Fluid and Electrolyte Homeostasis in Infants and Children

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Maintenance of body water and electrolytes is the result of tightly regulated balances of intakes and outputs mediated by elegant and complex physiologic mechanisms. Total body water (TBW) consists of extracellular fluid (ECF) and intracellular fluid (ICF) and, as a percentage of body weight, changes with age decreasing particularly rapidly within the first year of life (1). The relative proportion of ICF to ECF also changes and in parallel to the change in TBW, with the ECF volume rapidly decreasing in the first year, and especially the first months, of life. In contrast to early infancy, in older children the ECF volume correlates very closely to body weight and TBW.

Unlike sodium, whose distribution in the body is uneven because of active transport of the ion, water movement is passively determined in response to osmotic gradients. Body water, being freely diffusible, is therefore in equilibrium in relation to the distribution of its nondiffusible solutes. Sodium chloride, the principal solute of ECF, is primarily regulated by renal excretion with nonrenal losses being relatively quite small. Because NaCl is the major osmolyte in the ECF, gains and losses of NaCl are usually accompanied by corresponding gains and losses of water. Sodium retention causes volume expansion and depletion causes volume contraction. A net negative sodium balance results in a clinical state of ECF volume contraction, the most common cause worldwide being infectious diarrheal disease, which results in dehydration.

Maintenance of body water involves the control of both intake/absorption governed by the gastrointestinal tract and excretion, but principally by excretion controlled by the kidney. Under normal conditions, losses via the gastrointestinal tract are small but can increase appreciably in pathologic states. Unlike in other animals in which water intake is governed almost solely by thirst, water intake in humans is usually in excess of its obligate losses, with the excess excreted by the kidneys. Both thirst and renal water excretion are determined by body fluid tonicity.
REGULATION OF SODIUM

The balance between sodium intake and excretion determines total body sodium concentration. Sodium absorption takes place in the gastrointestinal tract and excretion governed primarily by the kidney with small amounts excreted in sweat and feces. In pathologic conditions, especially diarrheal disease, normal gastrointestinal mechanisms of homeostasis become disturbed and can result in large, sometimes life-threatening fluid and electrolytes losses.

The distribution of the cations sodium and potassium in body water is unbalanced (Fig. 1) (2). Sodium is the most abundant cation in the ECF compartment compared to ICF in which potassium is predominant. The intracellular and extracellular distribution of sodium and potassium is principally maintained by the Na⁺-K⁺-ATPase pump, also known as the sodium pump. Other mechanisms exist as well in different organs and organ sites and, while essential, make a relatively smaller contribution to overall regulation. The preservation of electroneutrality in all body water compartments is regulated by cation-anion balance with HCO₃⁻ and Cl⁻ the main anions in the ECF and phosphate and protein in the ICF. Because deviations in ECF volume represent life-threatening conditions, elaborate control mechanisms regulate organ function to normalize ECF volume.

The systems regulating renal NaCl and water excretion operate by a negative feedback loop consisting of an afferent (sensory) component, an efferent (messenger) component, and an effector organ (Table 1) (3). Afferent (sensory) mechanisms detect and respond to changes in the ECF volume. In the case of hypotension, such
as that induced by diarrheal dehydration, the net effect of the different regulatory systems is to maintain mean arterial pressure and cerebral and coronary perfusion. Sensors within the central circulation responsive to mechanical stretching of the arterial or cardiac wall induced by changes in arterial pressure result in a corresponding decrease or increase in sodium and water excretion. Atrial natriuretic peptide, a potent natriuretic and diuretic hormone stored within the cardiac myocytes, mediates natriuresis for the atrial sensors and generally antagonizes the sodium-retaining mechanisms of the renin-angiotensin system. ECF volume contraction manifested as reduced plasma volume and hypotension triggers carotid sinus and aortic arch baroreceptors leading to activation of the sympathetic nervous system and ultimately the renin-angiotensin system. The renal response is aimed at reconstituting ECF volume by decreasing the glomerular filtration rate and thus the filtered load of sodium and, even more critically, by promoting tubular reabsorption of sodium. Receptors located in the renal juxtaglomerular apparatus detect reduced ECF volume and sodium concentration and stimulate renal sodium retention in the proximal tubule via the renin-angiotensin cascade.

