Adaptation of Renal Function From Birth to One Year

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It is well established that the functional capacity of the kidneys is lower in newborns and young infants than in children and adults. This concept, put forward many years ago by the pioneering work of Barnett (1) and McCance (2), has been considerably expanded in recent years, owing to the application of more precise techniques of renal physiology. Most of the studies on developmental renal physiology have compared the neonatal and infantile renal functions with adult standards, using either weight or surface area as a corrective factor. However, using this quantitative concept, immaturity of renal function does not necessarily imply that this function is inappropriate for the current needs of the growing organism. As pointed out by Nash and Edelmann (3), so long as organ systems function in a manner appropriate for the organism’s size and increase their function as growth proceeds, we cannot speak of absolute immaturity. In fact, the normal growth of the infant does dictate increasing metabolic requirements, which stimulate appropriate functional development. However, understanding of this quantitative limitation of the developing kidney is necessary to keep the nutritional load within the limits of tolerance and thus allow for harmonious physical and biochemical growth.

ANATOMICAL DEVELOPMENT

In the human, metanephric development begins by the fifth week of gestation and is completed by the 34th week. The growth of the kidney is centrifugal, the first nephrons appearing in the innermost, i.e., juxtamedullary, portion of the cortex, whereas the last nephrons are formed in the superficial cortex. Formation of new nephrons ceases before full fetal maturity, but it continues for a variable period of time postnatally in premature infants. At the end of a term gestation, the kidney possesses a full complement of nephrons, approximately 850,000 to 1,000,000 per kidney. Maturation of renal function will thus depend on maturation of already existing nephrons. At birth, the superficial nephrons will be the more recently formed and the more immature, whereas the juxtamedullary nephrons will be almost
completely developed, morphologically and functionally. Postnatal maturation will proceed preferentially in the superficial nephrons, paralleling not only a marked increase in total renal blood flow but also a change in its pattern of distribution, since a larger portion is progressively shifted to the superficial cortex (4). Anatomical maturation of the kidney has been assessed by the size and histological appearance of the glomeruli and by the size and disposition of the tubules. Immature glomeruli are normally present for months after birth. The tubules increase in length and volume, convolutions become more coiled, and the tubular length becomes more uniform. Microdissection studies comparing the glomerular surface area to the proximal tubular volume have shown a morphologic preponderance of the glomeruli over the tubules during infancy, and also a high degree of nephronic heterogeneity, with great variation in the size of the tubules. During growth the composite glomerular/tubular ratios decrease and approach the greater homogeneity of the adult kidney (5). Renal growth during infancy and childhood follows a predictable allometric curve, and the size of the kidneys correlates with both age and usual parameters of somatic growth.

FUNCTIONAL DEVELOPMENT

Glomerular Function

The knowledge of the existence of a diminished glomerular filtration rate (GFR) during infancy derives from the classic work of Barnett (1). In the first few days of life, GFR in full-term infants may be as low as 30 to 40 ml/min/1.73 m², to reach values of 60 to 70 ml/min/1.73 m² by 2 to 3 months, and 100 to 110 ml/min/1.73 m² by the end of the first year (Table 1). Values in small premature infants are lower and increase at a slower rate (7).

The GFR through the capillary wall is the result of driving forces (hydrostatic pressure) and opposing forces (osmotic pressure), and is also dependent on the

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg) (50th percentile)</th>
<th>Surface area (m²)</th>
<th>GFR (ml/min/1.73 m²) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>3.4</td>
<td>0.23</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>3 Months</td>
<td>5.8</td>
<td>0.32</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>6 Months</td>
<td>7.6</td>
<td>0.38</td>
<td>75 ± 10</td>
</tr>
<tr>
<td>9 Months</td>
<td>9.1</td>
<td>0.44</td>
<td>80 ± 10</td>
</tr>
<tr>
<td>12 Months</td>
<td>10.1</td>
<td>0.48</td>
<td>85 ± 10</td>
</tr>
<tr>
<td>2 Years</td>
<td>12.6</td>
<td>0.56</td>
<td>105 ± 10</td>
</tr>
</tbody>
</table>

From Roy, ref. 6, with permission.
permeability of the glomerular membrane and on the total area of filtration. Studies on experimental animals, such as the rat or the guinea pig, have demonstrated that the marked increase in GFR that occurs during maturation is predominantly caused by an increase in the glomerular surface area, to a smaller extent by an increase in the ultrafiltration pressure, and only to a minimal degree by changes in hydraulic permeability of the glomerular capillary (8). These maturational changes take place preferentially in the superficial glomeruli (9).

