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THE FATE OF INGESTED WATER

THE INTAKE OF WATER

Except in some of the lower orders, virtual constancy of the volume of body water is a prerequisite for the normal function and indeed the survival of the organism. In terrestrial animals, particularly, adaptive mechanisms provide for physiological regulation of the amounts of water which leave and enter the body. Although solid foods provide a considerable quantity of preformed water to the body, variation in water intake is largely dependent upon the volume of liquid imbibed. Physiological regulation of this volume is accomplished by the mechanisms of thirst and the drinking of water in quantities sufficient to satisfy thirst.

Referring to observations in animals, presumably less influenced than man by emotional and sociological factors, Adolph[3] has written, "Regulation of body content of water, therefore, is accomplished not merely by the overflow of any excesses. Equally, it is adjusted by measured intakes. Drinking is just as reproducible as excretion, and water balance is approached with equal accuracy from both sides." Wolf[128, 129] has presented equations and diagrams describing the quantitative relationships between water requirement and water intake in the dog and man.

Although thirst may be properly regarded as an entirely subjective phenomenon, it hardly seems pertinent to argue the validity of the inference that thirst exists in a dehydrated burro who, when offered water, promptly imbibes several gallons. It had long been recognized that "in man any large loss of fluid, as by sweating, diarrhoea, or haemorrhage, gives rise to an intense thirst that has its natural reaction in increased intake of water by mouth" (Starling[108]). However, Gilman's[46] observations demonstrated that a decrease in total body fluid was not required to stimulate drinking since dogs given hypertonic saline intravenously drank copiously even though body water was increased. A comparable rise in total solute concentration was produced by infusion of an equi-osmolar solution of urea, which unlike

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sodium chloride enters cells freely and therefore does not influence the movement of water across the cell membrane. Failure of the urea solution to evoke an equally large drinking response led to the view that cellular dehydration constitutes the stimulus for thirst. This concept has been generally accepted but it required some modification when Holmes and Cizek[62] and Cizek, Semple, Huang, and Gregersen[28] demonstrated that chronically salt-depleted dogs, whose body fluids were hypotonic and whose cells were presumably overhydrated, manifested an *increased* water intake. The fluid exchange of such animals returned to control values when the salt depletion was corrected with consequent expansion of their contracted extracellular and plasma volumes and elevation of body fluid tonicity to normal. The drinking responses of these salt-deficient animals, like the thirst evoked by isotonic losses of body fluid, cannot be ascribed to hypertonicity or cellular dehydration. Peters[94] has stated: "Thirst is not, therefore, preoccupied with the disposition or composition of the fluids of the body to the neglect of volume. The stimulus to drinking in behalf of volume appears to be the volume of the circulating blood which diminishes when the concentration of the sodium in the serum falls."*

It seems entirely reasonable to regard cellular dehydration and contraction of the extracellular fluid volume (or plasma volume) as the two most important physiological stimuli for thirst. The hypothesis that an osmoreceptor is involved in response to extracellular hypertonicity[128, 129] has been strongly supported by the work of Andersson.[6-9] In a brilliant series of experiments this investigator demonstrated the following:

1. Injection of very small amounts of hypertonic saline directly into a hypothalamic area located medially in the vicinity of the third ventricle evokes an immediate and striking drinking response in goats. As much as eight liters of water may be drunk after a single hypertonic injection. Injection of isotonic saline does not produce such an effect.

2. Electrical stimulation of the same area also causes marked polydipsia.

3. In dogs destructive lesions involving the area concerned produce a marked decrease in water intake, without impairment of food intake. Marked dehydration develops in such animals.

The last observation suggests that integrity of the hypothalamic "thirst center" is required for appropriate drinking responses to be evoked by contraction of volume as well as by increase in tonicity, since both stimuli must have been present when dehydration ensued. It is of course possible that a separate "volume receptor" is located in this same area.

* This quotation is from the manuscript of the revision of *Quantitative clinical chemistry,* Vol. II, *Interpretations.*

The foregoing discussion of thirst in terms of osmotic and volumetric stimuli has omitted a number of relevant observations. Holmes and Montgomery[67, 68] studied the responses of blood donors and dogs bled up to 30 per cent of their blood volume. In the absence of circulatory shock thirst was not evoked. However, shocked dogs drank avidly.

Other studies indicate that not only cellular dehydration, but also total solute concentration influences water intake. In rats the administration of hypertonic urea solutions by stomach tube evoked a marked drinking response beginning in 15 minutes.[4] In Gilman's[40] experiments urea in hypertonic solution did evoke drinking of about half the amount taken after an iso-osmotic sodium chloride load; such comparisons were greatly extended by Holmes and Gregersen.[65, 66] Platt[95] has described his own thirst following urea ingestion, but does not indicate whether diuresis occurred before thirst ensued.

It should also be emphasized that reduction of salivary flow regularly accompanies thirst induced either by water loss or the administration of hypertonic saline.[63, 64] Moreover, sham drinking in esophagostomized dogs produces temporary inhibition of drinking responses,[1, 11, 113] as does distention of the stomach with fluid or balloons in various species.[3, 4, 11, 65, 88, 113] Such observations have led Montgomery and Holmes[88] to propose a multiple control system for metering the volume of fluid taken in response to a given thirst-producing stimulus:

1. Passage of water through the pharynx and esophagus gives satisfaction for 20 to 30 minutes.

2. Gastric distention becomes an effective inhibitor of additional drinking for the next hour.

3. During this hour absorption of the ingested water occurs with correction of hypertonicity and cellular dehydration and removal of the thirst-producing stimulus. (The time relations given apply to the dog.)

A variety of other determinants also modify drinking responses,[2, 4] including emotional and sociological factors at least in man. The proposed control system serves to integrate a variety of individual reflexes into an organized regulatory mechanism.

WATER IN THE ALIMENTARY TRACT

Ingested fluid represents an exogenous addition to the intrinsic secretions of the gastrointestinal tract. Even when tap water, virtually devoid of solute, is taken by mouth in large quantity, the ingested fluid tends to become isotonic. It acquires electrolyte by admixture with saliva, gastric juice, and secretions present in the intestinal lumen. The volume and com-

position of the gastrointestinal secretions has been described in detail elsewhere.[29, 43, 44, 45, 88, 92, 93] The copious secretions produced each day are of course reabsorbed almost completely. No technique has been devised to measure in the living organism the volume of fluid present in the gastrointestinal tract at any given time. Everyday clinical experience indicates that the stomach of man in the post-absorptive state normally contains at most 100 ml. of fluid.[57] The volume that can be aspirated is slightly smaller than the so-called "pooling space"[99] and does not include other "transcellular" fluid[36] such as that in the mucosal glands. It is well established that water in the gastrointestinal tract constitutes a very considerable fraction of the total body fluid in certain species. In rabbits[22, 49] and guinea pigs,[22] 12 to 20 per cent of the total body water is normally present in the gastrointestinal tract. In fed rats[22] and dogs[22] about 7 per cent is present, a value which falls below 5 per cent when food is withheld.

