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WATER AND SALT DEPLETION*

BY

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A great recent advance in knowledge has been the separation of the respective effects of water depletion on the one hand and of salt depletion on the other. The distinction seems to have been first made, through experimental work, by Kerpel-Fronius (1935); and the studies of McCance (1936, 1938) on salt metabolism greatly clarified the subject. In the clinical field Nadal, Pedersen, and Maddock (1941) have been pioneers. Water and salt are so closely associated in the body that for long the separate effects of their deficiencies have been confused. This has been unfortunate because it has led to wrong treatment. It is now realized that there often arise conditions of (*a*) pure water depletion; (*b*) pure salt depletion; and (*c*) mixed water and salt depletion. All are common and all result in dehydration, but in dehydration of two types which, as Nadal, Pedersen, and Maddock have said, "differ from each other not only in mechanism of production but also in symptomatology and treatment indicated. In fact almost the only similarity between the two conditions is that implied by the term 'dehydration.'" Nadal and his associates (1941, 1942) have called the two types simple dehydration and extracellular dehydration. I have termed them primary and secondary dehydration (Marriott, 1943). It is perhaps best to get away from the word "dehydration" and speak, in terms of causation, of water and/or salt depletion.

Pure water depletion occurs when water intake stops or is inadequate, and when there is no significant sodium chloride loss in secretions. The common causes are great weakness from any serious medical or surgical condition, coma of any causation, and dysphagia due to local conditions. Administration of saline to patients suffering only from water deficiency makes them worse (McCance and Young, 1944). Pure salt depletion arises when water and salt are lost in secretions—for example, in vomiting or diarrhoea—and water only is replaced. This situation is common nowadays, when there is general consciousness of the importance of dehydration but a tendency to think only in terms of water administration and to forget that water cannot be held in the body without salt. Fluid balance in patients so treated is usually recorded on intake and output charts, which, at least for a time, show satisfactory figures in regard to urine output. In spite of their theoretical hydration they continue to look dehydrated and go downhill. They are not thirsty, and this is regarded as further evidence that they cannot really be dehydrated. Their deaths are ascribed to "toxaemia" or "uraemia" or "circulatory failure" when they have, in fact, died from simple lack of salt and could easily have been saved. It is probably not an exaggeration to say that large numbers of patients die unnecessarily in these circumstances. On the other hand, others die from uncontrolled excessive saline administration.

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Basic Physiological Considerations

The main facts relating to body water are shown in Table I and Fig. 1 (Peters, 1935, 1942, 1944; Gamble, 1942; Abbott, 1946). The total salt content of the body is about 1/400 of the body weight (Bartlett, Bingham, and Pedersen, 1938). In a 70-kg. (154 lb. or 11 stones) man this means about 175 g., or 6 oz. Two thirds of it is in the plasma and tissue fluid; nearly all the rest is in the alimentary secretions, sweat, and urine. The composition of plasma and tissue fluid is shown in Fig. 2 (Gamble *et al.*, 1923, Gamble, 1942). The great predominance of sodium and chlorine is evident. It should be observed that the composition of plasma and tissue fluid, apart from the protein in the former, is identical. Indeed, these are not two fluids but the same single continuous fluid—the extracellular fluid. This conception of the continuity of the extracellular fluid is vital to understanding of the subject.

TABLE I.—*Normal Content of Body Water in a Man Weighing 70 kg. (11 stones)*

	% of Body Weight	Litres*
Intracellular	40–50	35
Extracellular:		
Tissue fluid	12–18	11
Plasma	4– 5	3
Total	70	49

* The British pint = 0·57 litre; the U.S.A. pint = 0·47 litre.

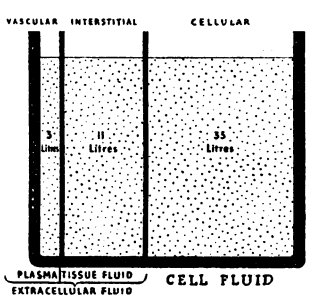

FIG. 1.—Body fluid compartments (man of 70 kg.).

