THE PATHOPHYSIOLOGY AND TREATMENT OF BODY FLUID DISTURBANCES

HANS G. KEITEL, A.B., M.D., F.A.A.P.

Professor and Head, Department of Pediatrics, The Jefferson Medical College of Philadelphia; Physician in Chief of Pediatrics, Jefferson Medical Center, Philadelphia; Physician in Chief of Pediatrics, Episcopal Hospital, Philadelphia, Pennsylvania.

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Preface

Disturbances of the body water compartments are easily recognized if edema or hypohydration is present. When fasting, thirsting, vomiting, and diarrhea are present, the presence of a fluid imbalance can be inferred with reasonable certainty. With increasing frequency, however, additional types of water and solute derangements are being recognized. Sometimes fluid balance disturbances may first result in ocular symptoms, abnormal psychologic and neurologic symptoms (as in potassium deficiency or hypercalcemia), failure of normal growth and development (as in Lightwood's syndrome), fractures or genitourinary symptoms (as with disturbances in calcium metabolism), or chronic skin disorders (pigmentation, as in Addison's disease). Therefore, a knowledge and understanding of water and electrolyte metabolism is needed by all physicians, generalists and specialists. Conversely, the clinician who treats a patient with marked hypohydration, renal failure, or adrenal failure must be on guard against the cliché, "a little learning is a dangerous thing," lest it apply to him. Iatrogenic fluid disturbances are being recognized with increasing frequency.

In writing this syllabus it was assumed that the reader has a background in the basic science subjects prerequisite for entrance to medical school. Not all readers will be tolerant to or be benefited by reading the syllabus consecutively. The following is recommended:

For preclinical student physicians: read and study Chapter 2 in detail; then read Chapters 1, 3, and 4. Do not read Chapter 5 until the onset of your clinical year.

For students in the clinical years: read Chapters 3 through 5, and carefully study the section on *Drug Dosage* in Chapter 1. Review Chapter 2 as necessary.

For house staff and clinicians: in order, read Chapters 1, 3, 4, and 5, and study parts of Chapter 2, as tolerated. It is recommended that all readers have full appreciation of Chapters 1 and 3 before Chapter 4 is read.

Slide rules and "foolproof" formulas are not offered as shortcuts to understanding physiologic and therapeutic principles. These principles are expressed as simply as possible in quantitative terms so that the clinician will be prepared to adjust to the many variables inherent in the treatment of serious fluid balance disturbances. The more precisely serious fluid disturbances are characterized, the greater the possibility that treatment will be customized so that such patients will survive.

Rapid learners may feel that there is excessive repetition and undue emphasis of quantitative data, particularly relative to drug (fluid) dosage. However, errors in judgement resulting in clinical catastrophes are not infrequently due to poor conceptual appreciation of the quantitative factors concerned with drug (fluid) dosage. Particularly disturbing to the physician are the number of approaches to fluid problems. This book is dedicated to a uniformity of approach, using the most basic simple methods to express data quantitatively.

To keep within the space alloted, compromises have been made in presenting concepts and data which are directly related, yet somewhat peripheral to the main issues to be considered. The reader will be referred to excellent contemporary reviews pertaining to renal function, ion transport, and calcium and phosphorus metabolism for more detailed information in these areas. Special attention will be paid to acute clinical conditions related to disturbances in body water content and to solute disturbances, particularly those involving hydrogen, sodium, potassium, chloride, and bicarbonate.

Acknowledgement is made to the following: 1, to the many pioneers whose investigations make a structured presentation of Clinical Fluid Balance Disturbance feasible (65, 94, 161, 166,

209, 244, 249, 254, 285, 301, 304, 323, 376, 400, 475, 503, 514, 554, 563, 601); 2, to others who previously have organized the vast amount of material that has already been published (69, 78, 170, 291, 297, 315, 441, 478, 519, 549, 558, 564, 582, 584, 620); 3, the inspiring teachers and investigators with whom the author has been associated in the past, particularly Doctors F. Albright, A. M. Butler, and N. B. Talbot of the Massachusetts General Hospital; Drs. R. Berliner, E. Cotlove, and T. Kennedy of the National Institutes of Health; and Drs. W. Ballinger, G. Haupt, F. Wagner, J. Barker, J. Killough, J. Clark, A. Cantarow, A. Friedman, and S. Ziegra of the Jefferson Medical College; 4, to Dr. M. Shigeta, who helped prepare the index; and 5, to Dr. F. Bartter, of the National Institutes of Health, and Dr. L. Wesson, of the New York University School of Medicine, who critically reviewed the manuscript.

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1

Introduction

The objective of this book is to describe the pathologic physiology of body fluids in *quantitative* terms. A quantitative approach to the understanding of fluid pathophysiology is essential, since the clinician must apply his understanding of the basic principles when he indicates in his orders the exact amount of water and solutes a patient is to receive.