A group of observations by Edelman and his colleagues[36, 49, 89, 110] show that the intestinal tract of human subjects examined at post-mortem contains a far smaller moiety of the body water. Direct measurement of fluid in 12 post-mortem examinations gave an average value for total gastrointestinal water of 1.4 per cent of predicted total body water, of which 0.4 per cent was in the stomach, 0.7 per cent in the small bowel, and 0.3 per cent in the colon. Average values for gastrointestinal sodium, potassium, and chloride ranged between 1 and 2 per cent of the predicted total exchangeable amounts. The authors properly emphasize the limitation imposed upon interpretation of these post-mortem data by possible changes in intestinal fluids occurring during terminal illness and in the hours after death.

It is clearly impossible to estimate the extent to which the composition of a given volume of tap water taken orally will be altered immediately by mixing with saliva, gastric, and intestinal contents. That some water may enter the duodenum virtually unaltered in composition is suggested by Ivy's[74] observation that water begins to leave the accessory stomach of Pavlov pouch dogs within a few seconds after it is introduced, the emptying time for 400 ml. being 30 to 60 minutes. Since man may deliver 400 ml. of water from stomach to duodenum in 15 minutes after it is drunk,[74] the inference is strong that this transport begins immediately after drinking, as in the dog. Moreover, it is well known that an aqueous suspension of barium sulfate may begin to pass through the pylorus almost as soon as it is swallowed. However, the available studies[42, 76, 86] indicate that after the administration of moderate amounts of water the duodenal and jejunal contents are soon restored to approximate isotonicity. Conversely, hypertonic solutions introduced into the alimentary tract decrease in total solute con-

centration. Isotonic saline instilled through a Miller-Abbott tube is altered in chemical composition, so that without change in total cation concentration, chloride is replaced by bicarbonate, the extent of such replacement being greater as the fluid moves in an aboral direction.[19] This observation concerning change in ionic pattern is consistent with many other studies in various species.[18, 27, 28, 121] Thus fluid added to the gastrointestinal contents tends not only to become approximately isotonic but also to acquire the ionic composition of the endogenous secretions present in the area.

Although there are conflicting reports concerning the presence of precise osmotic equality between gastric juice and plasma,[44, 47, 81, 111] there is no doubt that the tonicity of the gastric secretions varies directly with that of the plasma. A primary change in the total solute concentration of serum evokes a comparable change in the osmolarity of the gastric juice.[47, 111] Pancreatic juice[10, 45, 75] and hepatic duct bile[45, 98] are approximately isotonic. The jejunal secretions are isotonic and have been shown to be in osmotic equilibrium with the plasma.[85, 98]

The tendency of exogenous fluid to be rendered isotonic in the gastrointestinal lumen doubtless prevents the occurrence of significant hemolysis when plain water is drunk. That fluid need not approach isotonicity prior to absorption or during the process of absorption is most clearly established by the fact that hemolysis can be produced in portal vein blood of rats, cats, and rabbits by instilling large water loads directly into the duodenum.[80] Such hemolysis apparently takes place in the first few minutes during which absorption is thought to be rapid because of increase of intraluminal pressure[16, 90, 123, 124] and there has been little time for electrolyte to enter the instilled water. Hemolysis in portal blood would also be prevented by absorption of water via lymphatic pathways but this does not occur to a significant degree, at least in the rat.[12, 77] Important protection against hemolysis when water is taken by mouth is no doubt provided by the entrance of electrolyte into the water taken during its transit through the stomach.[5] Hunt has examined the possibility that gastric emptying is delayed when instilled solutions are hypotonic or hypertonic, permitting a change toward isotonicity before the fluid enters the small intestine.[69, 70] Examination of the responses to a variety of solutions led to the conclusion that although an osmoreceptor mechanism does indeed influence gastric emptying, its operation apparently does not serve to render isotonic the solutions delivered to the duodenum. Finally, it is possible that insofar as the intestinal mucosa may come into contact with fluid which is markedly hypotonic, injury to the epithelium is likely to occur[15, 80, 112] with delay in absorption and consequent lessening of the likelihood of hemolysis.

ABSORPTION OF WATER BY THE INTESTINE

The foregoing attempt to indicate the nature of change which occurs in the composition of ingested fluid during its sojourn in the gastrointestinal tract has dealt only with plain water and solutions of sodium chloride. Consideration of other solutions or foods will not be undertaken. It should be emphasized that change in the volume and composition of ingested fluids is not merely the result of admixture of intestinal content already present or of secretion added during gastrointestinal transit but also of absorption by the intestinal epithelium. Indeed, it is this very phenomenon of simultaneous movement of water and various solutes across the intestinal wall in both directions at different rates that has made the hypotheses concerning intestinal absorption inordinately complicated and contradictory. If the recent applications of isotopic tracer studies have not simplified the problem, they have at least provided answers to certain controversial matters of fact. For example, it had been accepted for many years that net absorption of water in the stomach is negligible.[108] However, tracer studies indicate clearly that D_2O rapidly enters the blood stream from the stomach and equilibrates with the water of the body.[24, 26, 105] Since the outflux of water is normally balanced by an equal or greater influx, no net transfer out takes place.

