

- study of folate deficiency in protein-calorie malnutrition. *Amer. J. Clin. Nutr.* 25:147, 1972.
- Wasserman, R. H., and Corradino, R. A.: Metabolic role of vitamins A and D. *Ann. Rev. Biochem.* 40:501, 1971.
- Wasserman, R. H., and Taylor, A. N.: Metabolic roles of fat-soluble vitamins, D, E, and K. *Ann. Rev. Biochem.* 41:179, 1972.
- Weinberg, T., Gordon, H. H., Oppenheimer, E. H., and Nitowsky, H. M.: Myopathy in association with tocopherol deficiency in cases of congenital biliary atresia and cystic fibrosis of the pancreas. *Amer. J. Path.* 34:565, 1958.
- Wendt, G., and Bernhart, F. W.: The structure of a sulfur-containing compound with vitamin B₆ activity. *Arch. Biochem. Biophys.* 88:270, 1960.
- Whehan, W. S., Fraser, D., Robertson, E. C., and Tomczak, H.: The rising incidence of scurvy in infants. *Canad. Med. Ass. J.*: 78:177, 1958.
- Williams, T. E., Arango, L., Donaldson, M. H., and Shepard, F. M.: Vitamin K requirement of normal infants on soy protein formula. *Clin. Pediatr.* 9:79, 1970.
- Williams, T. F., and Winters, R. W.: Familial (hereditary) vitamin D-resistant rickets with hypophosphatemia. *In* Stanbury, J. B., Wyngaarden, J. B., and Fredrickson, D. S. (eds.): *The Metabolic Basis of Inherited Disease*. 3rd ed. New York, McGraw Hill Book Co., 1972, p. 1465.
- Witting, L. A.: Lipid peroxidation in vivo. *J. Amer. Oil. Chem. Soc.* 42:908, 1965.
- Witting, L. A.: Recommended dietary allowance for vitamin E. *Amer. J. Clin. Nutr.* 25:257, 1972a.
- Witting, L. A.: The role of polyunsaturated fatty acids in determining vitamin E requirement. *Ann. N.Y. Acad. Sci.* 203:192, 1972b.
- Wolf, H.: Rachitisprophylaxe beim Säugling. *Dtsch. Med. Wschr.* 95:1530, 1970.
- Wolf, H., Kerstan, J., und Kreutz, F.-H.: Kontinuierliche Rachitisprophylaxe — schon beim Neugeborenen? *Mscr. Kinderheilkd.* 120:329, 1972.
- Woodruff, C. W.: Ascorbic acid. *In* Beaton, G. H., and McHenry, E. W. (eds.): *Nutrition*. Vol. II. New York, Academic Press, 1964, p. 265.
- Yoshida, T., Tada, K., and Arakawa, T.: Vitamin B₆-dependency of glutamic acid decarboxylase in the kidney from a patient with vitamin B₆ dependent convulsion. *Tohoku J. Exp. Med.* 104:195, 1971.

WATER AND RENAL SOLUTE LOAD

10

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Water requirement may be subdivided into renal and extrarenal categories. Water required for renal excretion is determined predominantly by the magnitude of the renal solute load and this, in turn, is largely dependent on the diet. In the case of healthy infants receiving commonly employed diets, renal solute load will ordinarily be low in relation to the amount of water available for its excretion. However, in the case of infants with various illnesses, unusual diets, adverse environmental conditions or combinations of these factors, understanding of the relation between renal solute load, renal concentrating ability and water balance may be essential in preserving the health of the infant. The present chapter will consider these relationships.

WATER

Water is required by the human infant to replace loss of water from skin and lungs and losses in feces and urine. In addition, a small amount of water is needed for growth. As a general formulation, one may consider that the requirement for water is the sum of four components: evaporative water losses (i.e., losses from skin and lungs), fecal water losses, water required for renal excretion of solutes and water

TABLE 10-1 ESTIMATED WATER EXPENDITURES OF NORMAL SUBJECTS OF VARIOUS AGES (CIRCUMSTANCES IN WHICH WATER REQUIREMENTS ARE MINIMAL)^a

SOURCES OF WATER LOSS	WATER REQUIREMENT (ML/DAY)			
	Age 1 Mo 4.2 kg	Age 4 Mo 7.0 kg	Age 12 Mo 10.5 kg	Age 36 Mo 15 kg
Growth	18 (6)†	9 (2)	6 (1)	5 (1)
Losses from skin and lungs	210 (64)	350 (66)	500 (63)	600 (63)
Fecal losses	42 (13)	70 (13)	105 (13)	140 (15)
Urine	56 (17)	105 (19)	182 (23)	203 (21)

^aAssumes average rate of growth (see text), thermoneutral environment, diet of low renal solute load (approximately equivalent to that of human milk) and ability to concentrate the urine to 1000 mosmol/liter.

†Values in parentheses indicate percentage of total water requirement.

required for growth. Under all conditions, water for growth accounts for a relatively small percentage of total requirement for water (Table 10-1). Therefore, for practical purposes, water requirement may be considered to consist of the amount needed for replacement of evaporative, fecal and urinary losses.

Water Intake

Preformed water is consumed either in the form of water or as a component of food. Cow milk and infant formulas of conventional caloric density (67 kcal/100 ml) provide approximately 90 ml of preformed water in each 100 ml of milk or formula consumed. Most commercially prepared strained and junior foods provide only slightly less water per unit of volume than do milk and formula (Chapter 16, Tables 16-2 and 16-3). In addition to preformed water, foods yield water of oxidation—0.41, 1.07 and 0.55 ml, respectively—from the complete combustion of 1 gm each of protein, fat and carbohydrate (Maxwell and Kleeman, 1962). Because some amino acids and fatty acids must be utilized in tissue synthesis, it is apparent that complete combustion of all foods does not occur. Therefore, calculation of the sum of preformed water and water of oxidation for each food would be likely to be misleading. With a variety of commonly consumed infant foods, our calculations suggest that preformed water plus water of oxidation amounts to about 95 per cent of the volume of the food. However, when caloric density of a formula approaches 100 kcal/100 ml, preformed water plus water of oxidation will amount to only 90 per cent of the volume of the food.

Water Losses

Evaporative Water Loss. Loss of water from skin and lungs accounts for the greatest part of water requirement, generally ranging from 30 to 70 ml/kg/day in healthy fullterm infants not exposed to extreme environmental conditions (Levine et al., 1929; Pratt et al., 1948; Cooke et al., 1950; Darrow et al., 1954; Heeley and Talbot, 1955; Drescher et al., 1962). Estimates of evaporative water losses by normal subjects under thermoneutral conditions are summarized in Table 10-1.

When infants are exposed to elevated environmental temperatures, water losses from skin and lungs may increase by 50 to 100 per cent (Levine et al., 1929; Cooke et al., 1950; Darrow et al., 1954). Although it is commonly assumed (Committee on Nutrition, 1957) that evaporative water losses increase approximately 10 per cent for each degree centigrade rise in body temperature, documentation of this value does not appear to be available.