In general, the diminished GFR imposes a severe limitation only during the neonatal period, especially in premature infants. Fluid overloading with hyponatremia is frequently observed in these sick infants (10). During the first trimester of life the decreased tolerance for sodium may be due in part to the low GFR, but tubular factors are also operative, as will be discussed below. Beyond 3 months of age the GFR is high enough to allow for a wider tolerance to water and solute loads.

Tubular Function

When the tubular function of an infant is examined by studying the reabsorption or excretion of an actively transported substance such as glucose or para-aminomhippurate (PAH), respectively, low values are found in comparison with those found in adults. The knowledge of this limited tubular excretory function is very important in neonatal pharmacology. Two tubular maximal reabsorptive capacity-limited mechanisms are recognized: one allows for the secretion of organic acids, such as PAH, penicillin, salicylic acid, and barbiturates, whereas the other permits the secretion of organic bases, including ammonia, thiamine, choline, etc. The pediatrician should always be aware of this limitation when prescribing any drug for the newborn or young infant.

In spite of the renal immaturity, the young infant is capable of maintaining a normal internal environment when an appropriate dietary intake is given and growth proceeds in a normal fashion. The different regulatory mechanisms are present and functioning, although they are quantitatively limited by the characteristics of glomerular and tubular functions. When the dietary intake is inappropriate or when the anabolism of growth is missing, the developing kidneys are easily overloaded and retention of excretory products follows. Adaptation of nutrition to the physiologic characteristics of the growing organism is one of the principal aims of pediatrics.

Urinary Dilution and Concentration

Renal mechanisms involved in excretion and conservation of water take place in the distal parts of the nephron: Henle's loop and distal and collecting tubules; the reabsorption of filtrate in the proximal tubule is iso-osmotic and has no influence on the final osmolality of the urine. Two basic tubular mechanisms are required:
creation of an osmotic gradient in the medullary interstitium, and variable permeability to water of the collecting tubules under the influence of antidiuretic hormone (ADH). Henle's loop works as a countercurrent multiplier, allowing the increasing concentration of urea and nonurea solutes from cortex to medulla. The disposition of the vasa recta along the Henle's loop allows these vessels to act as countercurrent exchangers and thus maintain the high osmolality created in the medulla.

During antidiuresis, when ADH secretion is maximal, the collecting tubules are freely permeable to water, which is passively reabsorbed due to the hypertonicity of the medulla. ADH increases the permeability of the luminal membrane of the collecting tubules by activating the enzyme adenyl cyclase and promoting the formation of cyclic AMP. When water diuresis takes place, ADH is absent and the collecting tubules are impermeable to water, thus allowing the excretion of a tubular fluid that has become more and more hypotonic by the active reabsorption of sodium along the ascending limb of Henle's loop and the distal nephron.

The release of ADH is mediated by changes of plasma osmolality acting on the osmoreceptors located in the anterior hypothalamus, near the neurohypophysis. When plasma osmolality is below a critical threshold level, values of circulating ADH are below 1 pg/ml and the urine is maximally diluted. When plasma osmolality increases about the threshold, a minimal 1% change of plasma osmolality is capable of initiating the mechanism of urinary concentration. At a plasma osmolality of 295 mOsm/kg, plasma concentration of ADH is about 5 pg/ml and the urine is already maximally concentrated. Further increases in plasma osmolality and ADH concentration do not include corresponding increases in urine osmolality. At this moment the defense mechanism is shifted from renal conservation of water to compulsive water intake through the initiation of thirst. The ingestion of water will cause the decrease of plasma osmolality and ADH concentration and the suppression of the mechanism of urinary concentration. Thus, plasma osmolality is maintained within narrow limits, which are determined by the two osmotic thresholds: one imposing the release of ADH, and the other the initiation of thirst (11).

