The Interpretation of Hyponatremia*

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The finding of a low concentration of sodium in the plasma is one which has been gravely misinterpreted since it became apparent that a low plasma sodium is a rather common occurrence in a wide variety of circumstances. Before the flame photometer came into general use, the determination of the plasma sodium concentration was a difficult and time-consuming procedure and available only to those with a strong investigative interest in electrolyte metabolism. So much effort was involved in doing the analysis that the clinician or, in this case, more accurately, the clinical investigator, determined the plasma sodium only when there was good reason to suspect that there was sodium depletion. It was therefore known that the plasma sodium was low in Addisonian crisis and in the presence of severe depletion of the extracellular fluid volume as in diarrhea, etc. The correlation between a low plasma sodium concentration and sodium depletion was therefore obvious and it was generally considered, without too much thought to the question, that hyponatremia and sodium depletion were synoynmous. Then the flame photometer came into general use and the determination of the plasma sodium concentration became a procedure available to almost everybody and involving only a few minutes' work. Plasma sodium concentrations were done under a wide variety of circumstances and it turned out that the sodium was low in many conditions other than dehydration shock and Addison's disease. Among these circumstances was severe cardiac failure—a condition in which it was well known that there was marked *impairment* of sodium excretion; yet the concentration of sodium was found to be low in patients with massive edema. Confusion then reigned —this was referred to as "the low salt syndrome" and the finding of a low plasma sodium was considered an indication for the administration of hypertonic saline solution. It took some time for it to become generally appreciated that hypertonic saline rarely did any good, and the procedure is now much less popular. However, there remains a considerable confusion as to the meaning of a low plasma sodium

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concentration. What I'd like to consider today is the interpretation of the plasma sodium concentration, the physiologic mechanism by which this concentration is regulated and how this mechanism may be disturbed by disease and physiologic stress.

The first difficulty that we must emphasize is that the concentration of sodium in the plasma must be interpreted in a manner different from the concentration of almost anything else. This is due to the circumstance that in almost every instance the forces which go into determining the concentration of a substance in the extracellular fluid operate directly upon the substance itself. For instance, the plasma glucose is regulated by the addition or subraction of glucose from the blood. The plasma potassium is determined by the distribution of potassium between cell contents and extracellular fluid and by the intake and output of potassium. But the concentration of sodium in the extracellular fluid is determined largely by the intake and excretion, not of sodium, but of water. The reason for this unique situation lies in the predominant position of sodium among the solutes of the extracellular fluid. Sodium, along with the anions that balance it, constitutes some 90% of the total osmotically active solute of the extracellular fluid, so that with minor reservations, we may say that changes in the plasma sodium concentration reflect changes in the osmotic pressure of the extracellular fluids. And since we have reason to believe that the osmotic pressure of extracellular fluid is identical with that of intracellular fluid, we may generalize further to say that the concentration of sodium in the plasma generally closely reflects the effective osmotic pressure of all of the body fluids.

(There is one exception to this statement which I would like to mention, because it is occasionally of some importance, and then with this exception dismissed return to our premise that the plasma sodium reflects the effective osmotic pressure of the body fluids. The exception is the situation where some relatively inert solute which does not readily penetrate cells has gained access to the extracellular fluid. Clinically we may meet this situation when the plasma glucose concentration is markedly elevated, experimentally when mannitol or hypertonic glucose solutions are infused. Under these conditions the relatively inert solute may constitute an appreciable fraction of the total effective osmotic material in the extracellular fluid and the sodium concentration may no longer reflect the total effective solute. This, however, is a relatively unusual situation and one ordinarily easily recognized. It is unusual because there are relatively few of the solutes of extracellular fluid the concentration of which can rise to considerable levels without causing marked, if not lethal, disturbances. The one other solute

which can increase to very high levels without marked physiologic effect is urea; urea, however, does not lower the plasma sodium concentration because it easily enters cells and therefore does not contribute to the *effective* osmotic pressure of the extracellular fluid.)