The historic controversy between those who argued that movement of water and electrolyte across the intestinal wall could be accounted for by osmotic and hydrostatic forces alone and those whose observations or interpretations required a "vital force" (Starling[109]) to explain such movement has been reviewed at intervals.[48, 60, 100, 117] Contemporary studies employing tracer techniques indicate that active transport dependent upon metabolic processes of the cells is clearly involved even though the direction and magnitude of such transport is regulated, at least in part, by osmotic relationships. The proponents of the adequacy of physical forces provided a great deal of information concerning the manner in which osmotic and hydrostatic pressures modify the processes of intestinal absorption. It has been repeatedly demonstrated that water is more rapidly absorbed from hypotonic than from isotonic sodium chloride solutions.[100, 101, 117] It is even more slowly absorbed from hypertonic sodium chloride solutions and there is no net absorption from isotonic solutions of nonabsorbable solutes, such as $MgSO_4$. Osmotic forces clearly influence movement of water across the intestinal epithelium. The possible actions of the osmotic pressure of colloids in intestinal lymph and the intraluminal hydrostatic pressure to promote water absorption have been emphasized by Wells.[123, 124] His suggestion that the protein-rich fluid of the lymphatics provided the high oncotic pressure to effect the movement of water out of the intestinal lumen was not

considered incompatible with ultimate transport via the portal venous system.[94, 118] However, subsequent studies have shown that when D_2O is ingested its specific activity rises markedly in portal vein blood but not in the mesenteric lymphatics of the rat.[12] The specific activity in lymph remains identical with that of arterial plasma. These observations would seem to exclude entrance of the absorbate into the lymph of the villi at any step in the process, a most serious objection to Wells' concept. On the other hand, it is generally accepted that increased intraluminal pressure may favor transfer of water out of the lumen.[16, 90] Of course, at high intestinal pressures important circulatory disturbances take place which interfere with absorption.[20, 33, 59]

The most extensive studies concerning intestinal absorption during the past twenty years are those of Visscher and his group who in 1938 proposed the fluid circuit theory.[71, 73, 91] This schema hypothesized a continuing circuit in which fluid leaves the intestinal lumen to enter the blood stream by passing through a membrane permeable to univalent ions such as Na^+ and Cl^- but impermeable to polyvalent ions such as Mg^{++} and $SO_4^=$. Fluid is returned to the lumen from the plasma through a membrane relatively impermeable to all ions. It was further postulated[73] that anomalous osmosis[54, 55, 82] provides the necessary pumping action to maintain the fluid circuit. The behavior of isotonic mixtures of NaCl and Na_2SO_4 or of NaCl and $MgCl_2$ instilled into the small intestine is consistent with Visscher's hypothesis. The former mixture becomes virtually chloride free, leaving an isotonic solution of $NaSO_4$;[21, 72] the latter mixture becomes markedly depleted of sodium leaving an approximately isotonic mixture of magnesium chloride and bicarbonate.[73] In each case one univalent ion is almost completely removed from the intestinal fluid. The univalent ion species which remains in the ileal fluid is restrained by the nondiffusible polyvalent ion of opposite charge. The impermeability of the membrane which restrains the return of univalent ions to the lumen was thought to be more complete for Cl^- than for Na^+, since Cl^- is more completely removed from the lumen than is Na^+. The virtually complete impermeability for Cl^- was also considered to be linked with the appearance of bicarbonate, producing a Cl^-—HCO_3^- exchange. However, the independent secretion of $NaHCO_3$ by intestinal glands would produce the same result.

Subsequent observations demonstrated unequal bidirectional fluxes of sodium and chloride, as well as of water, across the intestinal epithelium,[119, 122] requiring modification of the concept of one-way permeability for these ions. It was further shown that the net absorbate from an isotonic solution instilled into ileum is hypertonic,[81, 120] and that net transfers of water from solutions of various tonicities are far greater than predicted by osmotic

theory.[119] Osmotic forces were shown to influence the direction and amount of net transfer but could not account for the magnitude of the exchanges. The suggestion was made that the rôle of intraluminal osmolarity is to alter the water content of the surface epithelial cells which might in turn influence their activity in the transport of fluid.[121]

In discussing the observations of Visscher and his co-workers[119] concerning rates of water movement which differ from those predicted by osmotic theory Ussing[115] states, "There can be little doubt that active processes do play a rôle. . . . It seems, however, that the osmotic pressure of the gut contents is of greater importance than the active transport, judging from the fact that water enters the gut in excess when hypertonic solutions are applied. As we have seen above, the deviation from ideal behavior in itself does not, unambiguously, indicate active transport." Additional discussion is given elsewhere.[114, 116]

Although the fluid circuit schema in its original form has not been emphasized by Visscher in recent publications,[58, 118] the model remains useful as a dynamic description of the movement of fluid across the intestinal mucosa. The rates of influx and outflux of water and ions are presumably in part anatomically determined; thus the ileum is characterized by a relatively rapid outflux and slow influx of univalent ions. The tonicity of the intraluminal fluid exerts an all-important influence upon these rates of flux, at least the outflux of water and univalent ions. In this way the magnitude and direction of net transfer of water is controlled by the effective osmolarity of the intestinal fluid even if the energy for active transport must derive from the metabolic processes of the cells.

THE DISTRIBUTION OF ABSORBED WATER

The transport of ingested water across the intestinal barrier has long been assumed to take place quite rapidly. This assumption is an entirely reasonable inference based upon the remarkable consequence of the imbibition of a large amount of water, namely, the prompt excretion of an approximately equal quantity of watery urine. The phenomenon of water diuresis is discussed in another contribution[125] to this memorial issue. Some consideration will be undertaken here of the fate within the body of such a large oral intake of water.

The assumption of free permeability of virtually all cell membranes of the body to water leads to the prediction that the ingested water when absorbed would be uniformly distributed throughout the several compartments of body water if retained long enough to permit equilibration to occur. At equilibrium, the aggregate concentration of osmotically active solute would

be lowered equally in plasma, interstitial fluid, and cell water. The percentage fall in concentration would be equal to the percentage rise in volume of total body water. Moreover, the absorbed water would be allocated to the several compartments in proportion to their respective volumes. Thus if a 70-kilogram adult man drank and retained two liters of water, equivalent to 5 per cent of the total body water, at equilibrium there would be anticipated a 5 per cent fall in the total solute concentration and in the sodium and chloride concentrations as well. Moreover, if the plasma volume were expanded proportionately, a 5 per cent fall in serum protein concentration and a roughly equal fall in hemoglobin concentration would be observed.*

The classical experiments of Haldane and Priestley[56] in 1916 indicated, however, that little change in hemoglobin concentration took place when a large volume of water was taken orally. On the other hand, a distinct fall in conductivity of the serum, a measure of electrolyte concentration, was observed.[96] Although at this time no basis existed for predicting the magnitude of decrease in these values to be anticipated with a water load of given size, the unequal change in the two measures of hemodilution was most perplexing. The paradox was plausibly resolved by Priestley's[96] ingenious suggestion that the salts of the blood migrate into the gastrointestinal tract. However, in a subsequent paper Priestley[97] implied that the ingested water initially enters the blood stream and subsequently diffuses out into the tissues and alimentary canal, abstracting salts from the blood in the process. Moreover, the additional data he obtained indicate that although the fall of about 5 per cent in blood chloride observed after imbibing two liters of water is of a magnitude comparable to the previously reported decline in conductivity, there is actually a significant fall in hemoglobin and total solids as well, amounting to about 2 to 3 per cent in most experiments.