The intravascular portion of the extracellular fluid is said to lie within the "vascular compartment"; the tissue-space portion is said to occupy the "interstitial compartment." It must, however, be understood that there is constant to-and-fro filtration of the fluid between the two compartments. In every capillary there is hydrostatic ejection of fluid in the proximal portion, while in the distal portion, where the hydrostatic pressure gradient has declined, there is return of an equivalent volume of fluid under the influence of the osmotic pressure exerted by the plasma

protein molecules (Starling, 1895–6). The volume of oscillating filtrate is possibly of the order of hundreds of litres daily. The normal constancy of the plasma volume is evidence of the accurate balance struck between hydrostatic pressure and plasma protein osmotic pressure. If it were not for the latter, a man would lose the whole of his plasma into his tissue spaces within ten seconds (Landis, 1937).

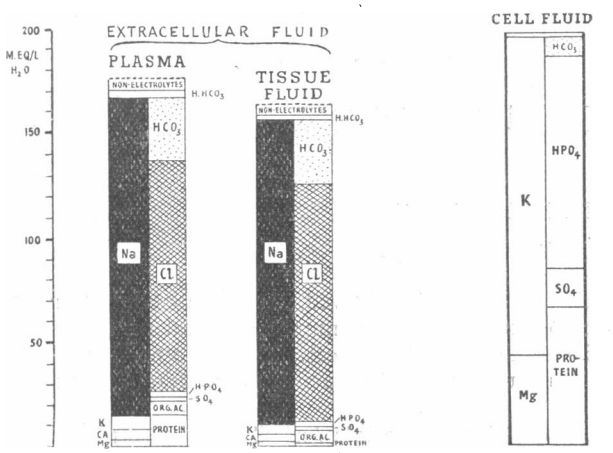

FIG. 2.—Composition of plasma and tissue fluid (extracellular) compared with that of intracellular fluid. The scale is graduated in milliequivalents per litre of water (= milligrammes per litre ÷ atomic weight × valency).

The back-and-forth movement of fluid between the vascular and interstitial compartments facilitates exchange of substances, so that the tissue fluid is maintained constant in all its properties. According to the concept of Claude Bernard the tissue fluid is the "internal environment" of the cells and the reason for the evolution of multicellular organisms wherein cells are assured of existence in a medium far more constant than the cells of unicellular or few-celled organisms can count upon from the external environment. Intracellular fluid is of quite different composition from extracellular fluid (see Fig. 2) and is practically devoid of sodium and chlorine except for the small amount of the latter in red blood cells (Lavietes, D'Esopo, and Harrison, 1935).

The distribution of water between cellular and tissue fluids is determined by their relative osmotic pressures, since cell membranes are freely permeable to water (Darrow and Yannet, 1935). Osmotic isotonicity of the tissue fluid is perhaps the most important of all the properties in regard to which constancy is required by the cells. Any osmotic imbalance must result in water being either sucked out of the cells or forced into them. In the osmotic equilibrium between intracellular and tissue fluid it is the electrolyte ions which play the chief part. In cell fluid the main ions are potassium kations and phosphate anions; in the extracellular fluid osmotic pressure is mainly exerted by sodium kations and chlorine and bicarbonate anions. The sodium ions are the most important because there is no substitute for them. Any lack of chlorine ions is automatically filled by bicarbonate ions, which are always freely available from tissue metabolism. The osmotic relationship between the body-fluid compartments is shown diagrammatically in Fig. 3. The dividing septa—the capillary and cell membranes—are freely permeable to water. The capillary membrane is also permeable to the electrolyte ions of the extracellular fluid, but confines the protein molecules within the vascular compartment. The cell membrane is relatively impermeable to the chief electrolyte ions.