The juxtaglomerular apparatus is a collection of specialized cells of the afferent arteriole and the part of the distal tubule that abuts the glomerular vascular pole, the macula densa (Fig. 2). Signals that stimulate release of renin are reduced renal perfusion pressure in the afferent arteriole and reduced sodium chloride concentration delivered to the macula densa. Renin cleaves angiotensinogen to form angiotensin I, which is converted to angiotensin II by angiotensin-converting enzyme. Angiotensin II directly stimulates sodium absorption through Na-H exchange in the proximal tubule. Angiotensin II also leads to aldosterone secretion, a mineral corticoid hormone produced in the adrenal gland and critical regulator of sodium in the distal convoluted tubules and collecting ducts.

The amount of sodium filtered through the kidney in a day is approximately 100 times sodium intake and greater than five times the total body amount of sodium. Total excretion is less than 1% of the total amount filtered through the kidney, with the rest being reabsorbed along the renal tubules. In conditions of sodium imbalance, total sodium excretion from that filtered can increase to 10% or more with sodium excess or to very low amounts in conditions of sodium depletion. Approximately two thirds of sodium delivered to the nephron is reabsorbed by the proximal tubule.
Receptors in the renal juxtaglomerular apparatus detect reduced extracellular fluid volume and sodium concentration and stimulate renal sodium retention in the proximal tubule via renin-angiotensin cascade.

and 20% by the loop of Henle (Table 2) (4). Reabsorption of sodium is achieved by active transport across tubular epithelium and by Starling forces active between the peritubular capillaries and interstitium. Filtered luminal sodium gains entry to the peritubular interstitium by passing both through and between epithelial cells. The entire process is driven by active transport of sodium via the Na\(^+\)-K\(^+\)-ATPase pump from within the cell across the basolateral membrane to the interstitium, creating a low intracellular sodium concentration (5). This electrochemical downhill gradient promotes the passage of luminal sodium into the epithelial cell mainly through secondary active transport (Fig. 3). Various transport proteins located on the apical (luminal) surface of the epithelial cell participate in sodium exchange, i.e., exchange

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of cations. The most important of these in renal tubular sodium transport is the exchange of sodium for hydrogen via the Na-proton antiporter. Smaller amounts of sodium are transported by cotransport with glucose, amino acids, and phosphate, among others.

Water reabsorption takes place in the descending part of the loop while most sodium reabsorption in the loop occurs in the ascending limb, primarily through active transport. Fine adjustments of sodium balance, accounting for approximately 12% of renal sodium absorption, happen in the distal renal tubule and collecting ducts. It is the reabsorption in the distal tubule that maintains sodium homeostasis and balance of excretion with intake. Sodium reabsorption at these sites is regulated by aldosterone, which is governed by the renin-angiotensin pathway.

**REGULATION OF BODY WATER**

The precise control of body water maintains a plasma solute particle concentration fairly constant at 285 to 295 mOsm/kg H₂O despite variations in sodium and water intakes. Body water equilibrium is maintained through the balance of total water gain (water through intake and that produced through metabolic processes) with water losses including renal and gastrointestinal losses as well as loss through the skin and lungs. Of the two, water excretion has a greater role than intake in regulating body water.
The two signaling mechanisms that control water balance are thirst and arginine vasopressin (6). Water intake is predominately controlled by thirst, the manifestation of a complex interaction of physiologic control systems and behavioral influences. Thirst is stimulated by two main homeostatic mechanisms: increased plasma osmolality and decreases in ECF volume, with as little as a 1% to 2% increase of the former and 10% or more of the latter sufficient to elicit the thirst response. Plasma osmolality is generally the primary driver for thirst although in conditions of reduced ECF volume, such as in severe dehydration, low blood volume assumes a greater role and will override tonicity when unusual, seemingly discrepant situations of low blood volume and low osmolality coexist. Central and perhaps peripheral osmoreceptors detect deviations in plasma osmolality and signal the anterior hypothalamus to maintain homeostasis via thirst and increased water intake. Decreases in blood volume detected by baroreceptors invoke a response leading to increased water and salt intakes as well as renal mechanism controlling excretion.