The ability of the newborn and young infants to dilute maximally the urine and to excrete a water load has been extensively studied. There is evidence that the diluting mechanism is very effective and that even premature infants are able to dilute urine as efficiently as adults. Young infants, however, seem unable to increase diuresis to levels comparable to those of adults, after a water load. This reflects probably the limitation imposed by the low glomerular function (12). This limitation makes the infant specially vulnerable to water intoxication when an excessive amount of hypotonic fluids is given. The pediatrician should also consider that during recovery from severe gastroenteritis the ability to excrete a water load is particularly impaired, probably owing to the salt deficit present and the consequent decrease of extracellular volume. If hypotonic fluids are administered too rapidly, severe water intoxication may follow (13).

Another established fact is the reduced concentrating ability of newborns and young infants. They are able to concentrate the urine up to 600 to 700 mOsm/kg, as compared to about 1200 mOsm/kg in the adult. At about 2 to 3 months of age, maximal urine osmolality may be as high as 1000 mOsm/kg, reaching adult values
in the second half of the first year of life (14). This physiologic defect is due to a combination of several intrinsic renal factors, since ADH is secreted appropriately even during fetal life. The shortness of Henle's loops, low capacity for tubular sodium transport, increased medullary blood flow, low urea excretion, and tubular unresponsiveness to ADH (due both to insensitivity of the adenyl cyclase system and to increased secretion of prostaglandins) may all contribute to a reduced urinary concentrating ability (15,16). The factors governing the maturation of the concentrating mechanisms are largely unknown. In humans, the process takes place progressively, the greatest increases in concentrating ability occurring during the first trimester of life, as a reflection of the overall anatomical and functional maturation of the neonatal kidney. In the rat, however, an accelerated development of the concentrating capacity occurs at the time of weaning, independent of changes in food composition and directly modulated by an abrupt increase in the secretion of corticosterone (17). Corticosterone stimulates the maturation of both intestinal transport systems and the renal enzymes necessary for the creation of a hypertonic medullary interstitium (17,18). A similar hormonal mechanism has not been identified in humans.

Regulation of Sodium Excretion

The sodium ion is the principal cation of the extracellular fluid, and its content is precisely regulated since variations in sodium mass will produce immediate changes in the extracellular fluid volume. In other words, the kidney regulates the extracellular fluid volume by regulating the content of its main cation: sodium. The volume control system, of course, must be also concerned with the regulation of water balance, but, as mentioned before, changes in ADH release and in water excretion are modulated via an osmoregulatory system rather than by the extracellular fluid volume. The volume receptors for ADH release are probably effective only in situations of extreme volume depletion, when volume regulation overrides osmoregulation.

Since no secretory mechanisms for sodium exist in the kidney, the amount excreted is controlled through variations of tubular reabsorption of filtered sodium. Normally, at any age, more than 99% of filtered sodium is reabsorbed along the tubules (19). The afferent limb of the regulatory system depends on the stimulation of volume receptors distributed in the vascular tree, on both arterial and venous sides. Main receptors are located in the chest (atrium, right ventricle, pulmonary capillaries), in peripheral and renal arteries, in the central nervous system, and in the liver. The efferent limb transmits the changes of extracellular fluid volume to the kidney, which immediately responds by changing the urinary excretion of sodium. Several factors play a role in this regulatory mechanism, but their relative importance has not been defined precisely:

a. Glomerular filtration rate and peritubular physical factors, such as colloid osmotic and hydrostatic pressures in peritubular capillaries, do influence the reab-
sorption of sodium in the proximal tubule, which represents more than 70% of total renal reabsorption.

b. Neurogenic factors: Hypovolemia stimulates the α-adrenergic system, liberating noradrenaline and enhancing sodium reabsorption, whereas hypervolemia stimulates the β-adrenergic system, liberating dopamine and inhibiting sodium reabsorption.

c. Hormonal factors: Aldosterone plays an important role in the day-to-day balance between sodium intake and sodium excretion, although it affects only a very small portion of the reabsorbed sodium. The renin–angiotensin–aldosterone system is fully operative in the healthy infant. The role of other substances (kallikrein, kinins, and prostaglandins) remains highly controversial. The evidence is also inconclusive as to the existence or physiologic importance of a specific natriuretic hormone released in response to volume expansion of the extracellular fluid.

d. Intrarenal distribution of filtrate: There is some evidence that redistribution of glomerular filtrate between cortical and juxtamedullary nephrons can influence the absolute rate of sodium excretion. Cortical nephrons possessing shorter loops of Henle will excrete a higher fraction of the filtered sodium than juxtamedullary nephrons, which will be better equipped for a more effective sodium reabsorption. A shift of the glomerular filtrate from the medulla to the cortex will tend to favor sodium excretion, and conversely, an increase in juxtamedullary function will favor sodium reabsorption.