Special attention will be paid to the usefulness and limitations of multielectrolyte solutions. Such solutions are serviceable for the prevention and treatment of most types of fluid disturbances, and they can be easily modified to meet the needs of special circumstances.

Reference will be made to numerous uncommon diseases and metabolic derangements (Addison's disease, base-losing nephritis, diabetes insipidus, vitamin D resistant rickets, water intoxication, compulsive water drinking, periodic paralysis, etc.). With knowledge of the pathophysiology of body water and solutes, the *diagnosis* as well as the treatment of these conditions becomes readily understandable.

Pathologic Findings in Patients with Fluid Disturbance

Increasing attention is now being paid to the pathophysiology of body fluids, even though inspection of pathology reports reveals that only rarely can death be attributed directly to water or electrolyte imbalance. This is due to the inherent difficulty, except in unusual instances, of diagnosing disturbances in body fluid composition on the basis of autopsy findings alone. There-

fore, the clinician is often left in ignorance as to whether a fluid balance disturbance existed before death. Although the pathologist is frequently unable to diagnose fluid disturbances, the clinician is able to appraise the status of the extracellular solutes, diagnose shock and anemia, and measure the size of the vascular fluid compartment.

Disturbances in body fluid composition associated with either generalized or localized *hypohydration*[1] or *edema* (hyperhydration of the interstitial compartment) can be appreciated clinically. However, disturbances in the concentration of extracellular solutes (hydrogen, calcium, potassium, etc.) can result in marked neuromuscular, central nervous system, gastrointestinal symptomatology, or death. Yet the etiology of such symptoms remains unrecognized unless *determination of plasma*[2] electrolyte concentrations are obtained. Even more difficult to diagnose are disturbances secondary to alterations in the electrolyte composition of cells.

Reasons for Divergent Opinions Relative to the Treatment of Fluid Disturbances

Kidney Function and Response to Fluid Therapy. There are many controversies in the field of fluid metabolism, but most of them can be reconciled. For example, the type and amount of fluid that can be administered successfully to patients with the same disease varies considerably. In a recent book by collaborat-

[1] The term dehydration signifies the total loss of water from tissue, a situation not found in man except as a result of a severe burn. The term *hypohydration* is better suited to describe partial deficiency of water.

[2] The term *electrolyte concentration of blood* almost always refers to the composition of plasma or serum. The electrolyte composition of red cells differs considerably from that of plasma; and contamination of plasma with cells, even if minimal, may invalidate plasma electrolyte studies. In the case of urea and glucose, whose concentration per unit volume is quite similar (not equal) in human red cells and plasma, partial contamination of serum or plasma with red cells will not invalidate the findings.

ing authors recommendation for fluid therapy of similar conditions varied by as much as 200 per cent. If *kidney function* is normal, the glomerular filtrate will be modified so that the composition of body fluids remains normal in the face of widely varying intakes of water and solutes. Therefore, it is not surprising that the administration of varying amounts of water and of electrolytes may be successful in the treatment of similar clinical conditions (583).

Blood Chemical Values in Normal Subjects. Differences of opinion in the field of fluid therapy are due in part to the fact that the blood electrolyte values of normal subjects, as reported by different clinical laboratories, are not in agreement. This apparent inconsistency is related to four major factors: the selection of normal subjects, the analytical method used, the analytical variability, and the sampling variability. The normal range of blood electrolyte values must be evaluated in light of these factors.

The Selection of Normal Subjects

Data obtained from hospitalized patients without evident electrolyte or water disturbances are frequently represented as being "normal," but we now appreciate that such patients may have disturbances in electrolyte metabolism. Therefore, "hospitalized normals" should not be used as control subjects when normal values are determined.

Age of the Subject. The plasma of normal infants and children varies in chemical composition from that of adults. Normal infants have a higher phosphorus and chloride, and a lower pH and CO_2 concentration of plasma than do normal adults. In the case of phosphorus, values in the adult range are frequently not found before puberty. The CO_2 and chloride concentration approach the normal adult range somewhere between the first and tenth year of life (see Table 1). The potassium concentration of plasma in infants also is higher, the degree depending chiefly on the potassium intake.

Table 1. The Concentration of the Dominant Solutes in the Plasma* of Normal Adults†‡ and of Infants

Solutes		Adults		Infants§	
		Mean Value	Approximate Standard Deviation§	Mean Value	Approximate Standard Deviation
Cations					
Sodium,	mEq./L.	140	2.5	(137)	(2)
Potassium,	"	4.3	0.25	(5.2)	(0.3)
Calcium,	"	5	(0.25)	(5)	(0.25)
	mg.%	10	(0.50)	(10)	(0.50)
Magnesium,	"	2	(0.2)	(2)	(0.2)
Hydrogen (as pH)		7.42	0.3	(7.33)	(0.4)
Anions					
Chloride,	mEq./L.	102	2.0	(107)	(3)
CO_2 (total)	"	26	2.0	(22)	(2)
Phosphorus, mg.%		3.5	(0.3)	5.4	(0.4)
Protein(ates), gm.%		7.0	(0.6)	6.0	(0.5)
Nonelectrolytes					
Glucose, mg.%		85	(10)	(75)	(10)
Urea, mg.%		14	(2)	(16)	(3)

* The solute composition of plasma is similar to that of serum, the small difference (usually less than one per cent) being due to the volume displacement of fibrinogen.