Now if we accept that the plasma sodium concentration reflects the effective osmotic pressure of the body fluids and since the effective osmotic pressure is regulated by the balance between intake and output of *water*, we are in a position to define the significance of a low concentration of sodium in the plasma or hyponatremia. Clearly, hyponatremia is an indication that the output of water has not been rapid enough to maintain a normal effective osmotic pressure. Although hyponatremia may occur with a deficit in the total body sodium or with an excess of total body sodium, the one thing we can be certain about is that it is related to a failure to excrete water with sufficient speed to keep osmotic pressure normal. This is not to say that primary losses of sodium may not be responsible for inability to excrete water normally, and we will see in what way this can come about, but it is clear that a low plasma sodium by itself does not tell us anything about losses of sodium. It indicates only relative retention of water.

In order to understand this phenomenon, then, we must have some picture of how the excretion and retention of water are ordinarily effected and regulated. The sources of water are too obvious to discuss and we will concentrate on mechanisms for excretion of water. Here, for practical purposes, we may limit our attention to the kidney as the only place where the proportion of water to solute lost from the body can be regulated over a wide range and with some precision. We should also, however, mention in passing that water certainly does leave the body by other routes—without solute as the insensible water loss of respiration and direct evaporation through the skin, with a variable amount of solute in the sweat, and by the loss of gastrointestinal secretions or extracellular fluids — in the latter instances generally as solutions more or less isotonic to the body fluids. However, none of these except for some regulation of the salt content of sweat, is subject to control and therefore can contribute to the regulation of the osmotic pressure of body fluids.

Turning our attention, then, to the kidney, let us consider where and how water and solute are reabsorbed as fluid passes from the glomerulus through the renal tubules. The reabsorption of water must be divided into three phases; in the first two phases the reabsorption of water is directly dependent on the reabsorption of solute; in the third, the reabsorption of water is presumed to be independent. The order in

which these three phases occur seems pretty well established; the identification of the anatomical sites, while not so definite, is probably adequately divided among: 1) the proximal tubule, 2) the remainder of of the nephron, but the distal convoluted tubule in particular, and 3) the collecting tubule and duct. All the evidence indicates that the proximal tubule is freely permeable to water and, consequently, as solute is reabsorbed in this segment water diffuses out so that the osmotic pressure of the fluid remains essentially identical with that of the surrounding extracellular fluid. The process which goes on in this segment therefore does not contribute to either the concentration or dilution of the urine and the water reabsorbed in the process is lost from the osmoregulatory process. Estimates as to the fraction of the glomerular filtrate reabsorbed in the proximal segment vary, although it is generally agreed that it is a large part of the total. For ordinary conditions an estimate between 70 and 85% of the filtered volume is probably reasonable. However, the fraction reabsorbed in the proximal convoluted tubule probably varies with the rate of glomerular filtration, increasing as filtration rate falls and vice versa. The distal tubule operates upon a smaller fraction of the glomerular filtrate, possibly 20%. The evidence indicates that the permeability to water of the distal tubule is quite different from that of the proximal segment. In the absence of pituitary antidiuretic hormone, the distal segment is relatively impermeable to water, so that it is able to maintain considerable differences of osmotic pressure between the urine in its lumen and the surrounding interstitial fluid and blood. Therefore, as solute is reabsorbed in this segment, water does not follow along proportionately, but remains behind and the urine becomes diluted. The bulk of the solute of plasma is sodium and the anions, chloride and bicarbonate. Although this situation is changed somewhat as urine flows down the tubule by concentration of those solutes which can not be reabsorbed, under ordinary conditions most of the solute reaching the distal tubule is still made up of sodium salts and certainly most of that which can be reabsorbed is sodium and balancing anions. It is, then, specifically by the reabsorption of sodium, chloride and bicarbonate in the distal tubule that the urine is diluted.