A number of investigators pursued this problem during the next twenty years. The variety of measurements employed to indicate the distribution of the ingested fluid included serum conductivity, concentration of chloride, bicarbonate, sodium and potassium, serum and whole blood total solids, as well as hemoglobin and serum protein concentrations. Comparison and generalizations are rendered exceedingly difficult, even if only studies in man are considered, owing to the diverse parameters employed as well as variation in the magnitude of water loads and the times of sampling. An extensive citation of the literature prior to 1937 is given by Findley and White.[41] The majority of the observations point to a demonstrable hemo-

* Given a 5 per cent increase in plasma water and red cell water the hemoglobin concentration per 100 ml. of whole blood *water* would decrease by exactly five per cent.

dilution as reflected by change in total solids, hemoglobin, or serum protein concentration, when water loads of more than a liter are taken by normal man. With much larger loads given to experimental animals, as in the studies of Greene and Rowntree[51] concerning water intoxication in dogs, very large changes in hemoglobin and serum protein concentrations were encountered. In the majority of studies the observed fall in serum electrolyte concentration is larger than the decline in blood colloids, suggesting diffusion of the crystalloids out of the vascular bed presumably into the water as yet unabsorbed from the intestinal tract.

The possibility that vasomotor changes might account for some of the inconsistencies in data pertaining to nondiffusible constituents of venous blood has been considered. The data of Govaerts and Cambier[50] obtained on arterial samples in ten women are usually consistent in showing an average fall of approximately 1.0 per cent in serum total solids, 1.4 per cent in conductivity and 1.7 per cent in serum chloride 30 to 60 minutes after the subject drank a liter of water. On the other hand, they reported very variable changes in hemoglobin.

The known effect of large oral water loads to reduce body temperature, even when the water taken is warmed,[52] supports the suspicion that the composition of peripheral venous blood after water drinking may be modified by changes in cutaneous blood flow. This has led to the employment of arterial or "arterialized"[87] samples in a number of contemporary studies.* After its oral administration the concentration of D_2O in peripheral venous blood exhibits fluctuations not observed in arterial samples.[24]

Moreover, attempts have been made to elucidate changes related to alimentary water exchange by comparing oral and parenteral routes of water administration. The most extensive study is that of Hollander and Williams[61] who compared the oral administration of tap water with the intravenous administration of a 4 per cent solution of invert sugar in a group of essentially healthy adult male subjects. The two techniques of water loading produced essentially the same decrease in the concentration of osmotically active solute. However, calculated changes in plasma volume indicated an actual reduction during oral loading in many of the studies, whereas intravenous administration was almost uniformly associated with an apparent expansion of intravascular volume. It should be noted that

* The writer is unaware of any systematic comparison of changes observed in conventional venous blood samples with those found in arterial blood after water loading in normal subjects. In a few studies in patients with hepatic cirrhosis, Birchard[13] found no consistent difference between venous and arterial changes, nor were the changes in arterial blood more uniform or predictable.

until the parenterally administered hexose enters cells it provides an effective osmotic force retaining water in the extracellular space. Hence the distribution of the administered water may be expected to differ from the uniform partition among the several compartments of body water to be expected if plain water were given. The plain water taken by mouth would produce a much smaller expansion of plasma and interstitial volumes if uniformly equilibrated through the body fluid compartment, but such equilibration could hardly produce a *contraction* of plasma volume. The authors infer, as did Welt and Nelson,[106] that the water imbibed continuously throughout the experimental period maintains a significant pool of solute-poor fluid in the gut lumen into which extracellular electrolyte migrates to produce hypotonicity of the interstitial fluid. Fluid segregated in the gut obviously cannot expand the volume of plasma or that of any other body fluid compartment. However, the induced hypotonicity of interstitial fluid produces an osmotic gradient for movement of extracellular water into cells, with reduction in interstitial and plasma volumes.

It must be emphasized that direct evidence for intestinal segregation of water in these experiments is lacking. Dicker[82] studied responses to water loading in rats with nutritional hypoproteinemia. The fall in serum chloride was similar to that observed in normal animals after water loading, but the increase in plasma volume observed in the normal animals was lacking. The inference of segregation in the gut would have been quite plausible if direct observation had not demonstrated that the protein-deficient animals absorbed water even more rapidly than did the normals. The area of pooling in these animals appeared to be in the connective tissues, particularly retroperitoneally. The possibility that patients with hepatic cirrhosis rapidly segregate ingested fluid in areas other than the intestinal lumen has been considered by Birchard and co-workers.[14]

It is obvious that equilibration of administered water cannot take place as long as a continuous addition is being made either orally or parenterally. If a water load is maintained by drinking a volume calculated to replace losses during water diuresis, the magnitude of the gastrointestinal pool of fluid will depend upon the net rate of absorption and also upon the rate of diuresis which determines the prescribed intake. Since the maximal rate of water diuresis tends to fall in seated subjects[104] and since water absorption may be less rapid in recumbency,[107] the size of the intestinal pool may be significantly influenced by posture. Nor is equilibration achieved by the normal organism when a single large water load is taken. The studies of Smirk,[108] who employed an ingenious technique of differential weighing of abdomen and legs, clearly demonstrated that normal men absorbed a liter

of ingested water in 25 to 55 minutes. This absorption is characteristically followed by a marked rise in renal excretion of water within half an hour. Thus, the diuresis is likely to begin before complete equilibration with the body fluids occurs.[84, 85]

Attempts to achieve equilibration have therefore been carried out when renal excretion of water has been eliminated surgically or minimized by pitressin administration. Other studies designed to elucidate the osmotic behavior of the cells have been made following the administration of solute loads. No final agreement has as yet been achieved concerning several most fundamental aspects of the distribution of body water.

It has been claimed that the osmotic pressure within cells exceeds that of the extracellular fluids and that water is continually being pumped out of the hypertonic cells by an active process. The literature concerning this question has been reviewed by Robinson.[102, 103] The interpretation of Conway and McCormack[25] that their cryoscopic measurements of various tissues demonstrate isotonicity of cells and surrounding fluid has been questioned by Brodsky and co-workers.[17] On the other hand, Leaf[78] has shown that water taken up by surviving tissues *in vitro* is accompanied by solute in approximately isotonic proportions; hence, swelling of cells under these circumstances cannot be taken as evidence that the intracellular fluids are normally hypertonic with respect to their extracellular environment.