† These data represent the average of many published data obtained from fasting normal subjects. (22, 211, 212, 218, 415, 427, 451, 469, 555, 652).

‡ Adult values are often found within 3 to 6 months of life. The phosphorus concentration remains elevated until puberty and the total CO_2 may be slightly lower for the first 2 years of life (72, 412).

§ Electrolyte concentrations of normal subjects are not distributed according to the classical Gaussian curve (221). However, the error incurred by using the mean and standard deviation method to describe the normal range is not great enough to be of practical importance.

Previous Food Intake of the Subject. Blood samples for electrolyte determination should be obtained from subjects who have fasted and thirsted for 12 to 18 hours. In the case of infants, the "normal" plasma values usually cited may differ to some degree from adult values because infants are not comparably prepared (350). Fasting and thirsting for 12 to 18 hours would

not place an infant in a physiologic state comparable to that of an adult similarly treated, because infants lose water and expend calories at about three times the rate (per kg. of body weight) of adults. Fasting and thirsting for four to six hours may place the noncrying infant in a physiologic state comparable to that of the adult who has fasted and thirsted for 12 to 16 hours.

Analytical Variability. The accuracy of most analytical methods is within plus or minus 1 to 3 per cent. In the case of calcium, analytical variability of plus or minus 5 per cent is found in many clinical laboratories. Analytical variability is not necessarily due to inexperience or carelessness on the part of the technician; inherent methodological or instrumental instability play an important role. Awareness of analytical variability is important since the physician is able to evaluate the possible need for *replicate determinations*. In some laboratories, unused serum or plasma is saved for several days in order that the test may be repeated in the event that the results are borderline. For example, if a plasma sodium is reported to be 135 mEq./L., and the analytical variability of the sodium method is plus or minus 2 per cent, the result could be 132 mEq./L., an abnormally reduced value, or 138 mEq./L., a normal value. Another advantage of saving unused serum or plasma is that additional studies can be ordered without requiring another venipuncture. For example, if the plasma sodium concentration is found to be 120 mEq./L., it may be desirable to determine other electrolyte concentrations. If serum or plasma is frozen, the sodium, potassium, calcium, magnesium, chloride, phosphorus, and CO_2[3] concentrations can be determined days or weeks after the blood sample has been obtained. It is important to thoroughly mix thawed samples before removing aliquots for analysis.

[3] The pH of blood may be seriously affected if whole blood or plasma is not kept under oil, which prevents the loss of CO_2. Since only a small fraction (about 5 per cent) of the total blood CO_2 is usually CO_2 of H_2CO_3, the total CO_2 value is not particularly affected if the sample has not been kept under oil (p. 89).

Sampling Variability. The significance of the "normal" range of electrolyte concentrations is of considerable importance to the clinician. It is important that *the mean value and standard deviation* are obtained from many (preferably 30 or more) normal subjects of comparable age and sex. If the mean value and standard deviation are known, one may determine the likelihood (statistical probability) that any given value is abnormal.

For example, the mean potassium concentration of plasma in adults is 4.3 mEq./L., with a standard deviation of 0.25. Plus or minus two standard deviations includes about 95 per cent of normal subjects, who have a plasma potassium ranging between 3.8 and 4.8 mEq./L. Plus or minus three standard deviations includes about 98 per cent of normal subjects who have a plasma potassium between 3.6 to 5.1 mEq./L. The normal range is usually accepted as including from 95 to 98 per cent of normal subjects (i.e., either a 2 or 3 standard deviation). It is important to memorize the mean plasma electrolyte values and their standard deviations, since the diagnosis and optimal treatment of certain fluid disturbances may be based on this information (see Table 1).

Indices to be Used for Guiding Fluid Therapy

A common source of confusion about fluid therapy results from the failure to specify what is meant by fluid requirement, and how much fluid should be given for maintenance or replacement to individuals of different size. The widely used term "fluid requirement" is rather poorly chosen since the amount recommended is *not* the *minimal requirement* but an amount which usually provides a liberal excess.

Hereafter, the term *fluid maintenance* will refer to the average (usual) daily intake in normal subjects of comparable age, living under normal (average) environmental conditions.

Body Weight versus Surface Area in Determining Drug Dosage. In currently available textbooks on Fluid Pathophysi-