From Table 10-1 it may be seen that evaporative water losses (i.e., those from skin and lungs) account for approximately two-thirds of the total water requirement during the first three years of life. Because evaporative water losses are closely related to energy expenditures, water requirement is sometimes expressed per unit of energy production, and Winters (1973) has suggested the convenient ratio of 1 ml/kcal. However, it is apparent that the ratio of water requirement to energy production will increase when extrarenal losses are unusually high (e.g., elevated environmental temperature) or when renal water loss is great (e.g., high renal solute load, especially in the presence of decreased renal concentrating ability).

Fecal Water Loss. Fecal water losses of normal infants generally average about 10 ml/kg/day (Pratt et al., 1948; Cooke et al., 1950; Darrow et al., 1954), thus amounting to about 13 per cent of total water requirement (Table 10-1). In infants with diarrhea, fecal water losses may easily be five or six times normal (Holt et al., 1915; Chung, 1948; Darrow et al., 1949).

Urinary Water Loss. When intake of water approaches requirement, the amount of water excreted in the urine will be determined by the renal solute load and renal concentrating ability. When intake of water is greater than the requirement, the excess water will ordinarily be excreted in the urine. There is no evidence that increases in water intake above the requirement influence the water utilized for growth or water losses through skin, lungs and gastrointestinal tract. In the case of healthy infants receiving usual diets, intakes of water are greatly in excess of requirement. For example, the estimated water requirement of a one-month-old infant is 326 ml/day under conditions in which water requirements are minimal (Table 10-1). As may be

seen from data presented in Chapter 2, actual intake of formula by such an infant might be 700 ml, equivalent to approximately 665 ml of water (i.e., preformed water plus water of oxidation — see Water Intake). Therefore, water available for renal excretion will be several times the quantity required. It is for this reason that normal infants ordinarily excrete dilute urine and that problems of water balance rarely develop in healthy infants fed usual diets.

RENAL SOLUTE LOAD

Solutes that must be excreted by the kidney are spoken of collectively as the renal solute load. Most commonly, the urinary excretion of renal solutes is expressed in milliosmols per day, and the concentration of the urine in milliosmols per liter. The renal solute load consists primarily of nonmetabolizable dietary components, especially electrolytes, ingested in excess of body needs, and metabolic end products. The latter consist mainly of nitrogenous compounds resulting from digestion and metabolism of protein.

Consideration of renal solute load in infant feeding is particularly important in the following circumstances: (1) low fluid intake, including the feeding of calorically highly concentrated diets (Chapter 2); (2) abnormally high extrarenal water losses, as in fever, elevated environmental temperature, hyperventilation and diarrhea; and (3) impaired renal concentrating ability, as in renal disease, protein-calorie malnutrition (Alleyne, 1967) and diabetes insipidus. Ability to concentrate the urine appears to be relatively low in the case of some otherwise normal full-term infants (Winberg, 1959; Edelman et al., 1960; Pólaček et al., 1965) and, presumably, such limitation of concentrating ability may be even more frequent in the case of premature infants. Thus, it is apparent that the importance of renal solute load must be kept in mind in a variety of circumstances.

Unfortunately, the solute concentration of a feeding is of little value in predicting its renal solute load. In most infant formulas, a high percentage of solutes will consist of disaccharides and polysaccharides of relatively small molecular weight. These will normally be metabolized and will yield few solutes for renal excretion. Protein, on the other hand, will contribute little to the solute concentration of the formula, but the metabolic end products of protein metabolism will comprise an important part of the renal solute load.

An estimate of renal solute load may be obtained by subtracting from the potential renal load resulting from ingestion of the diet that portion of the potential renal solute load excreted through extrarenal routes (mainly gastrointestinal tract and skin), and that portion of the potential renal solute load utilized for growth. In the great

majority of instances, however, a sufficiently accurate prediction of renal solute load may be made by the simplified approach of Ziegler and Fomon (1971). This approach will be utilized in the examples that follow. A more general (and more complicated) formula necessary for special circumstances, especially management of the low-birth-weight infant, is presented later in the chapter.

Simplified Prediction of Renal Solute Load

A simple estimate of renal solute load may be based on dietary intake of nitrogen and of three minerals — sodium, potassium and chloride. For reasons discussed by Ziegler and Fomon (1971), each gram of dietary protein is considered to yield 4 mosmol of renal solute load (assumed to be all urea), and each milliequivalent of sodium, potassium and chloride is assumed to contribute 1 mosmol.

This estimate of renal solute load was developed primarily from data pertaining to infants fed whole cow milk or other feedings that yield relatively high renal solute loads. Under these circumstances, the fraction of dietary nitrogen and various electrolytes incorporated into newly synthesized body tissue or lost through skin is relatively small.

When diets provide lesser amounts of protein and electrolytes, retention for growth and losses through skin constitute a larger fraction of the intake, and the proposed calculation will overestimate the renal solute load. However, problems arising from overestimating the size of the renal solute load are of less clinical importance than are problems arising from underestimating it. In addition, knowledge of the size of the renal solute load is more important when the renal solute load is large than when it is small.

FULLSIZE INFANTS WITHOUT CHRONIC DISEASE

The examples presented in Figures 10-1 to 10-4 concern fluid intake, renal solute load, extrarenal losses and osmolar concentration of the urine of a hypothetical four- or five-month-old infant weighing 7 kg. Each example concerns intake and excretion during a 24-hour interval.

Volume of Intake and Evaporative Water Losses

In Figure 10-1, the example concerns an infant fed either 1000 or 750 ml of whole cow milk; extrarenal losses of fluid are assumed to be

TABLE 10-2 DIETARY INTAKE OF PROTEIN, SODIUM, CHLORIDE AND POTASSIUM AND ESTIMATED RENAL SOLUTE LOAD FROM VARIOUS FEEDINGS

FEEDINGS	CALORIC DENSITY (KCAL/100 ML)†	DIETARY INTAKE					ESTIMATED RENAL SOLUTE LOAD°		
		Quantity (ml)‡	Protein (gm)	Na (meq)	Cl (meq)	K (meq)	Urea (mosmol)‡	Na+Cl+K (mosmol)	Total (mosmol)
Milks									
Whole cow milk	67	1000	33	25	29	35	132	89	221
Boiled skim milk	33	1000	46	35	40	49	184	124	308
Human milk	67	1000	12	7	11	13	48	31	79
Formulas									
SMA	100	1000	22	10	18	21	90	49	139
Similac	100	1000	24	17	24	28	97	69	166
Strained foods									
Pears	69	100	0.3	0.2	0.2	1.6	1	2	3
Applesauce	84	100	0.2	0.3	0.2	2.6	1	3	4
Beef with vegetables	104	100	6.5	13.3	10.6	3.7	26	28	54
Chicken with vegetables	100	100	7.2	5.7	4.6	1.8	29	12	41

°This simplified estimate of renal solute load is appropriate for use with respect to fullsize but not low-birth-weight infants (see text).
 †For strained foods, 100 gm rather than 100 ml.
 ‡Assumed to account for 70 per cent of nitrogen intake (Ziegler and Fomon, 1971).