A variable intake of water must be closely matched by daily fluid losses. In contrast to water losses through renal excretion and stool output, certain losses are not precisely regulated. Fluid evaporation from the respiratory tract through breathing and from skin are insensible losses, and are relatively constant under usual circumstances. Sweating is water lost through skin primarily as a mechanism to eliminate excess heat typically determined by ambient temperature and physical activity. The amount of water loss through sweating is highly variable but can reach relatively large volumes in hot environments or heavy exertion. Negative water balance due to insensible losses is usually prevented by thirst mechanisms although cumulative sweat Na losses can lead to hypovolemia.

Arginine vasopressin (AVP) is a peptide synthesized in pituitary neuronal cells of supraoptic and paraventricular nuclei and stored in the neurohypophysis (7). AVP is secreted in response to signals from osmoreceptors that are extremely sensitive to small changes in plasma osmolality. In the absence of AVP, the nephron collecting tubules are nearly impermeable to water, which prevents significant water reabsorption and enables a large loss of water into the urine. In contrast, in the presence of AVP, permeability greatly increases and enables most water to be reabsorbed. This is achieved by AVP-stimulation of the insertion of aquaporin-collecting ducts (preformed water channels) into the apical (luminal) epithelial cell membrane. When AVP acts on the cell, it combines with membrane receptors that cause the formation of c-AMP that in turn causes the phosphorylation of elements within the aquaporin vesicles and insertion into the apical membrane providing many areas of high water permeability. Permeability to water begins to increase within 30 to 40 seconds after exposure to AVP. The entire process is accomplished within 5 to 10 minutes and reverses equally as fast in the absence of AVP.

GASTROINTESTINAL REGULATION OF FLUIDS AND ELECTROLYTES

Under normal conditions, the main role of the gastrointestinal tract in fluid and electrolyte homeostasis is regulation of absorption. In pathologic states, fluid and
electrolyte losses via the gut can be substantial; diarrheal dehydration is the most common water and electrolyte abnormality worldwide. Several factors influence the characteristics of the ECF in dehydration including the composition of diarrheal losses, composition of ongoing fluid intake, effect of volume contraction, potassium depletion, metabolic acidosis, and redistribution of sodium and potassium between ECF and ICF.

The amount of water in the intestinal lumen is closely regulated. Various organs secrete large volumes of water to aid digestion and other processes. The daily fluid load varies but is approximately 9 l in a healthy adult (8). Approximately 98% of ingested and secreted fluid is absorbed/reabsorbed, with 65% to 80% of the fluid load absorbed in the small intestine in association with nutrient and electrolyte absorption and the remainder absorbed by the colon (Fig. 4). The functional design of the small intestine is one that amplifies its surface area through the structure of the microvillus membrane that results in a surface area 600 times larger than a simple cylinder with the diameter of the small bowel (8). In general, permeability decreases distally so that jejunum is the most permeable and the distal colon and rectum the least permeable to the passive movement of electrolytes and water (9).

The enterocyte is the main intestinal cell responsible for absorptive and secretory events of epithelium. Other cells present in lower numbers help regulate enterocyte functions. These include mucus-secreting goblet cells, specialized M cells, Paneth cells in the crypt as well as enteroendocrine cells containing hormones, neuropeptides, and serotonin that alter epithelial ion and fluid transport.

While functional differences related to fluid absorption and secretion along the crypt-villus axis have long been recognized, segmental differences in function and mechanisms of electrolyte and fluid flux along the length of the small and large intestine are more recently defined (8). More recent definitions of normal fluid electrolyte physiology have also led to better understanding of mechanisms of diarrheal disease with attendant implications for development of more specific and targeted therapeutic interventions.

Mechanisms of Intestinal Water Transport

Under normal circumstances, large quantities of sodium, chloride, and bicarbonate are absorbed via processes that ultimately consume cellular energy, while hydrogen and to some extent bicarbonate and chloride ions are secreted. Water moves across epithelium passively either through or around the epithelial cell, linked to movement of ions and solutes in response to osmotic fluxes. Electrolytes actively transported out from within enterocytes into the small spaces between cells during absorption or into the bowel lumen during secretion create an osmotic gradient causing water to passively follow by means of paracellular transit through the tight junctions. An different mechanism of water transport is enabled by ions accumulating within the epithelial cell resulting in an intracellular osmotic drive and subsequent passive transepithelial water flow. The tight junction between epithelial cells is variably permeable throughout the gastrointestinal tract, being "looser" in the proximal small bowel and becoming progressively "tighter" moving caudad (Fig. 4). Paracellular water transport is the main mechanism of water flow in the small bowel while transcellular water flow predominates where epithelia are tightly aligned and less permeable as in the distal colon.