If the remainder of the tubule were totally impermeable to water, the water excreted in excess of solute would be the exact osmotic equivalent of the sodium reabsorbed. However, there is reason to believe that the remainder of the tubule is not completely impermeable to water even in the absence of antidiuretic hormone. If two solutions of differing osmotic pressure are separated by a membrane, water will move from the more dilute to the more concentrated at a rate propor-

tional to the difference in concentrations and to the permeability of the membrane. Therefore, we will expect a larger fraction of the water initially freed by removal of salt to diffuse out of the tubule when: 1) the concentration which results from the removal of salt is low, and 2) when the permeability is high. Assuming that the permeability of the remainder of the tubule is never zero, we can see that the free water excreted in the urine is always something less than the osmotic equivalent of the salt reabsorbed in the distal tubule, and that the lower the amount of residual solute after the removal of this salt, the greater the amount by which the free water finally excreted will fall short of that initially freed by salt reabsorption. We can thus see two possible reasons why the rate of excretion of free water might fall far short of the maximum: 1) when the amount of salt reabsorbed in the distal tubule is small either because the amount delivered to it is small or because of some impairment of the removal mechanism, and 2) when total solute excretion is very small. Finally, we come to the most important factor in *not* excreting a maximal amount of water, involving the other factor in the loss of water from the tubule. This other factor, of course, is the permeablility of the tubule to water. If the permeability of the tubule is high, it will be unable to maintain a concentration gradient between the lumen and the blood and the water will tend to escape more rapidly. The extreme case occurs when the permeability of the tubule is so high that the water escapes as rapidly as solute is removed. Under these conditions the distal tubule behaves quite as does the proximal tubule and the fluid which leaves it is isotonic with the blood. It is thus apparent that the permeability of the distal tubule to water is a highly critical factor in determining whether or not water is excreted in excess of its equivalent of solute. And it is in the regulation of the permeability of the distal tubule to water that the antidiuretic hormone of the posterior pituitary is believed to act. In the absence of antidiuretic hormone the tubule approaches impermeability to water; in the presence of maximally effectives amounts, the permeability to water increases to the point where the tubule wall presents virtually no barrier to the movement of water.

Now it may seem strange that we have already described the action of antidiuretic hormone on the kidney without even mentioning the mechanism for elaborating a concentrated urine, when everybody knows that the effect of ADH is to lead to the formation of a maximally concentrated urine. While I would not mean to imply that ADH has nothing to do with the formation of a concentrated urine, I have purposely divided it off from immediate consideration to empha-

size that the most important action of ADH, from the standpoint of overall water economy, is to prevent the excretion of a dilute urine and only secondarily to promote the excretion of a concentrated urine. In the absence of antidiuretic hormone some twelve to twenty liters of urine may be excreted in a day, a volume some 10 to 18 liters greater than would be excreted if the same solute were excreted in an isotonic urine. On the other hand, rarely more than a liter or two of additional water is saved by putting out a concentrated rather than an isotonic urine. Therefore, it is clear that the important effect of ADH is the prevention of dilute rather than the formation of hypertonic urine. I do not mean to imply that the ability to save that extra liter or so of water by forming a hypertonic urine may not, at times, be quite important, but inability to concentrate the urine is still a long way from diabetes insipidus.

For the sake of completeness, let us now consider the final steps having to do with the concentration of the urine before we go on to consider the very important matter of the control of ADH secretion. We have seen that when ADH is present in optimally effective amounts isotonic urine leaves the distal tubule. Somewhere beyond this point, presumably in the collecting tubules and ducts, there is a mechanism capable of removing additional water to make the urine hypertonic. The nature of this mechanism is not yet clear. It has been shown that it is not entirely dependent on ADH since hypertonic urine can be produced when there is no circulating ADH. However, ADH can be viewed as unmasking the activity of this concentrating mechanism by: 1) assuring delivery to it of an isotonic rather than a hypotonic fluid, and 2) increasing the permeability of the tubules in the region of the concentrating process so that water is able to reach the mechanism which removes it.

To summarize briefly the renal factors concerned in the excretion of excesses of water in the body: the most important are 1) the removal of sodium salts in the distal tubule, and 2) the permeability of the distal portions of the nephron to water, this permeability being controlled by the antidiuretic hormone of the posterior pituitary. When we find then that an individual has a low plasma sodium concentration or in other words a low effective osmotic pressure of the body fluids, we may be quite certain that there is something abnormal about one of those factors (providing, of course, he has not been flooded with an excess of water too great for anyone to get rid of promptly).