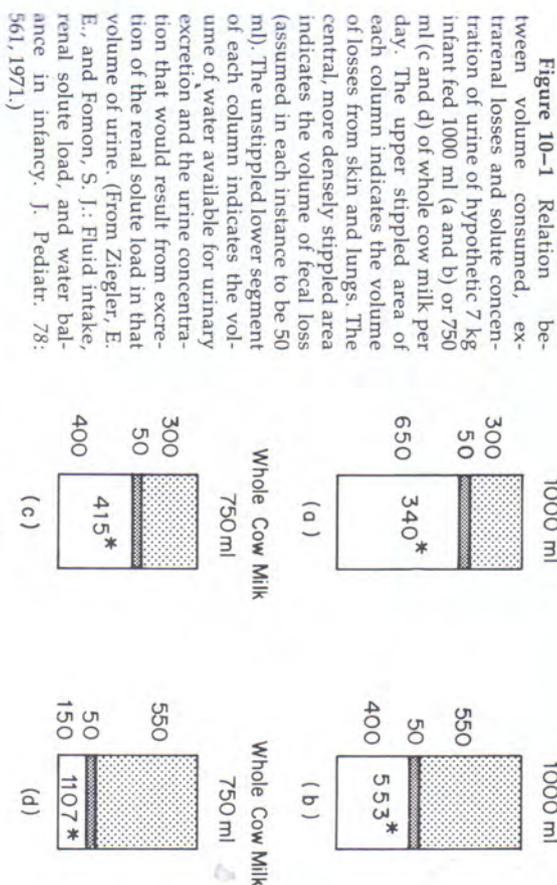


Figure 10-1 Relation between volume consumed, extrarenal losses and solute concentration of urine of hypothetical 7 kg infant fed 1000 ml (a and b) or 750 ml (c and d) of whole cow milk per day. The upper stippled area of each column indicates the volume of losses from skin and lungs. The central, more densely stippled area indicates the volume of fecal loss (assumed in each instance to be 50 ml). The unstippled lower segment of each column indicates the volume of water available for urinary excretion and the urine concentration that would result from excretion of the renal solute load in that volume of urine. (From Ziegler, E. E., and Fomon, S. J.: Fluid intake, renal solute load, and water balance in infancy. *J. Pediatr.* 78: 561, 1971.)

350 ml (300 ml from skin and lungs* and 50 ml in feces) when exposed to normal environmental temperature (Fig. 10-1a and c), and 600 ml (550 ml from skin and lungs and 50 ml in feces†) when exposed to elevated environmental temperature (Fig. 10-1b and d). As may be seen from Table 10-2, estimated renal solute load arising from 1000 ml of whole cow milk is 221 mosmol. At normal environmental temperature (Fig. 10-1a), this hypothetical infant consuming 1000 ml of milk has 650 ml of water available for renal excretion of these solutes; and urinary concentration is 340 mosmol/liter. At elevated environmental temperature (Fig. 10-1b), only 400 ml of water are available for renal excretion, and urine concentration is 553 mosmol/liter. Since nearly all normal infants will be able to concentrate the urine to more than 553 mosmol/liter (Winberg, 1959; Edelman et al., 1960; Polacek et al., 1965), there is no threat to water balance.

It should be noted that the assumed value (550 ml) for losses of water from skin and lungs at elevated environmental temperature is by no means extreme. Several reports (Cooke et al., 1950; Darrow et al., 1949, 1954) have documented situations in which water losses

*The examples in Figures 10-1 to 10-4, reproduced from the report by Ziegler and Fomon (1971), employ a slightly lesser evaporative water loss for a 7 kg infant than the value given in Table 10-1 (300 versus 350 ml/day).
 †Increased fecal losses will be considered separately (see Diarrhea).

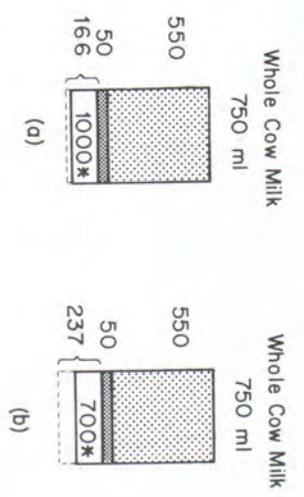


Figure 10-2 Influence of renal concentrating ability of 1000 mosmol/liter (a) or 700 mosmol/liter (b) on water balance of hypothetical infant with extrarenal losses of 600 ml and dietary intake of 750 ml of whole cow milk. Various areas of the columns have the same significance as in Figure 10-1. The segment of the column outlined by interrupted lines indicates the extent of negative water balance. (From Ziegler, E. E., and Fomon, S. J.: Fluid intake, renal solute load, and water balance in infancy. *J. Pediatr.* 78:561, 1971.)

through skin and lungs were greater.* Fever increases water losses through skin and lungs, probably to a lesser extent than does elevated environmental temperature; however, the literature provides little basis for quantitative estimation of the effect of fever. Using the commonly employed estimate of a 10 per cent rise in evaporative water loss per degree centigrade rise in body temperature, evaporative losses by the hypothetical 7 kg infant may be assumed to be 420 ml/day for an elevation of body temperature of 4°C.

If intake of cow milk is decreased to 750 ml, renal solute load will be decreased proportionately (221 mosmol/liter \times 0.75 liter = 166 mosmol). Since extrarenal water losses will be unchanged, at normal environmental temperature 166 mosmol will be excreted in 400 ml of available water (Fig. 10-1c), resulting in urine concentration of 415 mosmol/liter. It is apparent that decrease in the amount of intake of a specified diet will ordinarily lead to increased concentration of the urine (until the maximal concentrating ability has been reached).

If 750 ml of cow milk are consumed in the presence of extrarenal losses of 600 ml (Fig. 10-1d), urine concentration would need to be 1107 mosmol/liter to maintain water balance. Many infants will be able to achieve this urine concentration, particularly when the ratio of urea to nonurea solutes in the urine is high (Winberg, 1959; Drescher et al., 1962). However, it is apparent from the literature (Winberg, 1959; Edelmann et al., 1960; Pólacek et al., 1965) that some otherwise normal infants are unable to concentrate the urine above 600 or 700 mosmol/liter. With a specified diet (and therefore specified renal solute load), it is apparent that in this situation renal concentrating

*For the sake of simplicity, we have chosen to ignore observations (Cooke et al., 1960; Darow et al., 1964) suggesting that during heat stress there may be some tendency toward retention of electrolytes.

ability will determine how closely extrarenal losses may approach water intake before water balance will become negative.