Mechanisms of Electrolyte Transport

Different mechanisms operate to facilitate transfer of ions and solutes in and out of the epithelial cell including pumps, carriers, and channels (Fig. 3) (10).

Adenosine Triphosphatase Pumps

Low gut epithelial intracellular sodium concentration and electronegativity maintained by the sodium pump on the basolateral membrane are the two basic features of the epithelial cell interior that establish a favorable electrochemical gradient for passive Na$^+$ entry into the cell. This "downhill" movement of Na$^+$ into the cell is fundamental for most absorptive and secretory processes. Ions traverse the epithelium by passing through (transcellular) or between cells (paracellular) by mechanisms involving either passive or active transport. The active exchange of three ions of intracellular Na$^+$ for two ions of extracellular K$^+$ along the basolateral membrane by the energy-expending Na$^+$-K$^+$-ATPase (Na$^+$ pump) results in a net cationic loss and maintains the low intracellular Na$^+$ concentration and electronegativity.
responsible for the favorable conditions for Na\(^+\) influx via Na\(^+\) channels or cotransporters and exchangers for which Na\(^+\) is required. Other intestinal pumps that may be important in transporting ions across electrical and chemical gradients include an H\(^+\)-K\(^+\)-ATPase in the distal colon and Ca\(^{2+}\) and Mg\(^{2+}\)-ATPases.

**Carriers (Cotransporters and Exchangers)**

Many nutrients including glucose, amino, vitamins, and luminal solutes such as bile acids gain entry into epithelia coupled with sodium. Cotransportation of sodium with a specific carrier (SGLT-1) at the apical surface of the upper villus in the small intestine is responsible for most sodium and water absorption following a meal or ingestion of oral rehydration solution. SGLT-1 binds two sodium molecules to one glucose molecule and transports them into the cell. Glucose accumulates within the enterocyte in higher concentration than adjacent intercellular compartments and ultimately diffuses across the basolateral membrane mediated by a glucose transporter (GLT). The result is a hypertonic environment in the extracellular space, and water moves from the lumen through the paracellular tight junction to maintain osmotic balance. In most diarrheal disease states, the SGLT-1 is preserved and thereby forms the basis for oral rehydration therapy (11). The Na\(^+\) is ultimately extruded from the cell by the Na\(^+\)-K\(^+\)-ATPase pump at the basolateral membrane.

In the fasted state or between meals, most NaCl is transported from the lumen via exchange (Na\(^+\)/H\(^+\) and Cl\(^-\)/HCO\(_3\)^-) rather than cotransport mechanisms. In contrast to Na\(^+\)-solute cotransportation, Na\(^+\)/H\(^+\) exchange (cation exchange) occurs in all segments of the small and large intestine and in both the apical and basolateral membranes of villus cells. The tightly coupled exchange of one molecule of Na\(^+\) for one molecule of H\(^+\) occurs is electroneutral and has an important role in regulation of intracellular pH. Together with N\(^+\)/H\(^+\) exchange, Cl\(^-\)/HCO\(_3\)^- exchange (anion exchange) takes place in small and large intestine to mediate NaCl transport, but unlike the former occurs in crypt as well as villus cells.

**Ion Channels**

Channels act as a gated pores selective for certain ions, rapidly opening and closing in response to different signals including voltage, ionic concentrations, and intracellular mediators. Sodium channels in the apical membrane are responsible for electrogenic sodium absorption and allow more than a million ions per second down its electrochemical gradient when open. There are likely different classes of sodium channels in different parts of the small and large bowel that exhibit some heterogeneity in their regulation.