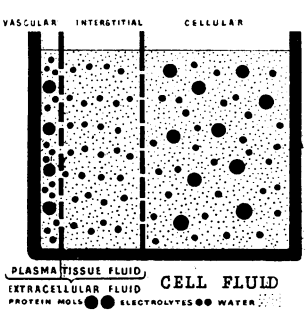

FIG. 3.—Showing the osmotic relationship between the body fluid compartments.

Osmotic Difference between Water and Salt Depletion

The difference between these conditions is shown diagrammatically in Fig. 4; it depends on the fact that the respective depletions produce opposite effects on extracellular fluid osmotic pressure. In simple water lack the extracellular fluid becomes hypertonic because water is lost from it, through the lungs, skin, and urine, without fully

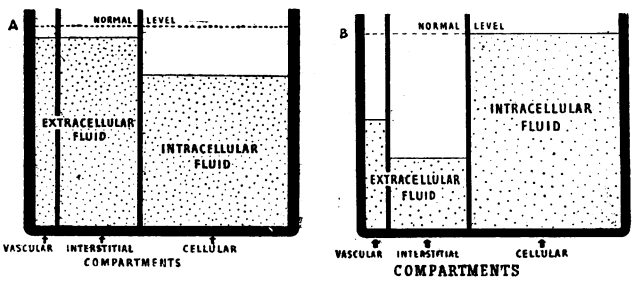

FIG. 4.—Showing the osmotic pressures in (A) pure water depletion (primary or simple dehydration) and (B) pure salt depletion (secondary or extracellular dehydration).

parallel salt loss. In consequence water is sucked out of the cells and the volume of the extracellular fluid tends to be maintained. The dehydration is chiefly a matter of loss of cellular water. In salt depletion the extracellular fluid becomes hypotonic from loss of electrolytes. There is no tendency for water to be sucked out of the cells. The volume of the extracellular fluid falls because the kidneys excrete water in the attempt to maintain extracellular isotonicity. The reduction in volume is relatively greater in the tissue fluid than in plasma, because the simultaneous decline in hydrostatic pressure, together with a rise of colloid osmotic pressure from concentration of plasma proteins, determines a relative shift of fluid into the vascular compartment from the interstitial compartment. This shift, however, is insufficient to prevent marked fall in plasma volume.

Body Water Balance

Under normal conditions water intake exceeds requirements and balance is maintained by renal excretion of the surplus. Average adult intake and output figures are given in Table II. If all water intake stops, unavoidable water

TABLE II.—*Average Water Intake and Output in an Adult*

Intake	ml.	Output	ml.
As fluid	1,500	Vaporization:	
As solid food	1,100	Lungs, 400 } ..	1,000
		Skin, 600 }	
		Urine	1,500
		Faeces	100
Total	2,600	Total	2,600

losses continue: by vaporization (through the lungs and skin), 1,000 ml.; and in the form of urine (minimum), 500 ml.: a total of 1,500 ml. So the body loses water at the rate of about 2% of body weight per day. Death occurs when the loss reaches approximately 15% of body weight or 20 to 22% of body water—in about 7 to 10 days.

Urine Water: Minimum Excretory Volume

Ordinarily, urine water consists of two parts: (*a*) minimum volume for excretion of waste products ("urine obligatoire" of Ambard and Papin, 1909); and (*b*) surplus

water. The minimum volume depends on the concentrating power of the kidneys and the amount of waste products. The relation of required minimum volume to maximum attainable specific gravity is shown in Fig. 5, constructed from the data of Newburgh *et al.* (1932, 1933, 1935). The relationship between urine volume, total solutes, and concentration is dealt with by Gamble and Butler (1944). Diminished renal concentrating power is common. It occurs in infancy (McCance, 1946), in old age, in chronic nephritis, and in other pathological conditions of the urinary tract, such as obstructive lesions—especially prostatic obstruction. It also occurs as a sequel to many conditions of severe illness or "shock" (Maegraith, 1945). Of particular relevance is that it follows upon any episode of severe or prolonged dehydration, especially of the salt-depletion type. Such episodes are often recurrent. Patients who can secrete only dilute urine may need to pass nearly 2 litres (3½ pints) daily; they very readily enter the common vicious circle shown in Fig. 6. It happens in many cases.