The next important question concerns the way that the secretion of ADH is controlled. Obviously if the rate of excretion of water is to to be regulated by the secretion of ADH and if the excretion of water

is to regulate the effective osmotic pressure of the body fluids, the rate of secretion of ADH must be determined by the effective osmotic pressure of the body fluids. And in the absence of complicating factors this is the case. The receptor organs which are believed to be those which control the secretion of ADH are located in the anterior hypothalamus. Looking at these receptor cells in a sort of idealized way they may be looked at as tiny osmometers, containing, when their size is normal, a certain amount of solute which can not escape from the cells, in a solution of concentration equal to that of the normal body fluids. Now if the extracellular fluid is diluted with water, so that its concentration is lower than normal, water moves into cells until their concentration is the same as that of the extracellular fluid. The movement of water into cells, including the receptor cells, causes them to swell and when the receptor cells swell they cause cessation of the secretion of antidiuretic hormone. As the antidiuretic hormone already circulating then disappears, the permeability of the renal tubules to water decreases and the urine tends to become dilute. As water in excess of solute is excreted in the urine, the effective osmotic pressure of the extracellular fluid rises drawing water out of cells to maintain uniformity. The cells thus gradually shrink and as the receptor cells in the hypothalamus again reach normal size they cause the liberation of antidiuretic hormone from the posterior pituitary and the antidiuretic hormone interrupts the water diuresis. The receptors thus behave much as a thermostat, maintaining the effective osmotic pressure of the body fluids at a normal level, by causing the secretion or non-secretion of antidiuretic hormone and detecting the normal level by reference to their own size.

Now this is an extremely effective and sensitive regulatory system for adjusting the osmotic pressure of the body fluids and it works very well in the normal individual, maintaining a constant osmotic pressure within a very few percent — and consequently maintaining the plasma sodium concentration within a similar narrow range. However, there are a number of ways it can break down and fail to regulate properly. It is well known that a number of stimuli can cause secretion of antidiuretic hormone for reasons not related to the effective osmotic pressure of body fluids. And if one of these stimuli happens to coincide with an inappropriate intake of water the result is dilution of the body fluids and hyponatremia. Unfortunately, under these conditions an inappropriately large intake is all too frequent — first, because the habits of an individual concerning fluid intake are likely to cause him to consume his usual volume of water whether he needs it or not —in fact, even though its continued intake may lead to the brink of water intoxication,

and second, because doctors and nurses have acquired the habit of forcing fluids and administering parenterally larger amounts of fluid than are necessary, depending on intrinsic regulatory mechanisms to get rid of the excess. This is safe when the regulatory mechanisms are working properly, but, of course, may be disastrous when they are not.

So let us consider some of the circumstances which may cause secretion of antidiuretic hormone in a way not related to an increase in the effective osmotic pressure of the body fluids. Then we will go back to some of the conditions in which hyponatremia has been observed to see how these various factors fit together in explaining the abnormalities.

It has been known for a long time that noxious stimuli of a wide variety can cause the release of antidiuretic hormone from the pituitary. Pain, nausea, even apprehension are adequate stimuli for marked antidiuresis (although for unknown reasons apprehension in some individuals may actually have the exact opposite effect — interrupting the secretion of ADH and causing a water diuresis).

Then it is known that a great many drugs of varying sort can cause the secretion of antidiuretic hormone. Possibly most pertinent among these are the cholinergic drugs because of the possibility of cholinergic transmission of the stimulatory impulses. But in addition such drugs as morphine, the barbiturates, BAL, derivatives of cinchoninic acid, and histamine have been found to cause the release of ADH. An interesting example of the converse is alcohol which suppresses the secretion of antidiuretic hormone and produces a familiar diuresis. Unfortunately, I do not think this suppression is sufficiently reliable to be used therapeutically to interrupt ADH secretion due to other extraneous causes nor to be used diagnostically to exclude excessive ADH secretion as the cause of hyponatremia in some particular instance.