Demonstration that intracellular and extracellular osmotic pressures are equal would constitute strong evidence that the cells behave as osmometers. The converse that if they do behave as osmometers, osmotic equality must pertain does not follow. As stated by McDowell, Wolf, and Steer,[84] "It may be true or not that osmotic pressure within cells exceeds that outside of cells; but neither case is necessarily incompatible with the finding that cells act volumetrically as if they were osmometers when osmotic stresses are applied."

The distribution of a large administered water load constitutes one test of the osmometric behavior of the cells. Detailed analysis of data which indicate transfers of water which deviate from predictions based on electrolyte balance have led to the hypothesis that the cellular constituents exhibit variations in their osmotic activity which modify the distribution of body water.[37–40] However, in two recent studies[79, 121] involving anuric dogs and one oliguric human subject, large administered water loads induced changes in plasma composition which were in accord with free permeability of the cells to water and constancy of the total cellular osmotic activity.

The majority of the studies which led to the hypothesis of change in the osmotic activity of cell constituents involved large external transfers of

electrolyte as well as of water. The recent studies of McDowell, Wolf, and Steer[84] may therefore be more pertinent to this general problem. Their studies indicate that in response to administration of hypertonic solutions of sodium salts and of sucrose, the osmolarity of the body fluids rises more than can be accounted for by the exogenous increment of solute alone. The "idiogenic" changes in osmotic pressure did not occur when urea loads were given, leading to the inference that cellular dehydration might evoke the formation of additional osmotically active particles. The possible relationship of such osmotic changes to muscular activity[127] and to anoxia[58] is recognized by the authors.

It appears therefore that even under rigorous experimental conditions designed to permit the attainment of equilibrium, the precise distribution of water within the body may not be predictable.[130] However, apparently anomalous behavior probably represents incomplete assessment of the osmotic forces operative rather than encroachment upon the freedom of water to move in response to such forces.

CONCLUDING REMARKS

The selection of topics for this discussion has been quite arbitrary; the treatment largely descriptive. No attempt has been made to choose material illustrative of a particular concept or principle. Despite the scattered array of isolated observation and general statement, there is ever apparent the dual aspect of the physiology of body water: regulation of volume and regulation of tonicity. If thirst is evoked by hypertonicity, water drinking is metered by a control system responsive to the volume of fluid in the stomach. The rate of water absorption in the intestine varies inversely with the tonicity of the solution presented to the mucous membrane. The volume of water normally remaining is very small, whether the fluid intake is less than a liter or several gallons and whether the concentration of absorbable solute is quite high or very low. Understanding of the immediate fate of ingested water is seriously limited because even though lowering of solute concentration in body fluids is a regular event, the changes in plasma and extracellular volume are variable and not susceptible of precise measurement. The volume of cells has been regarded as a function of the tonicity of extracellular fluid. The rôle of primary changes in intracellular osmotic activity in the regulation of cell volume requires further investigation. Certainly the provocative suggestion that the volume of the cells is determined by active transport of water rather than regulated by osmotic forces has already stimulated a search for new knowledge concerning these relationships within the cells themselves.

REFERENCES

1. Adolph, E. F.: Measurements of water drinking in dogs. Amer. J. Physiol., 1939, *125,* 75-86.
2. Adolph, E. F.: *Physiology of man in the desert.* New York, Interscience Publishers, 1947, pp. 241-253.
3. Adolph, E. F.: Thirst and its inhibition in the stomach. Amer. J. Physiol., 1950, *161,* 374-386.
4. Adolph, E. F., Barker, J. P. and Hoy, P. A.: Multiple factors in thirst. Amer. J. Physiol., 1954, *178,* 538-562.
5. Adolph, E. F. and Northrop, J. P.: Absorption of water and chloride (rat). Amer. J. Physiol., 1952, *168,* 311-319.
6. Andersson, B.: The effect of injections of hypertonic NaCl-solutions into different parts of the hypothalamus of goats. Acta physiol. scand., 1953, *28,* 188-201.
7. Andersson, B. and McCann, S. M.: A further study of polydipsia evoked by hypothalamic stimulation in the goat. Acta physiol. scand., 1955, *33,* 333-346.
8. Andersson, B. and McCann, S. M.: Drinking, antidiuresis and milk ejection from electrical stimulation within the hypothalamus of the goat. Acta physiol. scand., 1955, *35,* 191-201.
9. Andersson, B. and McCann, S. M.: The effect of hypothalamic lesions on the water intake of the dog. Acta physiol. scand., 1956, *35,* 312-320.
10. Ball, E. G.: The composition of pancreatic juice and blood serum as influenced by the injection of inorganic salts. J. biol. Chem., 1930, *86,* 449-462.
11. Bellows, R. T.: Time factors in water drinking in dogs. Amer. J. Physiol., 1939, *125,* 87-97.
12. Benson, J. A., Jr., Lee, P. R., Scholer, J. F., Kim, K. S., and Bollman, J. L.: Water absorption from the intestine *via* portal and lymphatic pathways. Amer. J. Physiol., 1956, *184,* 441-444.
13. Birchard, W. H.: Unpublished observations.
14. Birchard, W. H., Prout, T. E., Williams, T. F., and Rosenbaum, J. D.: Diuretic responses to oral and intravenous water loads in patients with hepatic cirrhosis. J. Lab. clin. Med., 1956, *48,* 26-35.
15. Blickenstaff, D. D.: Change in the ability of the intestine to absorb isosmotic NaCl solution following distilled water instillation. Amer. J. Physiol., 1954, *179,* 467-472.
16. Blickenstaff, D. D., Bachman, D. M., Steinberg, M. E., and Youmans, W. B.: Intestinal absorption of sodium chloride solutions as influenced by intraluminal pressure and concentration. Amer. J. Physiol., 1952, *168,* 303-310.
17. Brodsky, W. A., Dennis, W. H., Rehm, W. S., Appelboom, J. W., and Diamond, I.: The problem of isotonic versus hypertonic cell fluid in the light of cryoscopic measurements of tissue homogenates. J. clin. Invest., 1956, *35,* 694.
18. Bucher, G. R., Anderson, C. E., and Robinson, C. S.: Chemical changes produced in isotonic solutions of sodium sulfate and sodium chloride by the small intestine of the dog. Amer. J. Physiol., 1950, *163,* 1-13.
19. Bucher, G. R., Flynn, J. C., and Robinson, C. S.: The action of the human small intestine in altering the composition of physiological saline. J. biol. Chem., 1944, *155,* 305-313.
20. Burget, G. E., Martzloff, K., Suckow, G., and Thornton, R. C. B.: The closed intestinal loop. I. Relation of intraloop (jejunum) pressure to the clinical condition of the animal. Arch. Surg. (Chicago), 1930, *21,* 829-837.
21. Burns, H. S. and Visscher, M. B.: The influence of various anions of the lyotropic series upon the sodium and chloride content of the fluid in the intestine. Amer. J. Physiol., 1934, *110,* 490-498.
22. Cizek, L. J.: Total water content of laboratory animals with special reference to volume of fluid within the lumen of the gastrointestinal tract. Amer. J. Physiol., 1954, *179,* 104-110.
23. Cizek, L. J., Semple, R. E., Huang, K. C., and Gregersen, M. I.: Effect of extracellular electrolyte depletion on water intake in dogs. Amer. J. Physiol., 1951, *164,* 415-422.