**Potassium and Chloride Absorption**

Approximately 85% of potassium absorption occurs in the small intestine by passive diffusion driven by the prevailing electrochemical gradient. Most Cl\(^-\) absorption occurs by diffusion through paracellular spaces, driven by the electrochemical
gradient created by Na\(^+\) influx that promotes movements of anions. Cl\(^-\) absorption also takes place via the transcellular route coupled to Na\(^+\), mediated by the synchronous Na\(^+\)/H\(^+\) and Cl\(^-\)/HCO\(_3\)\(^-\)exchangers as described previously.

**Electrolyte Secretory Mechanisms**

**Chloride Secretion**

While sodium transport drives the absorption of fluid, Cl\(^-\) excretion is the driving force for fluid secretion and that occurs throughout the small and large intestine. Cl\(^-\) is taken up along the basolateral membrane of the epithelial cell by the electroneutral Na\(^+\)/K\(^+\)/2Cl\(^-\) cotransporter and accumulates within the cell above its electrochemical equilibrium. The Na\(^+\) and K\(^+\) that accompany Cl\(^-\) into the cell are recycled along the basolateral membrane with Na\(^+\) exit mediated by the Na\(^+\) pump fueled by Na\(^+\),K\(^+\)-ATPase and K\(^+\) through K\(^+\) channels.

Once within the cell, Cl\(^-\) exits into the intestinal lumen at the apical membrane via Cl\(^-\) channels that open in response to regulatory agonists. Na\(^+\) most likely follows passively through tight junctions of paracellular spaces to maintain electroneutrality between luminal and serosal compartments. Several Cl\(^-\) channels exist and are defined by their regulatory factor such as intracellular concentrations of cyclic nucleotides, Ca\(^{2+}\), and cell volume. One Cl\(^-\) channel of special interest is the defective product of the CFTR (cystic fibrosis transmembrane regulator) gene responsible for cystic fibrosis and is also the channel activated by stimuli implicated in secretory diarrhea.

**HCO\(_3\)\(^-\) Secretion**

Most HCO\(_3\)\(^-\) secretion occurs in the duodenum and it is largely neutralized by gastric acid. It contributes to the mucus-bicarbonate layer where it may be an important protective factor against duodenal ulceration. Duodenal HCO\(_3\)\(^-\) secretion is likely via different mechanisms with evidence indicating that the CFTR Cl\(^-\) channel might also function as a HCO\(_3\)\(^-\) channel. Lesser amounts are secreted in the ileum and colon although its role is not as well defined.

**Regulation of Electrolyte Transport**

**Intracellular Regulators of Ion Flux**

The signaling of extracellular events and translation into appropriate cellular responses modulating ion and fluid transport is mediated through an intricate system of second messengers. Two major classes of second messengers have long been recognized for their role in secretion; the cyclic nucleotides (including cyclic adenosine monophosphate [cAMP] and cyclic guanosine monophosphate [cGMP]) and ionized cytosolic calcium (Ca\(^{2+}\)). In response to external stimuli, Increased levels
of these messengers activate protein kinases that act directly on ion channels to cause increased efflux of Cl\(^-\) through Cl\(^-\) channels down its electrochemical gradient and inhibition of electroneutral NaCl-coupled influx.

The first step in activation of the second messengers is the binding by one of a variety of hormones, neurotransmitters, and secretagogues to receptors located along the epithelial cell membrane. The physiologic receptors for various external luminal stimuli including secretagogues elaborated by toxigenic bacteria are generally located at the apical membrane while most endogenous agonists such as hormones and inflammatory mediators bind receptors primarily along the basolateral membrane. The binding of ligand to receptor initiates the intracellular cascade involving second messenger molecules as key components and that control the activity of protein kinases and other effectors such as phosphatases.

**Intercellular Regulators of Ion Flux**

The intestine processes numerous inputs from the paracrine, immune, neural, and endocrine systems which are manifested as responses in the epithelial cell, permeability, blood flow, and motility, all of which determine clinical diarrheal disease. The regulatory agents responsible for maintaining fluid and electrolyte homeostasis include hormone peptides, active amines, arachidonic acid metabolites, and nitric oxide. Under normal conditions, the intestinal transport of water and electrolytes is a finely tuned transcellular and paracellular phenomena regulated by the complex interaction between the endocrine (bloodborne hormones from distant sites), paracrine (local hormones), immune, and enteric nervous systems. In reality these systems do not function as isolated units and their borders are indistinct and overlap (8,9,12). Examples include 5-HT and VIP that function as either hormones or neurotransmitters or both depending on the precise clinical situation. Certain bacterial toxins such as cholera simultaneously stimulate paracrine, neural, and immune responses, all of which may alter ion and water flux.

