
9:00- 10:00	Orientation and review of syllabus	LeFlore
10:15-12:00	Nutrition of the critically ill patient	Grein
12:00-1:00	Lunch	
1:00-2:30	Post-op heart, management	Corlett
2:45-5:00	PAH	Corlett
September 29, 2006		
9:00-11:00	Neurosurgical Emergencies	Harrington
11:00-12:00	Lunch	
12:00-2:00	Diagnosis & Mgmt of Acute Renal Problems	Milonvich
2:15-3:45	Dialysis	Milonvich
4:00-5:00	Acute Liver Failure/dx and mgmt	Milnovich
September 30,2006		
9:00-10:30	Test I	
10:45-12:30	Pneumonia/Respiratory Failure/ARDS	TBA
12:30-1:30	Lunch	
1:30-3:00	Sepsis/Shock/Multiorgan dysfunction	Knapp
3:15-5:00	Asthma/Hospital Management	Knapp
October 6, 2006		
9:00- 11:00	Traumatic Brain Injury/CVA/ICH/Diffuse AI	Molitor-Kirsch
11:15-12:30	Principles of ICP Monitoring/Mgmt	Molitor-Kirsch
12:30- 1:30	Lunch	
1:30-3:45	Tumor lysis/BMT, Acute Management	Cavender
4:00-5:00	CDM #2 Due meet with clinical advisor	

October 7, 2006		
9:00-10:45	Trauma	Moore
11-12:30	Neonatal Emergencies	LeFlore
12:30-1:30	Lunch	
1:30-3:00		
3:00-5:00	Case Presentations	

Beth Nachtsheim Bolick,
RN MS APRN BC
CPNP-AC CCRN
Assistant Professor/
Nurse Practitioner
Acute/Chronic Care
Pediatric Nurse Practitioner
Program Director

Department of Women's &
Children's Health Nursing
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RUSH UNIVERSITY
COLLEGE OF NURSING
RUSH MEDICAL COLLEGE
COLLEGE OF HEALTH SCIENCES
THE GRADUATE COLLEGE

June 20, 2006

Dear Karen:

Please accept our gratitude for the time you spent precepting our Acute/Chronic Care PNP graduate student, Kim Gensler, during the spring 2006 quarter.
Kim reported that you are knowledgeable, love to teach, and are extremely approachable. You left her interested in learning more. She can't say enough about how wonderful the experience was with your team. Your commitment to the education of Advanced Practice Nurses is obvious and we appreciate the time you have taken to work with our student. If you are interested in giving a lecture on cardiovascular issues during the winter quarter (first week in January) please let me know. Kim says you would be an asset to the lecture series.
Again, thank you.

Sincerely,

Beth Nachtsheim Bolick

Beth Bolick

Acute Care Pediatrics for Nurse Practitioners

July 28-30, 2006
Children's Medical Center Dallas
Moore Auditorium

children's
MEDICAL CENTER

This seminar is intended as an excellent source of review for those planning on taking the new Acute Care Pediatric Nurse Practitioner Exam offered by the Pediatric Nursing Certification Board. Check your eligibility for the exam at PNCB.org.

Remember, those of us with primary care PNP education only have until March of 2007 to register for this exam. Should provide evidence of continuing education with pediatric acute care content. This conference provides a systems-based review of pediatric acute care issues often faced by nurse practitioners.

Registration Fees

Includes breakfast, snacks and lunch on Saturday and Sunday. Heavy appetizers will be served Friday evening.

Full Conference
Children's Employees: $75.00
Non Children's employees $125.00

Daily Registration
Friday session $25.00
Saturday or Sunday Session $50.00 each day

REGISTRATION DEADLINE JULY 14, 2006
Cancellation Deadline July 21, 2006.
A $25.00 processing fee will be charged for refunds.
For additional information contact Sharon Posey at 214-456-2331

How to Register

Please fill out registration form and mail along with a check payable to Children's Medical Center Dallas to:

Children's Medical Center Dallas
ATTN Sharon Posey
Advanced Practice Services E03-325
1935 Motor Street
Dallas, TX 75235

Registration Form

Acute Care Pediatrics for Nurse Practitioners
July 28-30, 2006
Children's Medical Center Dallas
1935 Motor Street
Dallas, Texas 75235

Name _____

Employer _____

Address _____

_____

City _____

State _____ Zip _____

Phone _____

E-mail _____

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Schedule of Events

FRIDAY, JULY 28

5:30 - 6 p.m.	Registration
6 - 7 p.m.	**The Newborn**
	Debbie Thompson RN, CNS, PNP-BC
7 - 8:30 p.m.	**The Respiratory System**
	James Knapp RN, APRN-BC
8:30 - 8:40 p.m.	BREAK
8:40 - 9:40 p.m.	**Neurosurgery**
	TBA
9:40 - 9:45 p.m.	Questions

SATURDAY, JULY 29

7:30 - 8 a.m.	Registration
8 - 9:30 a.m.	**Cardiology**
	Karen Corlett RN, MSN, CPNP
9:30 -10:30 a.m.	**Neurology**
	Christina Harrington RN, MSN, CPNP
10:30 -10:45 a.m.	Questions
10:45 - 11 a.m.	BREAK
11 - 12:15 p.m.	**Hematology/Oncology**
	Joe Don Cavender MSN, RN, CPNP
12:15 - 1:30 p.m.	LUNCH
1:30 - 2:45 p.m.	**Endocrinology**
	Priscilla Rieves MS, RN, CPNP
2:45 - 3:45 p.m.	**Gastrointestinal Disorders**
	Robin Landgraf MSN, RN, CPNP
	Shabina Walji-Virani RN, MSN, CPNP
3: 45 - 4 p.m.	Questions
4 - 4:15 p.m.	BREAK
4:15 - 5:15 p.m.	**Genitourinary**
	William Strand MD
5:15 - 5:30 p.m.	Questions

SUNDAY, JULY 30

7:30 - 8 a.m.	Registration
8 - 8:45 a.m.	**Orthopedic Disorders**
	Shellye Crawford MS, RN, CPNP
8:45 - 9:30 a.m.	**ENT**
	Paula Dimmitt RN, MS, CPNP
9:30 - 9:45 a.m.	Questions
9:45 - 10 a.m.	BREAK
10 - 10:45 a.m.	**Adolescence**
	Amy McLaughlin RN, BC-PMHNP
	Barbie Drews RN, MS, CPNP
10:45 -11:30 a.m.	**Rheumatologic Disorders**
	Debra Glaab MSN, RN, PCCNP
11:30 - 11:45 a.m.	Questions
11:45 - 12:45 p.m.	LUNCH
12:45 - 1:45 p.m.	**Skin Disorders**
	Maury Contreras RN, MS, CNS
1:45 - 2:45 p.m.	**Infectious Disease**
	Lisa Milonovich RN, MSN, PCCNP
	Shabina Walji-Virani RN, MSN, CPNP
2:45 - 3 p.m.	Questions
3 - 3:15 p.m.	BREAK
3:15 - 4 p.m.	**Genetics**
	Joanna K. Spahis RN, CNS, APNG
4 - 4:30 p.m.	Questions, evaluations