The knowledge of the mechanisms regulating sodium excretion in the infant is still limited (20). There is evidence that healthy infants may adjust perfectly to moderate changes in sodium intake. However, although they can sustain sodium deprivation as efficiently as adults, there is a clear limitation in the ability to excrete a sodium load (21). This enhanced sodium reabsorption depends only in part on the decreased GFR and on the relative preponderance of juxtamedullary function, since the amount of sodium excreted after an oral salt load remains low when expressed per unit of GFR, and increases linearly during the first year of life (21). Micropuncture experiments in immature dogs, rats, and guinea pigs have convincingly demonstrated that the increased distal reabsorption characteristic of infancy takes place almost completely in the distal nephron (20). We have proposed that this increased sodium reabsorption is necessary to compensate for the simultaneous immaturity of the proximal tubule and thus maintain the equilibrium of sodium balance (22). The high stimulation of renin and aldosterone secretion during early life may contribute to the enhanced distal tubular reabsorption of sodium. In very premature infants, however, this situation is reversed, because the immaturity of the distal nephron makes it unresponsive to aldosterone, with ensuing sodium loss (23).

As pointed out by Spitzer (20), chronic retention of sodium, within certain limits, is a natural phenomenon in the growing child, which not only permits the effective maintenance of the physiologically increased extracellular space but also contributes to the positive sodium balance intrinsic to growth. Obviously, the need to excrete large amounts of sodium is not a physiologic phenomenon, but nevertheless no
abnormalities are to be expected if sodium intake is adapted to the range of tolerance. Requirements for sodium in the growing infant are estimated to be 2 to 3 mEq/100 kcal metabolized (1–1.5 mEq/kg/day).

Requirements for chloride are similar. Sodium chloride losses in feces and sweat are normally minimal, and the amount present in the urine would quickly adapt to the level of salt intake. The amounts of sodium and chloride required to sustain growth decrease from a maximum to 1.4 and 0.8 mEq/kg/day, respectively, during the first months of life, to a minimum of 0.5 and 0.3 mEq/kg/day, respectively, at the end of the first year (24). In general, 95 to 115 mEq of sodium are required for each kilogram of weight gain (25).

The daily salt intake of an infant receiving human milk (containing about 6 to 7 mEq/liter of sodium and 11 mEq/liter of chloride) is on the order of 1 mEq/kg/day of sodium and 1.5 mEq/kg/day of chloride, but these intakes are three or four times higher when a non-adapted formula is fed, or even 10 times higher when solid foods are added. Infants from 5 to 7 months of age have been found to go into very positive sodium balances when presented with more than 50 mEq of sodium per day (26). An excessive salt intake may jeopardize water metabolism in young infants and may, in the long term, increase the risk of essential hypertension in the adult life (27). On the contrary, efforts to further reduce the salt content of adapted formulas may lead to either sodium or chloride deficiency if other sources of intake are not present (28,29).

**Interaction of Factors Regulating Water Balance**

The interaction between infant feeding and water balance has been reviewed by Fomon and Ziegler (24,30). Several factors may be taken into account: intake of water, extrarenal losses of fluid, renal solute load, and concentrating ability of the kidney. The dietary solute load can be estimated by the sum of the total intake of electrolytes (sodium, potassium, and chloride), assuming that each milliequivalent corresponds to 1 mOsm, plus the solutes derived from protein intake, assuming that each gram of protein yields 4 mOsm of obliged renal excretion.