24. Code, C. F., Scholer, J. F., Hightower, N. C., Jr., and Dietzler, F. K.: Absorption of water from the upper part of the human gastrointestinal tract. Proc. Mayo Clin., 1954, *29,* 235-240.
25. Conway, E. J. and McCormack, J. I.: The total intracellular concentration of mammalian tissues compared with that of the extracellular fluid. J. Physiol. (Lond.), 1953, *120,* 1-14.
26. Cope, O., Blatt, H., and Ball, M. R.: Gastric secretion. III. The absorption of heavy water from pouches of the body and antrum of the stomach of the dog. J. clin. Invest., 1943, *22,* 111-115.
27. D'Agostino, A., Leadbetter, W. F., and Schwartz, W. B.: Alterations in the ionic composition of isotonic saline solution instilled into the colon. J. clin. Invest., 1953, *32,* 444-448.
28. de Beer, E. J., Johnston, C. G., and Wilson, D. W.: The composition of intestinal secretions. J. biol. Chem., 1935, *108,* 113-120.
29. de Beer, E. J. and Wilson, D. W.: The inorganic composition of the parotid saliva of the dog and its relation to the composition of the serum. J. biol. Chem., 1932, *95,* 671-685.
30. Dennis, C.: Injury to the ileal mucosa by contact with distilled water. Amer. J. Physiol., 1940, *129,* 171-175.
31. Dennis, C. and Visscher, M. B.: Studies on the rates of absorption of water and salts from the ileum of the dog. Amer. J. Physiol., 1940, *131,* 402-408.
32. Dicker, S. E.: Changes in the extracellular- and intracellular-fluid phases of tissues during water diuresis in normal and hypoproteinaemic rats. Biochem. J., 1948, *43,* 453-461.
33. Dragstedt, C. A., Lang, V. F., and Millet, R. F.: The relative effects of distention on different portions of the intestine. Arch. Surg. (Chicago), 1929, *18,* 2257-2263.
34. Edelman, I. S.: Exchange of water between blood and tissues. Characteristics of deuterium oxide equilibration in body water. Amer. J. Physiol., 1952, *171,* 279-296.
35. Edelman, I. S., James, A. H., Baden, H., and Moore, F. D.: Electrolyte composition of bone and the penetration of radiosodium and deuterium oxide into dog and human bone. J. clin. Invest., 1954, *33,* 122-131.
36. Edelman, I. S. and Sweet, N. J.: Gastrointestinal water and electrolytes. I. The equilibration of radiosodium in gastrointestinal contents and the proportion of exchangeable sodium (Na_e) in the gastrointestinal tract. J. clin. Invest., 1956, *35,* 502-511.
37. Elkinton, J. R. and Danowski, T. S.: *The body fluids.* Baltimore, Williams and Wilkins Company, 1955, pp. 91-93.
38. Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: Inactive cell base and the measurement of changes in cell water. Yale J. Biol. Med., 1944, *17,* 383-393.
39. Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: The importance of volume and of tonicity of the body fluids in salt depletion shock. J. clin. Invest., 1947, *26,* 1002-1009.
40. Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: Transfers of cell sodium and potassium in experimental and clinical conditions. J. clin. Invest., 1948, *27,* 74-81.
41. Findley, T., Jr. and White, H. L.: The response of normal individuals and patients with diabetes insipidus to the ingestion of water. J. clin. Invest., 1937, *16,* 197-202.
42. Follansbee, R.: The osmotic activity of gastrointestinal fluids after water ingestion in the rat. Amer. J. Physiol., 1945, *144,* 355-362.
43. Gamble, J. L.: *Chemical anatomy, physiology and pathology of extracellular fluid.* 6th ed. Cambridge, Harvard University Press, 1954.
44. Gamble, J. L. and McIver, M. A.: The acid-base composition of gastric secretions. J. exp. Med., 1928, *48,* 837-847.
45. Gamble, J. L. and McIver, M. A.: Acid-base composition of pancreatic juice and bile. J. exp. Med., 1928, *48,* 849-857.