Renal Concentrating Ability

Figure 10-2 concerns a hypothetical infant consuming 750 ml of whole cow milk and with extrarenal losses of 600 ml. The examples chosen are similar to those in Figure 10-1d, except that concentrating ability is limited to 1000 mosmol/liter or to 700 mosmol/liter. Because of the limitation of renal concentrating ability, excretion of the renal solute load of 166 mosmol cannot be accomplished in the 150 ml of water available from the diet. Negative water balance will therefore result. The extent of the negative water balance will be small (16 ml) when renal concentrating ability is 1000 mosmol/liter (Fig. 10-2a) and moderate (87 ml) when renal concentrating ability is 700 mosmol/liter (Fig. 10-2b). If renal concentrating ability of the infant in the example were severely limited (e.g., inability to concentrate urine above 300 mosmol/liter), it is apparent from Figure 10-1a that, even with an intake of 1000 ml of whole cow milk, water balance would be negative.

Feeding Choice and Renal Solute Load

In the case of high extrarenal water losses, low fluid intake or severe limitation of renal concentrating ability, the choice of feeding may be a critical factor in water balance. For example, the infant just mentioned with inability to concentrate the urine above 300 mosmol/liter was calculated to be in negative water balance when receiving 1000 ml of whole cow milk. However, if this infant received 1000 ml of human milk instead of 1000 ml of whole cow milk, it would be necessary for him to excrete only 79 instead of 221 mosmol (Table 10-2) in 650 ml of water, and water balance would be easily maintained. Even if extrarenal losses were high, as in Figure 10-3a, water balance would not be jeopardized.

Figures 10-3c and d concern the water balance of the same hypothetical infant with high extrarenal fluid losses when food intake, instead of consisting of 1000 ml of human milk or of whole cow milk, consists of 730 ml of cow milk and two jars (135 gm each) of commercially prepared strained food—one (pears) yielding a low renal solute load and one (beef and vegetables) yielding a high renal solute load. The renal solute load from 730 ml of whole cow milk is 161 mosmol (221 mosmol/liter \times 0.730 liter). Renal solute load from 270 gm of strained pears (Table 10-2) is only 8 mosmol. Thus, renal solute load arising from the combination of cow milk and pears would be 169



Figure 10-3 Influence of various diets on urine concentration and water balance of hypothetical infant with extrarenal losses of 600 ml. Various areas of the columns have the same significance as in Figures 10-1 and 10-2. (From Ziegler, E. E., and Fomon, S. J.: Fluid intake, renal solute load, and water balance in infancy. *J. Pediatr.* 78:561, 1971.)

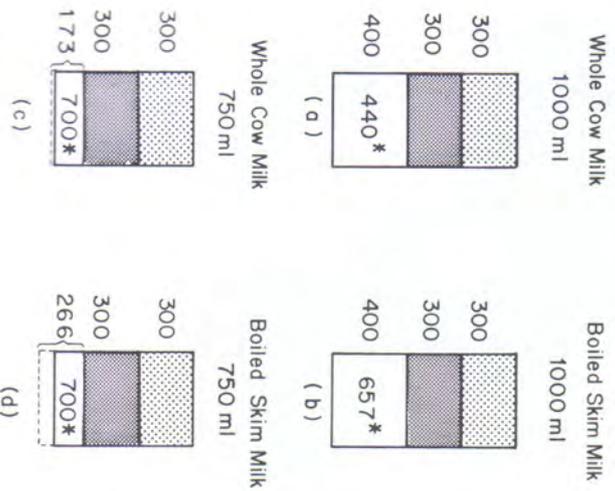


Figure 10-4 Urine concentration and water balance of hypothetical infant with diarrhea fed 1000 ml or 750 ml of whole cow milk or boiled skim milk. Various areas of the columns have the same significance as in Figures 10-1 and 10-2. (From Ziegler, E. E., and Fomon, S. J.: Fluid intake, renal solute load, and water balance in infancy. *J. Pediatr.* 78:561, 1971.)

mosmol, a lesser load than that presented by an approximately similar total volume of intake from cow milk alone.

If, however, protein and electrolyte content of the strained food were high, total renal solute load might be substantially greater than that depicted in Figure 10-3b. In Figure 10-3d, it is assumed that 270 gm of strained beef and vegetables are fed, presenting a renal solute load of 146 mosmol. Total renal solute of strained food plus milk would be 307 mosmol and, with renal concentrating ability limited to 700 mosmol/liter, 439 ml of urine would be required for excretion. With extrarenal water losses of 600 ml, the infant would be in negative water balance.

Most commercially prepared formulas as well as cow milk with added carbohydrate and water will yield renal solute loads that are considerably less than that from whole cow milk, though greater than the renal solute load presented by human milk (Table 10-2). The greater margin of safety provided by these feedings will be of little significance under most circumstances, but may be of considerable value during illness or under adverse environmental conditions.

DIARRHEA

When fecal losses of fluid are increased because of diarrhea, fecal losses of solutes are also increased. Although the actual solute concentration of diarrheal fluid may be somewhat greater, loss of solutes that would otherwise require excretion in the urine amounts to approximately 150 mosmol/liter (Holt et al., 1915; Chung, 1948; Darrow et al., 1949; Finberg et al., 1960; Kooch and Metcalf, 1963; Bruck et al., 1968). Figure 10-4 indicates the renal solute load and fluid balance of a hypothetical infant who is assumed to lose 300 ml of diarrheal fluid (Holt et al., 1915; Chung, 1948; Darrow et al., 1949) containing 45 mosmol of substances that would, if absorbed, contribute to renal solute load. Therefore, the renal solute load, as calculated in the earlier examples would, in the presence of diarrhea, be decreased by 45 mosmol.

When 1000 ml of whole cow milk are consumed by the hypothetical infant (Fig. 10-4a), 176 mosmol ($221 - 45 = 176$) will be excreted in a urine volume of 400 ml, resulting in urine concentration of 440 mosmol/liter. Because boiled skim milk is still recommended by some physicians in management of diarrhea, Figure 10-4b has been included for comparison with Figure 10-4a. It is important to recognize that, per unit of volume, skim milk provides a slightly greater renal solute load than does whole milk, and solute concentration is further increased by loss of water during boiling. We have assumed that skim milk, after gentle boiling for five minutes, will yield a renal solute load of 308 mosmol/1000 ml (Table 10-2). With an intake of 1000 ml of

boiled skim milk (Fig. 10-4b) and fecal loss in diarrheal fluid of 45 mosmol of potential renal solute load, there will remain 263 mosmol to be excreted in 400 ml of urine, resulting in urine concentration of 657 mosmol/liter.