Because water is continuously lost insensibly, solutes arising from the diet must be excreted with only a fraction of the water intake, and the amount of water necessary for this renal excretion will depend on the concentrating ability of the kidney. When water intake decreases or the insensible water losses are high, maximal conservation of water will be required and a positive water balance will be maintained only in case there is no limitation of concentrating ability. When feedings yielding a high solute load are given without supplementary intake of water, this will lead to additional water loss and in a young infant almost constantly to a negative water balance. A liter of human milk yields approximately 75 mOsm/liter, whereas the renal solute load of non-adapted cow's milk formulas may be as high as 184 to 248 mOsm/liter, depending on the protein content. Plasma osmolality was much higher when infants aged 1 to 3 months were fed an artificial formula.
than when fed only breast milk, and still higher when solid food was introduced early. Hyperosmolality (more than 300 mOsm/kg) was observed only during artificial feeding (31). These infants in precarious water balance were specially predisposed to severe hyperosmolality when, due to intercurrent circumstances (fever, warm and dry climate, gastroenteritis), the amount of water disposable for renal solute excretion was further limited (32). The high frequency of hypertonic dehydration observed during the 1960s and early 1970s was probably due to this fact. We have found that among 12,998 infants with acute gastroenteritis cared for from 1973 to 1980, the incidence of hypernatremic dehydration decreased linearly from a maximum of 4.6% in 1973 to a minimum of 1.2% in 1980. The incidence of severe hypernatremia (160 mEq/liter) also fell from 41% of the cases with hypertonic dehydration to 20% during the same period of observation (33). This phenomenon corresponded exactly to the increase in consumption of adapted formulas during those years. The risk of severe hyperosmolality can be further aggravated when excessive amounts of dried milk powder are used to reconstitute the formula, due to compulsion or poor cultural background of the mothers (34). At present, the increasing popularity of breast feeding, the almost exclusive use of adapted formulas, the late introduction of solid foods, and improved health education, have all contributed to the progressive decrease in the incidence of hypertonic dehydration in developed countries (35).

**Acid–Base Balance**

One of the important consequences of intermediary metabolism is the continuous production of acid residues, which must be excreted by the kidney. Pulmonary function is important for the maintenance of neutrality of body fluids, but only the kidney can regulate the hydrogen ion balance, by controlling the concentration of bicarbonate in plasma.

Both the reabsorption of filtered bicarbonate and the generation of new bicarbonate (which is equivalent to the excretion of hydrogen ion) take place in the renal tubular cell by a single mechanism: the exchange of reabsorbed sodium ions for secreted hydrogen ions. The hydrogen ions secreted derive from the hydration of metabolic CO$_2$, a reaction facilitated by the presence in the renal tubular cell of the enzyme carbonic anhydrase. This reaction takes place along the entire length of the nephron, but has different consequences depending on the composition of the tubular fluid that receives the secreted hydrogen ion. In the proximal tubule, most of the secreted hydrogen ion combines with luminal bicarbonate, contributing to its almost complete reabsorption. In the distal and collecting tubules, hydrogen ion secretion is utilized to complete bicarbonate reabsorption and to titrate other urinary buffers, such as dibasic phosphate (HPO$_4^{2-}$) and ammonia (NH$_3$). This process requires acidification of the urine to pH 5 or below. The combined excretion of titrable acid (mostly in the form of H$_2$PO$_4^-$) and ammonium (NH$_4^+$), minus the final excretion of bicarbonate (if present), expresses the “net acid excretion” and
ADAPTATION OF RENAL FUNCTION IN FIRST YEAR

represents the real contribution of the kidney to the generation of new bicarbonate. The net acid excretion should be equivalent to the amount of hydrogen ion delivered to the body fluids by the catabolism of foodstuffs and the process of growth, approximately 1.5 to 2 mEq/kg/day (36).

The observation that infants maintain lower concentrations of bicarbonate in blood than children and adults led to the conclusion that they must have some limitations in their capacity to acidify the urine and to excrete the endogenous acid load (37). Different studies have shown, however, that with the possible exception of the first weeks of life, especially in the premature infant (38–40), the capacity to acidify the urine is comparable with that observed later in life, although the distribution of hydrogen ion in urinary buffer may be different. In infants fed cow’s milk, titrable acid excretion is higher because of the elevated phosphate content of the urine, and ammonium excretion is lower because of the relative reduction in glomerular filtration rate (41,42). Development of renal capacity for hydrogen ion excretion during the first weeks of life is related primarily to gestational age but is also influenced by the excretory needs imposed by the protein content of the diet (38,39).