46. Gilman, A.: The relation between blood osmotic pressure, fluid distribution and voluntary water intake. Amer. J. Physiol., 1937, *120,* 323-328.
47. Gilman, A. and Cowgill, G. R.: Osmotic relations between blood and body fluids. II. The osmotic relation of blood and gastric juice. Amer. J. Physiol., 1933, *103,* 143-152.
48. Goldschmidt, S.: On the mechanism of absorption from the intestine. Physiol. Rev., 1921, *1,* 421-453.
49. Gotch, F., Nadell, J., and Edelman, I. S.: Gastrointestinal water and electrolytes. IV. The equilibration of deuterium oxide (D_2O) in gastrointestinal contents and the proportion of total body water (T.B.W.) in the gastrointestinal tract. To be published.
50. Govaerts, P. and Cambier, P.: Recherches sur la composition du sang artériel au cours de la diurèse par l'eau chez l'homme. Bull. Acad. Méd. Belg., 1930, *10,* 522-539.
51. Greene, C. H. and Rowntree, L. G.: The effect of the experimental administration of excessive amounts of water. I. On the volume and concentration of the blood. Amer. J. Physiol., 1927, *80,* 209-229.
52. Greene, C. H. and Rowntree, L. G.: The effect of administration of excessive amounts of water on body temperature. Amer. J. Physiol., 1927, *80,* 230-235.
53. Grim, E., Lee, J. S., and Visscher, M. B.: Water exchange between intestinal contents, tissues and blood. Amer. J. Physiol., 1955, *182,* 359-363.
54. Grollman, A. and Söllner, K.: An experimental study of negative osmosis. Trans. electrochem. Soc., 1932, *61,* 477-485.
55. Grollman, A. and Söllner, K.: Experimental verification of a new theory concerning the mechanism of anomalous osmosis. Trans. electrochem. Soc., 1932, *61,* 487-497.
56. Haldane, J. S. and Priestley, J. G.: The regulation of excretion of water by the kidneys. I. J. Physiol. (Lond.), 1916, *50,* 296-303.
57. Ham, T. H.: *A syllabus of laboratory examinations in clinical diagnosis.* Cambridge, Harvard University Press, 1950, p. 313.
58. Hamburger, J. and Mathé, G.: Sur un phénomène inédit de rupture de l'équilibre hydrique au cours de l'anoxie. Presse méd., 1951, *59,* 265-267.
59. Herrin, R. C. and Meek, W. J.: Distention as a factor in intestinal obstruction. Arch. intern. Med., 1933, *51,* 152-168.
60. Höber, R.: *Physical chemistry of cells and tissues.* Philadelphia, The Blakiston Company, 1945, pp. 531-552.
61. Hollander, W., Jr. and Williams, T. F.: A comparison of the water diuresis produced by oral and intravenous loading in normal subjects. J. Lab. clin. Med. (in press).
62. Holmes, J. H. and Cizek, L. J.: Observations on sodium chloride depletion in the dog. Amer. J. Physiol., 1951, *164,* 407-414.
63. Holmes, J. H. and Gregersen, M. I.: Relation of the salivary flow to the thirst produced in man by intravenous injection of hypertonic salt solution. Amer. J. Physiol., 1947, *151,* 252-257.
64. Holmes, J. H. and Gregersen, M. I.: Origin of thirst in diabetes insipidus. Amer. J. Med., 1948, *4,* 503-510.
65. Holmes, J. H. and Gregersen, M. I.: Observations on drinking induced by hypertonic solutions. Amer. J. Physiol., 1950, *162,* 326-337.
66. Holmes, J. H. and Gregersen, M. I.: Role of sodium and chloride in thirst. Amer. J. Physiol., 1950, *162,* 338-347.
67. Holmes, J. H. and Montgomery, A. V.: Observations on relation of hemorrhage to thirst. Amer. J. Physiol., 1951, *167,* 796.
68. Holmes, J. H. and Montgomery, A. V.: Thirst as a symptom. Amer. J. med. Sci., 1953, *225,* 281-286.
69. Hunt, J. N.: The inhibitory action of sucrose on gastric digestive activity in patients with peptic ulcer. Guy's Hosp. Rep., 1954, *103,* 161-173.
70. Hunt, J. N.: Some properties of an alimentary osmoreceptor mechanism. J. Physiol. (Lond.), 1956, *132,* 267-288.

71. Ingraham, R. C., Peters, H. C., and Visscher, M. B.: The movement of materials across living membranes against concentration gradients. J. phys. Chem., 1938, *42,* 141-150.
72. Ingraham, R. C. and Visscher, M. B.: The production of chloride-free solutions by the action of the intestinal epithelium. Amer. J. Physiol., 1936, *114,* 676-680.
73. Ingraham, R. C. and Visscher, M. B.: Further studies on intestinal absorption with the performance of osmotic work. Amer. J. Physiol., 1938, *121,* 771-785.
74. Ivy, A. C.: Contributions to the physiology of the stomach. XLVIII. Studies in water drinking. Amer. J. Physiol., 1918, *46,* 420-442.
75. Johnston, C. G. and Ball, E. G.: Variations in inorganic constituents of the pancreatic juice during constant drainage of the pancreatic ducts. J. biol. Chem., 1930, *86,* 643-653.
76. Karr, W. G. and Abbott, W. O.: Intubation studies of the human small intestine. IV. Chemical characteristics of the intestinal contents in the fasting state and as influenced by the administration of acids, of alkalies, and of water. J. clin. Invest., 1935, *14,* 893-900.
77. Kim, K. S. and Bollman, J. L.: Effect of electrolytes on formation of intestinal lymph in rats. Amer. J. Physiol., 1954, *179,* 273-278.
78. Leaf, A.: On the mechanism of fluid exchange of tissues *in vitro.* Biochem. J., 1956, *62,* 241-248.
79. Leaf, A., Chatillon, J. Y., Wrong, O., and Tuttle, E. P., Jr.: The mechanism of the osmotic adjustment of body cells as determined in vivo by the volume of distribution of a large water load. J. clin. Invest., 1954, *33,* 1261-1268.
80. Lee, J. S.: Intravascular hemolysis during water absorption from small intestine. Amer. J. Physiol., 1954, *178,* 103-110.
81. Lifson, N., Varco, R. L., and Visscher, M. B.: The relationship between the total osmotic pressure of gastric juice and its acidity. Gastroenterology, 1943, *1,* 784-808.
82. Lifson, N. and Visscher, M. B.: Osmosis in living systems, in Glasser, O., *Medical physics.* Chicago, Year Book Publishers Inc., 1944, pp. 869-892.
83. Lockwood, J. S. and Randall, H. T.: The place of electrolyte studies in surgical patients. Bull. N. Y. Acad. Med., 1949, *25,* 228-243.
84. McDowell, M. E., Wolf, A. V., and Steer, A.: Osmotic volumes of distribution. Idiogenic changes in osmotic pressure associated with administration of hypertonic solutions. Amer. J. Physiol., 1955, *180,* 545-558.
85. McGee, L. C. and Hastings, A. B.: The carbon dioxide tension and acid-base balance of jejunal secretions in man. J. biol. Chem., 1942, *142,* 893-904.
86. McGee, L. C. and Hastings, A. B.: The osmotic pressure of fasting jejunal secretions in man. Gastroenterology, 1945, *4,* 243-250.
87. Meakins, J. and Davies, H. W.: Observations on the gases in human arterial and venous blood. J. Path. Bact., 1920, *23,* 451-461.
88. Montgomery, A. V. and Holmes, J. H.: Gastric inhibition of the drinking response. Amer. J. Physiol., 1955, *182,* 227-231.
89. Nadell, J., Sweet, N. J., and Edelman, I. S.: Gastrointestinal water and electrolytes: II. The equilibration of radiopotassium in gastrointestinal contents and the proportion of exchangeable potassium (K_e) in the gastrointestinal tract. J. clin. Invest., 1956, *35,* 512-521.
90. Nassett, E. S. and Parry, A. A.: Passage of fluid and certain dissolved substances through the intestinal mucosa as influenced by changes in hydrostatic pressure. Amer. J. Physiol., 1934, *109,* 614-625.
91. Peters, H. C. and Visscher, M. B.: On the mechanism of active absorption from the intestine. J. cell. comp. Physiol., 1939, *13,* 51-67.
92. Peters, J. P.: *Body water.* Springfield, Charles C Thomas, 1935, pp. 178-185.
93. Peters, J. P.: Water balance in health and in disease, in G. A. Duncan, Ed., *Diseases of metabolism,* 3d. ed. Philadelphia, W. B. Saunders Co., 1952, Ch. 6.
94. Peters, J. P.: Unpublished.
95. Platt, R.: Structural and functional adaptation in renal failure. Brit. med. J., 1952, *1,* 1372-1377.