The inadvisability of using boiled skim milk in treatment of diarrhea can be demonstrated more dramatically by considering a hypotonic infant with moderately decreased volume of intake (750 ml) and renal concentrating ability limited to 700 mosmol/liter. Volumes of intake by infants with diarrhea are, in fact, often low (Bruck et al., 1968). Renal concentrating ability of such infants does not appear to be less than that of healthy infants (Bruck et al., 1968) but, as already mentioned, renal concentrating ability of some otherwise normal infants is limited to 700 mosmol/liter.

Under these circumstances, feeding of whole cow milk (Fig. 10-4c) will yield a renal solute load of 121 mosmol (166 mosmol of potential renal solute load provided by diet minus 45 mosmol assumed to be lost in diarrheal fluid) and will require 173 ml of urine for excretion, resulting in slightly negative water balance. Feeding of 750 ml of boiled skim milk (Fig. 10-4d) will yield a renal solute load of 186 mosmol (231 mosmol of potential renal solute load provided by diet minus 45 mosmol assumed to be lost in diarrheal fluid) and require 266 ml of urine for excretion. The magnitude of the negative water balance will therefore be considerably greater when boiled skim milk is fed than when whole cow milk is fed.

FEEDING CALORICALLY CONCENTRATED DIETS TO FULLSIZE INFANTS

Infants with severe congenital heart disease, with various neuromuscular disorders and with certain other chronic diseases may have difficulty in consuming sufficient volume of conventional feedings to promote adequate growth. Under these circumstances, it is reasonable to utilize more concentrated feedings. With adequate monitoring of water balance, it is usually feasible to feed commercially prepared formulas diluted to a concentration of 100 kcal/100 ml instead of to the conventional concentration of 67 kcal/100 ml. The discussion that follows applies to water balance and renal solute load of fullsize infants fed calorically concentrated formulas. Other aspects of nutritional management of fullsize infants with chronic disease are considered in Chapter 19. Water balance and renal solute load in feeding of low-birth-weight infants are considered later in this chapter.

As has already been mentioned, the simplified approach to prediction of renal solute load utilized in Table 10-2 is primarily applicable to diets consisting of whole cow milk or other feedings yielding

relatively high renal solute loads. Under these circumstances, the fraction of dietary nitrogen and of various electrolytes incorporated into newly synthesized body tissue or lost through the skin is relatively small. When the ratio of protein and electrolytes to calories in the diet is relatively low, as will be the case in those diets proposed for infants who are to be fed calorically concentrated diets, retention of nitrogen and minerals for growth and losses through the skin may constitute a larger fraction of the intake, and the proposed calculation is likely to overestimate the renal solute load. For these reasons, the safety of feeding formulas concentrated to 100 kcal/100 ml is probably greater than the calculations would suggest.

As will be discussed below, urinary osmolality should be determined at frequent intervals and dietary adjustment should be made as necessary. Calculations are useful for the purpose of comparing the renal solute load of various foods in relation to their contribution of calories and essential nutrients, but these calculations should be used only as a rough guide. The safety of the diet will be much better evaluated by repeated determinations of urinary osmolality.

Milk and Formula

For purposes of illustrating the importance of the renal solute load in the nutritional management of infants with severe congenital heart disease, Fomon and Ziegler (1972) have considered a hypothetical nine-month-old boy weighing 7 kg and unable to consume more than 750 ml of food daily. If such an infant were fed whole cow milk or formula providing 67 kcal/100 ml, his intake would amount to only 72 kcal/kg/day, and his rate of growth would at best be extremely slow. If he were fed a formula providing 100 kcal/100 ml, 750 ml would provide 107 kcal/kg/day, and satisfactory growth would be more likely.

That formulas providing 100 kcal/100 ml do not necessarily yield excessive renal solute loads may be seen from the examples presented in Figure 10-5. Assuming extrarenal expenditures of water at normal environmental temperature to be 400 ml (350 ml from skin and lungs* and 50 ml in feces), 350 ml of water will be available for renal excretion. Examples included in Figure 10-5 are (1) SMA, a partially demineralized formula, at a concentration of 100 kcal/100 ml; (2)

* Because water losses from the skin and lungs of infants with congenital heart disease are often greater than those of normal infants (Morgan and Nadas, 1963; Elliott and Cooke, 1968; Puyau, 1969; Stocker et al., 1972), losses of 350 ml/day were assumed for the examples in Figures 10-5 and 10-6 rather than the 300 ml/day assumed for normal infants (Figs. 10-1 to 10-4).

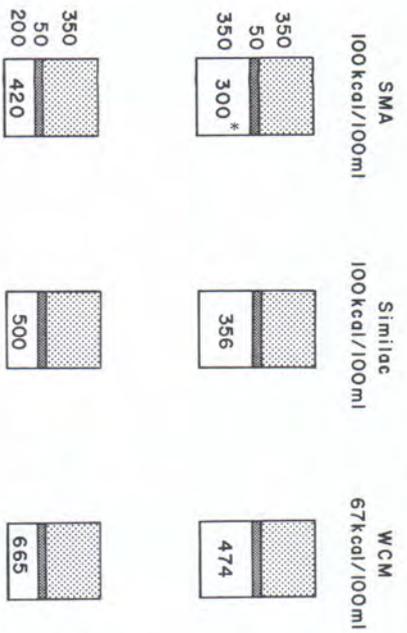


Figure 10-5 Water balance of hypothetical nine-month-old infant with congenital heart disease and daily food consumption limited to 750 ml (upper set of bar graphs) or to 600 ml (lower set of bar graphs). It is assumed that the entire caloric intake is provided by 100 kcal/100 ml of formula or by whole cow milk. Various areas of the columns have the same significance as in Figure 10-1.

Similac at a concentration of 100 kcal/100 ml; and (3) whole cow milk. Estimated renal solute load from consumption of each of these feedings is presented in Table 10-2.

Consumption of 1000 ml of SMA at a caloric density of 100 kcal/100 ml may be seen to yield an estimated renal solute load of 139 mosmol (Table 10-2). The estimated renal solute load from 750 ml of 100 kcal/100 ml SMA is therefore 105 mosmol; excretion of 105 mosmol in 350 ml of urine (Fig. 10-5, upper set of bar graphs) results in urine concentration of 300 mosmol/liter. Similarly, 750 ml of Similac would yield a renal solute load of 125 mosmol. Excretion of 125 mosmol in 350 ml of urine water would be accomplished with a urine concentration of 356 mosmol per liter. As may be seen from Table 10-2, whole cow milk (67 kcal/100 ml) provides a greater renal solute load than do the other feedings at 100 kcal/100 ml. The estimated renal solute load from 750 ml of whole cow milk is 166 mosmol; yet, 750 ml of whole cow milk would provide only 503 kcal compared with 750 kcal from an equal volume of 100 kcal/100 ml SMA or Similac.