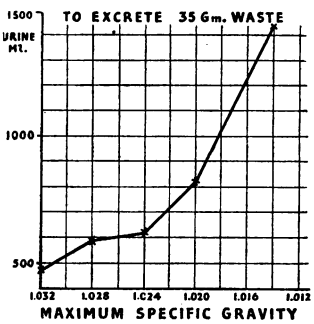

FIG. 5.—Chart to show the relation of required minimum volume to maximum specific gravity of urine.

A useful device suggested itself to me some ten years ago in regard to a man, 80 years of age, with damaged kidneys, who invariably forgot to carry out instructions to drink 6 pints (3.4 litres) a day. On three occasions he became uraemic and passed into the vicious circle of Fig. 6; each time he was rescued by intravenous infusions. After the third attack he was supplied with a large measuring cylinder with a red ring painted round it at the 2,000-ml. mark; and he was told to pass all his urine into it and reach the red ring every 24 hours *or he would die.* This clear demonstration of the purpose before him, plus its automatic action as a reminder, achieved what exhortation had failed to do. The same device, using old glass rum jars, secured an adequate output of urine from sweating soldiers on sulphonamides in hospitals in India and Burma. It is especially applicable to the conditions of general practice, but is also very useful in hospital work.

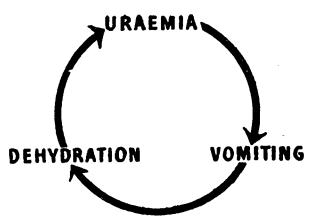

FIG. 6.—Vicious circle due to inadequate volume of urine.

The other factor which determines the minimum excretory volume of urine is the quantity of waste products. This is relatively much greater in infants and children because of their greater metabolism. It is raised in any condition increasing metabolism in individuals of any age, such as muscular exertion, fever, and thyrotoxicosis; it is also increased in water depletion (Black *et al.*, 1944). It is particularly raised after haemorrhage into the alimentary tract (Black, 1939, 1940a, 1942; Chunn *et al.*, 1941a and b). A severe haemorrhage from a peptic ulcer may discharge as much protein into the gut as a meal of 5 or 6 lb. (2.26–2.7 kg.) of meat. Raised blood urea is important when dehydration enters into the picture, because it promotes a "forced diuresis." (Avery Jones, 1939; Black, 1942.)

Water Balance in Children

I introduce this subject with diffidence as I have little paediatric experience. However, no consideration of water and salt depletion would be complete that did not mention these states in children, in whom they are doubly important. The relatively greater metabolism of infants and children causes greater loss of water by vaporization, since this is a function of energy metabolism. It also, as already stated, causes a proportionately greater amount of waste products, necessitating a relatively larger minimum excretory urine volume. Gamble (1942) estimates the unavoidable water losses of a 7-kg. (15½-lb.) infant as:

	ml.
Vaporization (lungs and skin)	200
Minimum urine	100
Total	300

The total unavoidable losses for a 70-kg. (11-stone) man have been put at 1,500 ml. Therefore the unavoidable water depletion of an infant is proportionately twice as great and represents a daily loss of 4% of body weight. Recent work showing the inability of infants to secrete a concentrated urine (McCance and Young, 1941; McCance, 1946) suggests that the figure for minimum urine is higher than that stated above. It is evident why infants ingest so much more water, in proportion to relative body weights, in their milk than do adults from their beverages and solid food. The relative amounts are between three and four times as great. It is also evident why infants withstand water deprivation so badly: their total store is depleted at twice, or more than twice, the rate of adults and so they die in less than half the time.