96. Priestley, J. G.: The regulation of excretion of water by the kidneys. II. J. Physiol. (Lond.), 1916, *50,* 304-311.
97. Priestley, J. G.: The regulation of excretion of water by the kidneys. J. Physiol. (Lond.), 1921, *55,* 305-318.
98. Ravdin, I. S., Johnston, C. G., Riegel, C., and Wright, S. L., Jr.: Studies of gall-bladder bile. Amer. J. Physiol., 1932, *100,* 317-327.
99. Rehm, W. S., Schlesinger, H., and Dennis, W. H.: Effect of osmotic gradients on water transport, hydrogen ion and chloride ion production in the resting and secreting stomach. Amer. J. Physiol., 1953, *175,* 473-486.
100. Reid, E. W.: On intestinal absorption, especially on the absorption of serum, peptone, and glucose. Phil. Trans., 1900, *B192,* 211-297.
101. Reid, E. W.: Intestinal absorption of solution. J. Physiol. (Lond.), 1902, *28,* 241-256.
102. Robinson, J. R.: The active transport of water in living systems. Biol. Rev., 1953, *28,* 158-194.
103. Robinson, J. R.: Secretion and transport of water, in Symposium of the Society for Experimental Biology, Number VIII. *Active transport and secretion.* New York, Academic Press, 1954, pp. 42-62.
104. Rosenbaum, J. D., Nelson, W. P., III, Strauss, M. B., Davis, R. K., and Rossmeisl, E. C.: Variation in the diuretic response to ingested water related to the renal excretion of solutes. J. clin. Invest., 1953, *32,* 394-404.
105. Scholer, J. R. and Code, C. F.: Rate of absorption of water from stomach and small bowel of human beings. Gastroenterology, 1954, *27,* 565-577.
106. Smirk, F. H.: The rate of water absorption in man and the relationship of water load in tissues to diuresis. J. Physiol. (Lond.), 1933, *78,* 113-126.
107. Smirk, F. H.: The effect of water drinking on the blood composition of human subjects in relation to diuresis. J. Physiol. (Lond.), 1933, *78,* 127-146.
108. Starling, E. H.: *The fluids of the body.* Chicago, W. T. Keener and Company, 1909, pp. 43-44.
109. *Ibid.,* p. 81.
110. Sweet, N. J., Nadell, J., and Edelman, I. S.: Gastrointestinal water and electrolytes. III. The equilibration of radiobromide in gastrointestinal contents and the proportion of exchangeable chloride (Cl_e) in the gastrointestinal tract. To be published.
111. Thull, N. B. and Rehm, W. S.: Composition and osmolarity of gastric juice as a function of plasma osmolarity. Amer. J. Physiol., 1956, *185,* 317-324.
112. Tidball, M. E. and Tidball, C. S.: Changes in rate of intestinal absorption of sodium chloride solutions. Amer. J. Physiol., 1956, *185,* 313-316.
113. Towbin, E. J.: Gastric distension as a factor in the satiation of thirst in esophagostomized dogs. Amer. J. Physiol., 1949, *159,* 533-541.
114. Ussing, H. H.: Transport of ions across cellular membranes. Physiol. Rev., 1949, *29,* 127-155.
115. Ussing, H. H.: Some aspects of the application of tracers in permeability studies. Advanc. Enzymol., 1952, *13,* 21-65.
116. Ussing, H. H.: Active transport of inorganic ions, in Symposium of the Society for Experimental Biology, Number VIII. *Active transport and secretion.* New York, Academic Press Inc., 1954, pp. 408-411.
117. Verzar, F. and McDougall, E. J.: *Absorption from the intestine.* New York, Longmans, Green and Company, 1936, pp. 71-97.
118. Visscher, M. B.: Electrolyte and water movement across the intestinal wall. Ann. N. Y. Acad. Sci., 1953, *57,* 291-297.
119. Visscher, M. B., Fetcher, E. S., Jr., Carr, C. W., Gregor, H. P., Bushey, M. S., and Barker, D. E.: Isotopic tracer studies on the movement of water and ions between intestinal lumen and blood. Amer. J. Physiol., 1944, *142,* 550-575.
120. Visscher, M. B. and Roepke, R. R.: Osmotic and electrolyte concentration relationships during absorption of salt solutions from ileal segments. Amer. J. Physiol., 1945, *144,* 468-476.

121. Visscher, M. B., Roepke, R. R., and Lifson, N.: Osmotic and electrolyte concentration relationships during the absorption of autogenous serum from ileal segments. Amer. J. Physiol., 1945, *144,* 457-463.
122. Visscher, M. B., Varco, R. H., Carr, C. W., Dean, R. B., and Erickson, D.: Sodium ion movement between the intestinal lumen and the blood. Amer. J. Physiol., 1944, *141,* 505.
123. Wells, H. S.: The balance of physical forces which determine the rate and direction of flow of fluid through the intestinal mucosa. Amer. J. Physiol., 1940, *130,* 410-419.
124. Wells, H. S. and Johnson, R. G.: The intestinal villi and their circulation in relation to absorption and secretion of fluid. Amer. J. Physiol., 1934, *109,* 387-402.
125. Welt, L. G.: The influence of disease on the renal excretion of water. Yale J. Biol. Med., 1956, *29,* 299-315.
126. Welt, L. G. and Nelson, W. P., III: Excretion of water by normal subjects. J. appl. Physiol., 1952, *4,* 709-714.
127. Welt, L. G., Orloff, J., Kydd, D. M., and Oltman, J. E.: An example of cellular hyperosmolarity. J. clin. Invest., 1950, *29,* 935-939.
128. Wolf, A. V.: *The urinary function of the kidney.* New York, Grune and Stratton, 1950, pp. 116-129.
129. Wolf, A. V.: Osmometric analysis of thirst in man and dog. Amer. J. Physiol., 1950, *161,* 75-86.
130. Wolf, A. V.: Relative tonicity of cellular and extracellular fluid *in vivo.* J. appl. Physiol., 1956, *8,* 674-676.
131. Wynn, V.: A metabolic study of acute water intoxication in man and dogs. Clin. Sci., 1955, *14,* 669-680.