If the hypothetical infants just discussed were to receive only 600 ml of formula daily instead of 750 ml, the calculated renal solute loads would be decreased to 84, 100 and 133 mosmol/day, respectively. These renal solute loads would need to be excreted in only 200 ml of urine (Fig. 10-5, lower set of bar graphs), with resultant urine concentrations of 420, 500 and 665 mosmol/liter. Because most normal infants

(and probably most infants with congenital heart disease) can achieve urinary concentrations of at least 700 mosmol/liter, the water balance would probably be maintained in all the examples presented in Figure 10-5.

Assuming that extrarenal losses of fluid by these hypothetical infants remain at a level of 400 ml/day, one can readily calculate the effect of further decreases in fluid intake. With intakes of 500 ml/day, the infant fed whole cow milk would be in negative water balance unless he were able to concentrate the urine to 1105 mosmol/liter; the infant fed 100 kcal/100 ml Similac would be in negative water balance unless he were able to concentrate the urine to 830 mosmol/liter.

Similarly, one may calculate the influence of increased losses of water through the skin and lungs, as might occur with moderate increases in environmental temperature or with fever. An infant consuming 750 ml/day of 100 kcal/100 ml SMA and losing 650 ml/day through extrarenal routes would almost surely be in negative water balance.

Liquid Versus Powdered Formulas. When calorically concentrated formulas are to be fed, accuracy in dilution is of great importance. For this reason, commercially prepared liquid products are preferred to products supplied in powdered form. Three parts of commercially prepared concentrated liquid product (133 kcal/100 ml) mixed with one part of water will yield 100 kcal/100 ml.

Foods Other Than Formula

For some infants with chronic disease associated with decreased ability to consume usual amounts of food, bottle feeding may be extremely difficult and a greater quantity of food may be consumed if a portion of the food is fed by spoon. If foods other than formula are to be fed, they should be selected with attention to caloric density, digestibility, sodium content and renal solute load as discussed in Chapter 19. With the exception of most fruits and a few desserts and puddings, commercially prepared strained foods with caloric densities approaching 100 kcal/100 gm generally present unduly high renal solute loads (Table 10-3). The ratio of protein to calories in strained fruits is low, and it is therefore recommended that no more than 20 percent of caloric intake be supplied from this source.

The importance of proper choice of strained foods may be seen from the examples presented in Figure 10-6. The calculated renal solute load resulting from the consumption of 100 gm of strained applesauce or 100 gm of strained chicken with vegetables is indicated in Table 10-2.

TABLE 10-3 ESTIMATED RENAL SOLUTE LOAD FROM COMMERCIALLY PREPARED STRAINED AND JUNIOR FOODS*

PRODUCT CATEGORY	ESTIMATED RENAL SOLUTE LOAD (mosmol)†	
	Per 100 gm Mean	Per 100 kcal Mean
Strained Juices	5	8
Fruits	10	12
Vegetables		
Plain	56	135
Creamed	51	91
Dinners and soups	67	118
High-meat dinners	135	164
Meats	187	179
Egg yolks	102	53
Desserts	27	28
Junior		
Fruits	10	12
Vegetables		
Plain	56	134
Creamed	56	96
Dinners and soups	64	108
High-meat dinners	151	183
Meats	194	190
Meat sticks	419	265
Desserts	26	30

*Average of foods included in Table 16-2.

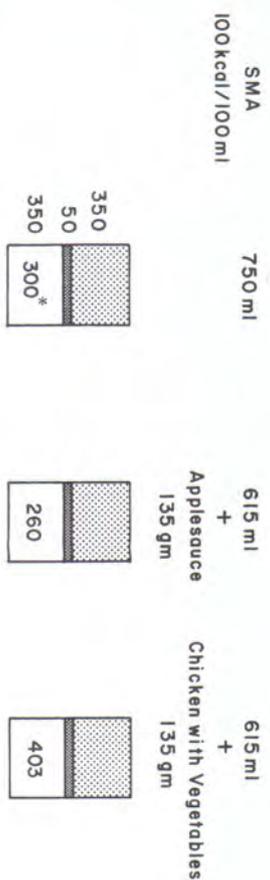
†Calculated according to the method of Ziegler and Fomon (1971).

‡Standard deviation.

Means of Assuring Safety

Means of evaluating the diet with respect to maintenance of adequate water balance will be discussed in this section. More general considerations of dietary management and evaluation of the progress of growth of infants with congenital heart disease will be discussed in Chapter 19.

Parents of infants receiving calorically concentrated feedings should be instructed in formula preparation and in maintaining accurate records of the infant's fluid intake. They should observe the frequency of urination (number of wet diapers) and the color of the urine. At the time of each clinic visit, osmolality of a sample of recently prepared formula should be determined as well as that of several randomly voided specimens of urine. Major inaccuracies in formula dilution may be detected by determining formula osmolality. We suggest that osmolality of the urine (average osmolality of two or three consecutively voided specimens) be maintained below 400 mosmol/liter.



*mosmol/l

Figure 10-6 Effect of substituting commercially prepared strained foods for an equal quantity of 100 kcal/100 ml formula. Various areas of the columns have the same significance as in Figure 10-1.

When growth progress is not satisfactory and urinary concentration is consistently less than 300 mosmol/liter, use of a diet of greater caloric density is indicated. When urinary concentration approximates 400 mosmol/liter and growth is unsatisfactory, the renal solute load should be reduced. By increasing the percentage of calories supplied from carbohydrate and fat, it will ordinarily be possible to reduce the renal solute load without decreasing caloric intake. As discussed in Chapter 19, metabolic balance studies may be desirable to obtain a quantitative estimation of amount of fat excreted in the feces.

When the infant is exposed to elevated environmental temperatures, additional water should be provided. During illness or at other times when the volume of intake is less than that usually consumed, a more dilute feeding is likely to be required. The need for use of a diet of lesser caloric density may be determined by measuring the osmolality of the urine. Through careful monitoring of water balance, it will be possible to avoid most of the hazards of feeding a concentrated diet.

FEEDING CALORICALLY CONCENTRATED DIETS TO LOW-BIRTH-WEIGHT INFANTS

It has been recognized for some time that weight gain by low-birth-weight infants is more rapid when they are fed calorically concentrated formulas than when they are fed conventional formulas providing 67 kcal/100 ml (Snyderman and Holt, 1961; Falkner et al., 1962). Perhaps because of limited stomach capacity, low-birth-weight infants—especially those with weights less than 1500 gm—seem unable to consume a sufficient volume of 67 kcal/100 ml formula to

promote rapid growth. However, rapid growth may occur when calorically concentrated formulas (e.g., 100 kcal/100 ml) are given. Under these circumstances, attention must be paid to maintenance of water balance.

The simplified estimate of renal solute load thus far discussed was developed on the basis of observations of fullsize infants receiving diets that provided relatively generous intakes of protein and minerals. The estimate is not appropriate for management of low-birth-weight infants. As already mentioned, problems of renal solute load and water balance rarely occur in healthy, fullsize infants who are growing rapidly. Because small infants grow rapidly in relation to body size, a relatively large percentage of the "potential renal solute load" may be utilized for growth and therefore will not require renal excretion.