The explanation for the "physiologic acidosis of infancy" lies on the finding that the renal bicarbonate threshold, which defines the blood concentration of bicarbonate above which it appears in the urine, is lower in infancy (about 22 mEq/liter) than in adulthood (between 24 and 26 mEq/liter) (41,43). The explanation for this maturation-dependent leak of bicarbonate is not known, but both extrinsic renal factors such as physiologic expansion of extracellular volume and intrinsic renal factors such as morphologic or functional tubular immaturity may contribute to its development.

The pediatrician must take into account that, although the young infant possesses a well-developed mechanism for distal hydrogen ion excretion, in conditions of high protein intake and rapid growth this mechanism is working almost maximally, and the infant's potential for increasing this excretion severalfold under conditions of stress, as occurs during acute gastroenteritis, is limited.

CONCLUSIONS

During the first year of life the kidneys mature both morphologically and functionally. These changes are especially manifest during the neonatal period and the first months of life. Glomerular filtration rate is very low in neonates, particularly in the premature, reaching two-thirds of the fully mature levels by the age of 3 months. Tubular function operates at an even lower level, but the different regulatory mechanisms responsible for maintenance of body homeostasis are present and functioning. During the first months of life there are, however, important limitations to sustain the stresses of salt, water, and acid loads or of water deprivation. During the second semester of life most of these limitations are completely overcome, but there persists some inability to handle a salt loading. During infancy, the process of growth is an important subsidiary to the kidney by reducing the renal solute
load, although bone formation releases hydrogen ion and thus contributes to the endogenous acid load imposed by the diet.

REFERENCES


**DISCUSSION**

**Dr. Anantharaman:** Is it entirely correct to express urine output or free water output in infants per 1.73 square meter body surface?

**Dr. Rodriguez-Soriano:** The whole question applies to the quantification of renal function in infants. Ever since the introduction of this concept by Barnett, we have become accustomed to expressing renal function per body surface area. However, I would agree that it is probably not the most physiological way of expressing renal function. As far as water excretion is concerned, it would probably be more accurate to express it for 100 metabolized kilocalories, but this is very impractical in clinical practice and we therefore prefer to express water excretion per 1.73 m² body surface.

**Dr. Anantharaman:** Has there been any neurophysiological or neurobehavioral response described in children with a high sodium intake?

**Dr. Rodriguez-Soriano:** To my knowledge, no.

**Dr. Anantharaman:** I would like to make a short comment. A high solute intake, besides primarily causing thirst and dehydration, can also simultaneously produce some behavioral
changes. The question is whether these changes are permanent, or do they disappear if the solute intakes are normalized?

Dr. Rodríguez-Soriano: I have no answer with regard to sodium excess. We have some experience on chloride deficiency. Babies who received low-chloride formulas during the first months of life now present, at 3 years of age, with some behavioral abnormalities.

Dr. Rey: Have you ever observed a sodium deprivation syndrome or any manifestations of sodium deprivation?

Dr. Rodríguez-Soriano: No, I have not. However, it is clear that efforts to further reduce the salt content in infant formulas may lead to either sodium or chloride deficiency if other sources of intake are not present.

Dr. Boulton: In a developing country, when the weight of a child of, let us say, 6 months, is 5 kg, and his poorly nourished mother provides him with 750 ml breast milk per day and no extra food, then this child would only get about 4 mmoles sodium per day, whereas his needs are more or less 10 mmoles. One effect of this low sodium intake is poor growth. In industrialized countries, one only sees this when excessive amounts of sodium are being lost, for example, in children with congenital adrenal hypoplasia. In this situation inadequate salt intake results in poor growth as well.

Dr. Ballabriga: May we perhaps come back to sodium excess. In my country, about 10 years ago, we observed an epidemic of hypernatremic dehydration due to the use of concentrated foods, particularly concentrated and inadequately diluted milk. We then observed plasma sodium concentrations as high as 160 mEq/liter inducing behavioral abnormalities, such as irritability. Postmortem examination showed brain damage and cerebral hemorrhages. The same pathological observations have been made in newborns after administration of large quantities of sodium bicarbonate. I would appreciate the comments of our colleagues from developing countries on this subject.

Dr. Ashfaq Ahmad: In a study we carried out on 1,000 children with acute gastroenteritis, divided into two groups—breast- and formula-fed babies—there was a high incidence of hyponatremia in bottle-fed babies because diarrhea is a disease of lower social classes and the mothers tend to dilute the milk in order that the tin will last a bit longer. The problem of hyponatremia is more common in formula-fed babies than in breast-fed babies in the developing countries.