In pathologic conditions, bacteria colonize the bowel and with subsequent adherence or invasion of the epithelium (12). Pathogenic microbes may produce enterotoxins that initiate the generation of intracellular second messengers that disrupt ion flux while others produce cytotoxins that damage epithelial cell integrity. Immune cells induced by bacteria or their products may release an assortment of active components effecting ion and water flux, either directly on epithelium via components such as oxygen radicals or by stimulating mesenchymal cells or neurons to release prostaglandins or acetylcholine.

**Other Regulatory Factors**

Other factors influence fluid and electrolyte transport indirectly and include acid-base homeostasis, gut motility, luminal flow rates, intestinal permeability, blood
oncotic pressure and plasma volume, venous and arterial pressure, and physical and psychological stress.

REFERENCES


DISCUSSION

Dr. Michael J. G. Farthing: George, you stressed the importance of changes in body composition during the early period of life. Would you like to comment on other difficulties with water and the electrolyte regulation that occur particularly during the neonatal and period of infancy, which make that age group so vulnerable to fluid losses?

Dr. George J. Fuchs: Thank you, Michael. Well, there may be others. The one in which I am particularly interested is the effect of kidney function very early in infancy. An infant's ability to handle renal solute load is compromised compared to an older child or adult, so its ability to handle a large volume of sodium is compromised. It turns out in practice, though, that it's remarkably resilient even though the ability to handle renal solute load is not the same. It can withstand most of the challenges put to it, but in extreme cases of fluid loss in extremely hot weather or marked increased renal solute load by virtue of what the infant is feeding, for example high protein or high sodium concentrate, it can then experience some untoward effects. But again, not as much as was initially feared. Ken Brown and others have shown that breastfed infants, for example, generally don't require supplemental water in relatively extreme conditions of heat and that they are able to handle that renal solute load effectively to maintain health, but there are some extreme situations in which that does come into play. Are there any others that you had in mind?

Dr. Michael J. G. Farthing: You were interested in receptor expression of some enterotoxins and we know that they come and go with age and I just wondered what sort of evidence there was that, for instance, sodium and water retrieval mechanisms change in the gut, particularly in the distal ileum and colon as we mature.
Dr. George J. Fuchs: Well, I'm not familiar with that and maybe I should put that to the audience, but you're right, it wouldn't be surprising if there are some differences.

Dr. Wolf Endres: What you told us about fluid homeostasis is true, not only for adults, but also for infants and children, but where are the differences? There are some diseases, which we cannot observe, or to my knowledge, we cannot observe in adults, for example the hypernatremic dehydration. Why is that observed in infants? It is known that there's a high level of plasma sodium and we know from the treatments that the treatment can only be successful, if we administer enough sodium in our infusion therapy. So it appears that there's a disturbance of the membrane transport in the brain cell and this disease, as you know, often or sometimes is observed also in infants not having diarrhea.

Dr. George J. Fuchs: Among the conditions we're seeing, at least in Dhaka when I was there, hypernatremic dehydration was predominantly in situations in which excess sodium was given. In these cases, hypernatremic dehydration was related to excess sodium, generally due to the inappropriate preparation of oral rehydration solution at home.

Dr. George A. Bray: You listed under your regulation of afferent signals, 5 different organ systems and you gave us details about four of those five but not the hepatic vascular one. Is there something secreted from the liver or portal system that influences this process, or is it sympathetic, or is there something I'm missing?

Dr. George J. Fuchs: I think it is primarily sympathetic. It is a more recently described or identified regulatory signaler in this process, but it appears that, much like the baroreceptors in the carotid artery, it initiates a sympathetic nervous response which has a net effect of changing glomerular filtration rate and amount of sodium delivered to the juxtaglomerular process.

Dr. Suporn Treepongkaruna: Could you comment on the short-chain fatty acid in the carborated non absorption. We know that bacteria can ferment. Do we know about short-chain fatty acids also the stimulus for sodium and water absorption in the colon? How about excess short-chain fatty acid, can this cause osmotic diarrhea aspects or not?