The designation "potential renal solute load" is utilized to include all of the solutes of dietary origin that would need to be excreted in the urine if none were diverted into synthesis of new tissue and none were lost through nonrenal routes. (In fact, loss through nonrenal routes is small and may be ignored). Thus, the potential renal solute load consists of minerals absorbed from the diet and solutes derived from metabolism of dietary protein. For the sake of clarity, we prefer to express this model by means of an equation.

Urinary osmolar concentration (C_{urine} , expressed as mosmol/liter) may be written as

$$C_{\text{urine}} = \frac{S_{\text{food}} - S_{\text{growth}}}{W_{\text{food}} - W_{\text{extrarenal}}}$$

where S_{food} denotes total potential renal solute load derived from food consumed, expressed as mosmol/day. Table 10-4 shows how potential renal solute load may be derived from composition of food consumed. S_{food} may be computed as potential renal solute load (mosmol/kcal) \times food intake (kcal/day).

S_{growth} denotes amount of potential renal solute load utilized for synthesis of new tissue, expressed as mosmol/day. One gram of weight gain is assumed to contain 0.9 mosmol of potential renal solute load (calculations based on data of Widdowson and Dickerson, 1964).

W_{food} denotes amount of water available from dietary sources (i.e., preformed water plus water of oxidation, expressed as liters/day) and is assumed to be 0.90 liter of water per liter of concentrated (e.g., 100 kcal/100 ml) formula and 0.95 liter of water per liter of standard (67 kcal/100 ml) formula consumed (see Water Losses).

$W_{\text{extrarenal}}$ denotes extrarenal water losses—i.e., losses from skin, lungs and intestines, expressed as liters/day. Although extrarenal, especially insensible, losses of water are extremely variable

TABLE 10-4 POTENTIAL RENAL SOLUTE LOAD OF THREE INFANT FORMULAS (UTILIZED IN CALCULATIONS RELATING TO LOW-BIRTH-WEIGHT INFANTS)

FORMULAS	DIETARY INTAKE/100 KCAL					POTENTIAL RENAL SOLUTE LOAD/100 KCAL ^o			
	Protein (gm)	Na (meq)	Cl (meq)	K (meq)	P (mg)	Urea (mosmol)	Na+Cl+K (mosmol)	P (mosmol)	Total (mosmol)
Similac	2.40	1.75	2.41	2.78	65.4	13.7	6.94	2.21	22.9
Enfamil	2.24	1.64	1.79	2.84	67.9	12.8	6.27	2.19	21.3
SMA	2.24	1.05	1.70	2.09	49.3	12.8	4.84	1.59	19.2

^oThe estimate ignores the contribution of organic acids, sulfate, calcium, magnesium and other lesser urinary solutes. The combined contribution of these to renal solute load is considered insignificant in relation to that of protein, sodium, chloride, potassium and phosphorus.

in low-birth-weight infants, we have utilized a value of 0.07 liter/kg/day (Fanaroff et al., 1972).

As already discussed, extrarenal losses of potential renal solute load and the amount of water required for formation of new tissue are small. Therefore, these factors have been omitted from the equation.

If a 1.5 kg infant consumes 225 kcal of Similac in a volume of 225 ml (i.e., 100 kcal/100 ml) and gains 30 gm/day, the predicted value for urine concentration will be 250 mosmol/liter. If this infant were given 225 kcal of Similac in a volume of 170 ml (i.e., 133 kcal/100 ml), the predicted value for urine concentration would be 510 mosmol/liter. This predicted value can serve as a useful guide in the planning of feeding but is likely to differ from the observed value because of wide variations in extrarenal water losses. Therefore, for the low-birth-weight infant, as for the infant with congenital heart disease, urine concentration should be monitored at frequent intervals and should be maintained at values less than 400 mosmol/liter.

ERRORS IN FORMULA DILUTION

Inaccuracies or gross errors in dilution of milk or formula may result in a formula of low caloric density, with eventual development of undernutrition, or in a formula of high caloric density, with a threat to maintaining normal hydration. When formulas of high caloric density are fed, infants accept small volumes of intake so that renal solute load is high in relation to water available for renal excretion.

Although errors may occur in the dilution of concentrated liquid products, such errors are much more common and often more serious in use of powdered products. Many individuals who prepare formulas from powdered product and water appear to add the powder rather generously, using, for example, a heaping rather than a level scoop as a measure. Taitz and Byers (1972) found that sodium concentrations exceeded anticipated values in 21 of 32 formulas prepared from powdered product in the home. In one instance, the concentration of sodium was two and one-half times the expected value.

Gross errors in formula preparation have been reported as causes of serious illness and even death. Formulas providing 133 kcal/100 ml have been fed because of failure to dilute concentrated liquid product (Colle et al., 1958; Roloff and Stern, 1971) or because of the assumption that a tablespoonful of water was equal to 1 ounce (Simpson and O'Duffy, 1967). More commonly, instructions meant to be applied to dilution of concentrated liquid products have been applied to dilution of powder (Skinner, 1967; Jung and Done, 1969; Coodin et al., 1971). Such mixture of one part of powder with one part of water yields a formula of approximately 266 kcal/100 ml. Feeding of these

highly concentrated formulas results in exceedingly low volumes of intake, weight loss, oliguria, fever, irritability and cyanosis. Eventually, hypernatremia may occur with convulsions and coma. Although appropriate treatment will usually prevent death, brain damage is a possible sequela (Macaulay and Watson, 1967).

A different type of error occurred in 1962 when, in a hospital formula room, salt was used instead of sugar in preparing infant formulas. Of 14 infants receiving the formula, 11 developed symptoms of hypernatremic dehydration and six died (Finberg et al., 1963).