Dr. Shanti Ghosh: This is only partially true. It is true that if a mother wants her tin of milk to last longer, then she will make it very weak and consequently there is a problem of severe underfeeding, but this has nothing to do with what kind of milk it is. However, from time to time, in otherwise adequately fed babies, there is definitely hypernatremia because of the high sodium content, which does not occur in breast-fed babies. This becomes much worse in any kind of situation in which there is water loss, like diarrhea, vomiting, or inadequate intake of fluid.

Dr. Ashfaq Ahmad: In theory I agree with Dr. Ghosh, but have you conducted any studies in India showing that hypernatremia is more common in acute gastroenteritis with bottle-fed babies than breast-fed babies?

Dr. Shanti Ghosh: The real problem that one encounters is in children with diarrhea; malnutrition is an important factor, and hardly any of these children are adequately fed, so I think the comparison would be rather fallacious. One could only compare these two groups of children with diarrhea if they were all well nourished and adequately fed. The problem is not really bottle versus breast, but rather a problem of severe underfeeding and malnutrition. We do not see much hypernatremia, I agree with you. The reason therefore has nothing to do with breast or bottle, but with underfeeding and malnutrition.
Dr. Davies: In the United Kingdom during the early 1970s, there was a lot of concern over the early introduction of solid foods, contributing not only to obesity but also to the rather alarmingly high incidence of hypernatremic dehydration. In a study undertaken in Cardiff in 1971, we found that about 60% of children who were already introduced to non-milk foods at the age of 2 months had plasma osmolalities greater than 300 mOsm/kg. Would people agree with the general statement that—provided infants are introduced to a non-milk food at a sensible time, determined by their own needs and behavior—then immaturity of renal function does not impose any constraint or handicap on the child’s physiological mechanisms?

Dr. Poskitt: I agree with Dr. Davies’ conclusion, except that one of the problems was the fact that babies at that time were given cow’s milk and now they receive adapted formulas. But what about sodium loss in sweat? Does it effectively create a need for babies in some countries to receive extra sodium?

Dr. Rey: Sodium excretion in sweat is very low. Under normal circumstances, an adult loses about 3 mEq sodium per day.

Dr. Guesry: A group working in the south of Israel published a paper a few months ago showing that in some breast-fed infants there was no need to provide a supplement of sodium, even in a very warm and dry climate.

Dr. Rodriguez-Soriano: Further to this, it is interesting to notice that the picture of hypochloremic alkalosis in cystic fibrosis patients was almost never observed until the late 1970s, when adapted formulas came onto the market. This means that the amount of sodium contained in these preparations is sufficient to maintain a normal sodium balance in healthy babies, but not in cystic fibrosis patients.

Dr. Boulton: In Australia, amongst well-nourished children, we do not have a problem with hypernatremia. I think the difference is that during our summer everyone drinks a lot and a child’s need for water is very well recognized. Historically, we never had a problem of a sudden epidemic of hypernatremia. I presume that is just because everyone has to drink all the time. Normal children do not become depleted of sodium either, since salt losses from sweat are absolutely minimal, in the range of a couple of millimoles of sodium per liter of sweat.

Dr. Rey: Dr. Rodríguez-Soriano, could you go a bit further into detail on the role of bone formation in hydrogen ion production?

Dr. Rodríguez-Soriano: When you calculate hydrogen balances in healthy adults, you only have to take into account the hydrogen ions yielded by protein catabolism. The catabolism of the sulfur amino acids yields sulfuric acid; hydrogen has to be excreted or generation of bicarbonate has to compensate for it. But, in the growing child, to the hydrogen yielded by protein catabolism, you should add hydrogen ions generated by growth itself. Bone formation liberates hydrogen ions during the synthesis of hydroxyapatite. As a matter of fact, you can calculate the amount of hydrogen liberated from the amount of calcium retained during a calcium balance. Hydrogen ion formation in an adult on a standard protein diet is about 1 mEq/kg/day, whilst it is between 2 and 3 mEq/kg/day in an infant. The infant has therefore twice as much hydrogen to excrete as an adult. This explains why any stress in infants, such as gastroenteritis, leads very quickly to metabolic acidosis.