Dr. George J. Fuchs: Well, I think probably Dr. Ramakrishna is going to take on this topic in detail later in the program. But short-chain fatty acids have, of course, many different functions in the normal situation and as well in a pathologic situation with inflammation of the large bowel. In the normal situation, short-chain fatty acids promote sodium uptake by stimulating the sodium/hydrogen exchange in the colon, and that's the principal mechanism by which it increases fluid absorption in the large bowel. It's also a principal source of energy for the colonocytes, so there are a variety of the mechanisms by which short-chain fatty acids maintain homeostasis of the large bowel. I'm not so familiar with their role as a diarrheogenic agent, perhaps others can comment.

Dr. B. S. Ramakrishna: If I may just comment on the short-chain fatty acid and diarrhea. I think the view that short-chain fatty acids induce diarrhea has largely been given up, and if we take children with lactose malabsorption as an example, if the bowel flora is not sufficiently mature, the malabsorbed lactose is not fermented and these children have diarrhea. Elegant studies by Rimbaud in Paris have shown this, and if the children do have a mature bowel flora, the lactose is fermented to short-chain fatty acids and the major clinical symptom then becomes gaseousness.

Dr. Santosh Kumar Mittal: Malnutrition is a very common problem in children. Would you like to comment on electrolyte and fluid homeostasis in malnourished children? And secondly, we know that kidney compensates for a lot of disturbances in protoelectrolyte, but what happens if the kidney itself is damaged, does the intestine take its place or take over some
sort of homeostasis mechanism? Can compensatory mechanisms come from the intestines to compensate for renal disturbances?

**Dr. George J. Fuchs:** To the second question first, I think the large intestine has quite limited ability to compensate. Those of us familiar with conditions that damage the kidney recognize the role for dialysis for example, and if the kidney is sufficiently compromised, then there’s no substitute really. So I think the ability of the gut to regulate normal homeostasis is quite limited. With regard to electrolyte homeostasis or metabolism fluid transport, in and the malnourished child, I think there are a lot of unanswered but important questions, and I referred to one of them related to proper oral hydration solution. There is a lot of speculation, or I should say different conceptual frameworks, for what is actually going on there and some of the more recent clinical work would propose to challenge some of these conceptual frameworks. Specifically we know that total body sodium, for example, is in great excess in malnourished children, despite what I would refer to as a paradoxical hyponatremia. The flux and the rate of movement of sodium that was presupposed might not happen quite as quickly as originally believed, so that giving a relatively hypotonic solution orally may have some adverse consequences. It’s not completely clear, but this is an area that’s really ripe for research and there are some unanswered questions there.

**Dr. Mohammad Juffrie:** Very often in severe malnutrition we found an electrolyte imbalance. The question is what role does the kidney play in compensating the electrolyte imbalance in these cases?

**Dr. George J. Fuchs:** I’m not a nephrologist, but I think kidney function is remarkably preserved, even in severe malnutrition. So I think it turns out not to be as you might predict that there in this regard, impaired function that would limit how we replace fluid and electrolytes. On the contrary, kidney function is actually fairly well preserved and recovers quite quickly.

**Dr. Wolfgang Langhans:** In relation to kidney function or the preservation of kidney function, isn’t it the case that the concentrated capacity of the kidney is markedly decreased in protein malnutrition, because of the function of urea during concentration?

**Dr. George J. Fuchs:** Not that I’m aware of, at least to the point of it being a clinical problem, but maybe I’m just not familiar with that.

**Dr. B. S. Ramakrishna:** You mentioned that the total body sodium is increased in malnutrition with an apparent hyponatremia. Do you know if that’s just a dilutional hyponatremia, or is the intracellular sodium increased? And the reason I ask that is that we used to consider this syndrome called sick cell syndrome where we’ve got the sodium/potassium interference activity limited by energy deficiency, and that might lead to an increase in intracellular sodium with decreased extracellular sodium and an increase in the total body sodium.

**Dr. George J. Fuchs:** There may be a dilutional component, but it’s principally a genuine, absolute increase of intracellular sodium. And I think this has been shown in experimental animal models, where tissue sodium has been analyzed.