Mention should also be made of the commonly held view that secretion of ADH may be secondarily controlled by a receptor responsive to changes in the volume rather than osmotic pressure of the body fluids. I'd like here to make it quite clear that I am referring only to responses of water excretion and retention to changes in volume. It seems fairly certain that there are responses to changes in volume that involve the retention and excretion of sodium, largely mediated through the adrenal. This however, is an entirely separate problem. The teleological basis for believing that such a volume-oriented secretion of ADH might exist is clear enough. If for one reason or another there is loss of sodium from the body and if the osmotic pressure of the body fluids is maintained by appropriate excretion of the water

then in excess of the solute, the volume of the extracellular fluid will shrink in proportion to the sodium loss. Retention of water through secretion of ADH would then tend to maintain the extracellular fluid volume in the face of the sodium loss. Now it is quite clear that there is often a failure of water excretion when sodium is lost for one reason or another. The question is whether or not this water retention is due to volume-oriented secretion of antidiuretic hormone and I do not think that the other possible mechanisms have been adequately excluded.

I have mentioned the major factors involved in getting rid of excess water; each of these must be considered as possibilities when hyponatremia, signifying an effective osmotic pressure lower than normal, is encountered. To re-enumerate these before considering some of the specific conditions in which hyponatremia is a common finding, the major factors are: 1) the delivery of adequate amounts of sodium salts to the urine-diluting mechanism in the renal tubule, 2) the adequate operation of this mechanism which dilutes the urine by the removal of sodium salts, and 3) the permeability of the renal tubule to water — a factor under the control of the antidiuretic hormone of the posterior pituitary, release of the hormone in turn being modulated by the hypothalamus.

In considering the conditions in which a low plasma sodium concentration is commonly encountered, we might begin with Addison's disease — the one in which a low plasma sodium first became generally recognized. As I have said, this was interpreted as being due to loss of sodium from the body — with which it is certainly associated. However, this does not fully explain the observation because normal operation of the osmoregulatory system should return the plasma sodium to normal. Actually in Addison's disease there is an abnormality of water excretion which is not dependent upon loss of salt from the body, because it is present even in patients receiving plenty of salt and maintained on large amounts of DOCA. It is, of course, the basis of the Kepler-Power water test. The basis of the abnormal water excretion is still the subject of debate. It has been attributed to excessive, so-called inappropriate, secretion of ADH or to abnormal sensitivity of the tubule to ADH; it has also been proposed that the adrenal hormones exert a specific effect opposed to ADH. However, I have a feeling, based on no better evidence than anybody else has, that the defect, which, incidentally, is reversed by cortisone if not by DOCA, is in some combination of the delivery of sodium salts to the diluting mechanism and its ability to remove them. In any case my reason for bringing up Addison's disease was

not to explain the abnormality but to point out that even in the classical example of a low plasma sodium associated with sodium depletion, the low sodium concentration is really due to a separate defect.

The next situation which we might consider is the one in which a low plasma sodium concentration is most obviously *not* due to sodium depletion-that is, the hyponatremia so frequently seen in the severely decompensated, edematous cardiac. Such patients obviously have a great excess of sodium in the body and are known to be virtually totally unable to excrete sodium. Some confusion arises because usually large amounts of diuretics specifically intended to increase the excretion of sodium are given to such patients. Of course, the point has frequently been overlooked that diuretics in these patients are frequently strikingly ineffective so that they can hardly be responsible for sodium depletion. So the low plasma sodium here again is clearly due to inadequate excretion of water. Again the exact mechanism involved is not clear and in this case it seems probable that the mechanism may be different in different patients. In some it may be due to continued secretion of antidiuretic hormone, despite dilution of the body fluids; such secretion of ADH is probably frequent in gravely ill patients with a number of diseases. In some instances it appears to be due to a setting of the osmoregulators at the wrong osmotic pressure — corresponding to a thermostat setting at the wrong temperature. Such an event could be due to loss of solute from the osmotic pressure receptors; —if the stimuli they set off are related to their degree of swelling, loss of some of their solute content would mean that they achieve normal size only when their osmotic pressures had been reduced below normal by the inward movement of water. Under these conditions one would expect to find a low plasma sodium concentration, but a normal output of water when additional water is given; the water diuresis should cease when previous low plasma sodium concentration is reached. This has been found to be the case in some hyponatremic cardiacs. Finally we have the possibility, which, it is my feeling, is an important one, that the combination of a low rate of glomerular filtration with an extraordinary avidity of the tubules for sodium may produce a situation where all or virtually all the sodium is reabsorbed before the tubule fluid reaches the diluting segment and therefore no dilution can be effected.