REFERENCES

- Alleyne, G. A. O.: The effect of severe protein caloric malnutrition on the renal function of Jamaican children. *Pediatrics* 39:400, 1967.
- Bruck, E., Abal, G., and Aceto, T., Jr.: Pathogenesis and pathophysiology of hypertonic dehydration with diarrhea. *Amer. J. Dis. Child.* 115:122, 1968.
- Chung, A. W.: The effect of oral feeding at different levels on the absorption of foodstuffs in infantile diarrhea. *J. Pediatr.* 33:1, 1948.
- Colle, E., Ayoub, E., and Raile, R.: Hypertonic dehydration (hypernatremia): the role of feedings high in solutes. *Pediatrics* 22:5, 1958.
- Committee on Nutrition, American Academy of Pediatrics: Water requirement in relation to osmolar load as it applies to infant feeding. *Pediatrics* 19:339, 1957.
- Coodin, F. J., Gabrielson, I. W., and Addiego, J. E.: Formula fatality. *Pediatrics* 47:438, 1971.
- Cooke, R. E., Pratt, E. L., and Darrow, D. C.: The metabolic response of infants to heat stress. *Yale J. Biol. Med.* 22:227, 1950.
- Darrow, D. C., Cooke, R. E., and Segar, W. E.: Water and electrolyte metabolism in infants fed cow's milk mixtures during heat stress. *Pediatrics* 14:602, 1954.
- Darrow, D. C., Pratt, E. L., Flett, J., Jr., Gamble, A. H., and Wiase, H. F.: Disturbances of water and electrolytes in infantile diarrhea. *Pediatrics* 3:129, 1949.
- Drescher, A. N., Barnett, H. L., and Troupkou, V.: Water balance in infants during water deprivation. *Amer. J. Dis. Child.* 104:366, 1962.
- Edelman, C. M., Jr., Barnett, H. L., and Troupkou, V.: Renal concentrating mechanisms in newborn infants. Effect of dietary protein and water content, role of urea, and responsiveness to antidiuretic hormone. *J. Clin. Invest.* 39:1062, 1960.
- Elliott, D. A., and Cooke, R. E.: Insensible weight loss in normal children and cardiacs. In Cheek, D. B. (ed.): *Human Growth: Body Composition, Cell Growth, Energy, and Intelligence*. Philadelphia, Lea & Febiger, 1968, p. 494.
- Falkner, F., Steigman, A. J., and Cruise, M. O.: The physical development of the premature infant. I. Some standards and certain relationships to caloric intake. *J. Pediatr.* 60:895, 1962.
- Fanaroff, A. A., Wald, M., Gruber, H. S., and Klaus, M. H.: Insensible water loss in low birth weight infants. *Pediatrics* 50:236, 1972.
- Finberg, L., Cheung, C.-S., and Fleishman, E.: The significance of the concentrations of electrolytes in stool water during infantile diarrhea. *Amer. J. Dis. Child.* 100:809, 1960.
- Finberg, L., Kiley, J., and Luttrell, C. N.: Mass accidental salt poisoning in infancy. *J.A.M.A.* 184:121, 1963.
- Fomon, S. J., and Ziegler, E. E.: Nutritional management of infants with congenital heart disease. *Amer. Heart J.* 83:581, 1972.
- Healey, A. M., and Talbot, N. B.: Insensible water losses per day by hospitalized infants and children. *Amer. J. Dis. Child.* 90:251, 1955.
- Holt, L. E., Courtney, A. M., and Fales, H. L.: The chemical composition of diarrheal as compared with normal stools in infants. *Amer. J. Dis. Child.* 9:213, 1915.
- Jung, A. L., and Done, A. K.: Extreme hyperosmolality and "transient diabetes" due to inappropriately diluted infant formula. *Amer. J. Dis. Child.* 118:859, 1969.

- Koob, S. W., and Metcalf, J.: Physiologic considerations in fluid and electrolyte therapy with particular reference to diarrheal dehydrations in children. *J. Pediatr.* 62:107, 1963.
- Levine, S. Z., Wilson, J. R., and Kelley, M.: The insensible perspiration in infancy and in childhood. I. Its constancy in infants under standard conditions and the effect of various physiologic factors. *Amer. J. Dis. Child.* 37:791, 1929.
- Macaulay, D., and Watson, M.: Hypermnatremia in infants as a cause of brain damage. *Arch. Dis. Child.* 42:485, 1967.
- Maxwell, W. H., and Kleeman, C. R. (eds.): *Clinical Disorders of Fluid and Electrolyte Metabolism*. New York, McGraw-Hill Book Co., 1962.
- Morgan, C. L., and Nadas, A. S.: Sweating and congestive heart failure. *New Eng. J. Med.* 268:580, 1963.
- Pólaček, E., Voček, J., Neugebauerová, L., Šebková, M., and Věchetová, E.: The osmotic concentrating ability in healthy infants and children. *Arch. Dis. Child.* 40:291, 1965.
- Pratt, E. L., Bienvenu, B., and Whyte, M. M.: Concentration of urine solutes by young infants. *Pediatrics* 1:181, 1948.
- Puyau, F. A.: Evaporative heat losses of infants with congenital heart disease. *Amer. J. Clin. Nutr.* 22:1435, 1969.
- Roloff, D. W., and Stern, L.: Hypertonic dehydration due to improperly prepared infant formula: a potential hazard. *Canad. Med. Ass. J.* 105:1311, 1971.
- Simpson, H., and O'Duffy, J.: Need for clarity in infant feeding instructions. *Br. Med. J.* 3:536, 1967.
- Skinner, A. L.: Water depletion associated with improperly constituted powdered milk formulas. *Letter to the editor. Pediatrics* 39:625, 1967.
- Snyderman, S. E., and Holt, L. E., Jr.: The effect of high caloric feeding on the growth of premature infants. *J. Pediatr.* 58:237, 1961.
- Stocker, F. P., Wilkoff, W., Miettinen, O. S., and Nadas, A. S.: Oxygen consumption in infants with heart disease. *J. Pediatr.* 80:43, 1972.
- Taitz, L. S., and Byers, H. D.: High caloric/osmolar feeding and hypertonic dehydration. *Arch. Dis. Child.* 47:257, 1972.
- Widdowson, E. M., and Dickenson, J. W. T.: Chemical composition of the body. In *Comar, C. L., and Bronner, F. (eds.): Mineral Metabolism*. Vol. II, Part A. New York, Academic Press, 1964, p. 1.
- Winberg, J.: Determination of renal concentration capacity in infants and children without renal disease. *Acta Paediatr. Scand.* 48:318, 1959.
- Winters, R. W. (ed.): *The Body Fluids in Pediatrics*. Boston, Little, Brown & Co., 1973.
- Ziegler, E. E., and Fomon, S. J.: Fluid intake, renal solute load, and water balance in infancy. *J. Pediatr.* 78:561, 1971.

11

MAJOR MINERALS

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Because of their relative abundance in the human body, the major minerals are considered to be sodium, chloride, potassium, calcium, phosphorus, magnesium and sulfur.* This chapter will review some aspects of these minerals as they relate to growth and health of the infant and toddler. Estimated requirements, advisable intakes, the extent of absorption and urinary excretion, and data on usual intakes in the United States will be considered. In addition, we shall consider concentrations of calcium, phosphorus and magnesium in serum in health and disease and the possible implications of amounts of salt consumed by normal infants.

ESTIMATED REQUIREMENTS AND ADVISABLE INTAKES

As is discussed in Chapter 5, the requirement for any nutrient strictly applies only to the exact circumstances under which it was determined. With respect to requirements for certain of the minerals, it is particularly important to recognize factors known to affect intestinal absorption of the mineral under consideration—the chemical form of the mineral, amounts of other nutrients, including other major minerals, in the diet, and the presence or absence of substances that inter-

*Sulfur is unique among the major minerals in that it probably functions as a trace element except for the appreciable requirement for sulfur-containing amino acids.