**Dr. Ravindra Chittal:** In mild and critically ill children, one could do without the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Is there any way we can anticipate, prevent or manage a sick child who has the big added problem of SIADH? Why does it happen in the first place? I mean is there a defense mechanism in the body that leads to SIADH?

**Dr. George J. Fuchs:** I’m not aware of any means to predict very accurately.

**Dr. Ravindra Chittal:** But what leads to SIADH primarily?

**Dr. George J. Fuchs:** I’m not sure. Maybe someone in the audience can answer that question.
**Dr. Deba Prasad Banerjee:** I would like to know how much the fluid in electrolyte homeostasis will be affected, if there is an anatomy congenital abnormality of the gut, like malnutrition of gut or short gut. How much the fluid and electrolyte will affect homeostasis, if there's a congenital abnormality of the gut?

**Dr. George J. Fuchs:** Well, homeostasis can be adversely affected either in absorption, that is uptake of ions and fluid, or enhanced secretion or malabsorption, if you will, of the ions. So it rather depends on the specific pathologic condition.

**Dr. Michael J. G. Farthing:** When we sat down to lunch, the first thing that was put on the table was probably not the food but it was the water, and one of the things that intrigues me is, whether there is association or complete disassociation between feeding and food behavior and drinking and fluid behavior. And it’s unfair just to direct it to you, George, but I wonder whether Gareth might like to comment. I mean I know there are situations in disease-related states, where food intake and fluid intake aren’t associated. Are there any clever central mechanisms that begin to link these two together, that don’t just relate to ADH as you mentioned?

**Dr. Gareth Williams:** A lot of centrally-acting factors stimulate food intake and also stimulate water intake. It’s hard to dissociate how much one is due to the other, but Steve Woods has recently presented some data in which he managed to dissect the two in behavioral terms. The example showed that a new peptide called Orexin-A does stimulate food intake weakly, but has a much more robust effect on water intake. So food and water intake are often linked, but it is possible under some circumstances to dissociate the two.

**Dr. Christoph Beglinger:** Perhaps an additional comment. There is a paper on rats from a Danish group looking at the effect of GLP-1 on sodium excretion and water intake in rats, and this shows that if you give the peptide, I can’t remember whether it gave it IV or into the central nervous system, but you could reduce fluid intake and at the same time increase sodium excretion.

**Dr. Dilip Mahalanabis:** I think, George, this was a very detailed analysis of the situation. However, in real life situations, when you face the problem of deciding how you are going to engineer an oral rehydration solution to beat diarrhea, then comes the question what mechanisms are really important in that situation, as you pointed out in your last slide. We really do not know. That is the point, where you land up really finding humans to experiment on and the disease mortal becomes the only recourse. This very difficult and that is the reason why you end up with so many frustrations, because it’s a guessing game about which mechanisms are in quantitative terms more important than others, because there are so many elegant mechanisms of secretion and absorption. What mechanisms really play the main role in terms of the bulk secretion or bulk absorption in an intact animal or human being? This is difficult to study, and not only difficult to study, but it is also not really elegant or attractive to the scientific community in general or to the donors, in particular, who give money for doing science. So that’s why many of these studies have not continued since maybe the mid-1950s and have been given up, because they’re no longer fashionable research subjects. Like the concentrating capability of infants, young infants or newborns were studied during the second world war in England by people like Winifred Young working with the Macans. They obviously presume that newborn babies cannot concentrate their urine and somebody elegantly gave urea to these babies, and low and behold, they were able to concentrate their urine, but then that is a very artificial situation. Under normal situations, the newborn baby’s kidney has a problem of concentrating urine beyond certain levels. Whether these same things happen in severely malnourished older infants and children, of course, has been studied, but it’s
possible that, because of the lack of enough protein products, they're also not able to con-
centrate the urine. Whether that factor impacts in a real therapeutic situation or not, we really
do not know. And finally, the question of glucose absorption. We learn by mistake that young
infants cannot absorb glucose given per se beyond certain limits of concentration at a time.
There's a very limiting effect of glucose absorption and we'll learn not so much from basic
physiological studies but by making mistakes and trying to engineer various oral rehydration
fluids. So it seems that our current basic scientific knowledge does not stand up to testing
in practice, and we do not have enough information to make our judgments as to what would
be the best paradigm for approaching certain situations.