The circumstances in decompensated hepatic cirrhosis are very similar to those in cardiac failure and hardly need separate consideration except to mention that it has been proposed that in cirrhosis the defect may be not in excessive production but in inadequate

destruction of ADH. Actually the evidence so far produced does not support the view that impaired breakdown of ADH is often, if ever, responsible for impairment of water excretion.

The low plasma sodium concentration of many postoperative patients, especially patients subjected to mitral valvulotomy, has attracted a great deal of interest in the last few years and a number of of papers have been published to describe studies designed to find out where the disappearing sodium has gone. It is hardly surprising that nobody has been able to determine where it went, because it hasn't gone anywhere at all. The problem here is too much 5% glucose in patients who, as a reaction to surgery and anesthesia, secrete large amounts of antidiuretic hormone for several days. The reason for its particular prominence in patients undergoing cardiac surgery is clear, since we have all been thoroughly indoctrinated with the fact that cardiacs can not excrete salt and that to give them saline may be dangerous. But we've also been indoctrinated with the idea that large amounts of fluid are needed by surgical — or in fact almost any sick patient. So we give them the next best thing — water as 5% glucose. Oliguria, even beyond the effect of ADH, is to be expected in the postoperative patient because in addition to putting out a concentrated urine he puts out virtually no salt as another part of the reaction to trauma. In such patients fluid should be given only to replace losses. And at least if we insist on administering 5% glucose let us not be surprised to find a low plasma sodium concentration.

It is appropiate to point out that the entrance of sodium into cells will *not* yield a low plasma sodium concentration although this explanation of hyponatremia is often suggested. The reason why it can not produce a significant lowering of plasma sodium is this: sodium can go into cells in one of two ways, by entering with an equivalent amount of some anion from the extracellular fluid or by exchanging for some cation from the inside of the cell. But if sodium and an equivalent amount of anion were to enter cells, this would lower the osmotic pressure of the extracellular fluid and increase the osmotic pressure of the intracellular fluid. Water would then move into cells until equilibrium was re-established and both compartments would have the same osmotic pressure as before the shift of sodium. The same extracellular osmotic pressure means, essentially, the same plasma sodium concentration. On the other hand an exchange of sodium in for some other cation out can mean only sodium in and potassium out. This could lower the plasma sodium concentration but only by an amount equal to the increase in the potassium concentration. Since the potassium concentration of plasma can increase only three or four milli-

equivalents per liter without producing serious to lethal consequences, the sodium could decrease by only this amount and this would not be sufficient to yield detectable hyponatremia. If the potassium coming out of cells were excreted in the urine, normal excretion of water would return the plasma sodium concentration to normal. So the entrance of sodium into cells is not a cause of hyponatremia. The problem with respect to bone is somewhat more complicated but for now it's sufficient to say that although many people have looked for entrance and exit of sodium in bone to explain hyponatremia, it has never been found to contribute.

One could go on considering instances of hyponatremia but the physiologic basis is similar in most instances and most often involves excessive ADH secretion.

Finally, just a word about hypernatremia. A number of descriptions of patients with remarkably high plasma sodium concentrations have been published. These are most often patients with neurological disorders. In any case, hypernatremia means inadequate water intake, diabetes insipidus or both. Failure of the thirst mechanism or its inadequate expression in drinking (as in the neurological patient) may be responsible for the inadequate water intake. It is to be remembered that solute diuresis as in uncontrolled diabetes or in patients receiving very high protein intakes (urea loads) may greatly increase the intake required for maintenance of a normal osmotic pressure. But there is no abnormality of *sodium* metabolism, except the sudden intake of massive amounts of sodium salts, which can produce significant hypernatremia.