Causation and Effects of Pure Water Depletion

Pure water depletion may be caused by: (1) Conditions in which water is unavailable, as in the case of shipwrecked men in boats, men lost in the desert, or immobilized by injuries and unable to reach a water supply. (2) Inability to swallow, due to (*a*) dysphagia from such causes as quinsy, diphtheria, or carcinoma of the oesophagus; (*b*) coma of any causation; (*c*) great weakness. In practice the last is the chief cause, for great weakness may arise in any serious medical or surgical condition. "Extremely enfeebled patients cannot make their need for water effective. Thirst, the normal protection against dehydration, loses its insistence, and their weak state renders the satisfaction of even such thirst as they do feel an intolerable effort. They really cannot rouse themselves to the exertion of drinking: a few sips and they give up and feebly shake their heads." (Marriott and Kekwick, 1937.)

Knowledge of the effects of pure water depletion is derived partly from clinical observations on patients, but more precise information has come from experimental water deprivation of animals and of volunteers (Coller and Maddock, 1935; Black, McCance, and Young, 1944; McCance, 1945). Thirst is the earliest symptom and tends to be progressive (Dill, 1938). Dryness of the mouth, due to decreased salivation, soon follows and is also progressive; it may make the swallowing of dry food impossible. The urine volume falls to the minimum and the urine becomes as concentrated as the renal concentrating power will allow. Given normal kidneys and a normal solute load, the volume will be approximately 500 ml., the content of dissolved solids 6 to 8 g. per 100 ml., and the specific gravity will rise to more than 1030 and may even exceed 1040. The kidneys are faced with the dilemma of having to attempt simultaneously to excrete waste and salt and yet to economize water. Loss of weight is proportional to the water deficit. Weakness is progressive but is not marked until three or four days have passed. Patients look ill and their faces have a "pinched" grey appearance. Temperamental peculiarities become exaggerated. Black, McCance, and Young (1944) state: "Serious people become sombre;

while others, normally cheerful, exhibit a somewhat hollow vivacity." Mental power is eventually impaired and the patient may suffer from confusion and hallucinations.

The sodium chloride content of the plasma tends to rise; according to Black *et al.* (1944) plasma sodium increases by 30 mg. per 100 ml. after three or four days. The blood urea slowly rises, though normal glomerular filtration tends to be maintained—at least up to moderately severe hydropenia (Black, McCance, and Young, 1942; McCance, 1945). Evidence of alteration in the plasma volume, so far as I have been able to discover, is scanty. There seems to be very little shrinkage of plasma volume, and consequent haemoconcentration, at levels of water depletion around 6% of body weight (Coller and Maddock, 1935; Black, McCance, and Young, 1944). It would be of great interest to know the facts in regard to the late stages. Evidence of circulatory changes is also inadequate. Water absorption is very rapid and the patient's condition improves within a matter of minutes after water ingestion.

The mechanism of death is far from being finally settled. Kerpel-Fronius (1935) and Black, McCance, and Young (1944) consider the probable cause of death to be a rise of the osmotic pressure of the body.

Quantitative Correlation of Manifestations and Deficit

Existing information permits the division of cases of water depletion into three grades:

(1) Early.—Thirst definite but other effects not yet present: a deficit of approximately 2% of body weight, equivalent to 1.5 litres, or 3 pints, in a 70-kg. man.

(2) Moderately Severe (three to four days without water).—Marked thirst and dryness of mouth, oliguria, weakness, ill appearance, slight personality changes; still capable of fair mental and physical performance: a deficit of approximately 6% of body weight (4.2 litres, or 1 gallon, in a 70-kg. man).

(3) Very Severe.—All the above manifestations with in addition marked impairment of mental and physical capacity: a deficit of 7 to 14% of body weight (5 to 10 litres, or 1 to 2¼ gallons, in a 70-kg. man).

Body Salt Balance

Salt balance is normally maintained in a similar way to water balance; that is, intake (average, 8 to 15 g. daily) exceeds requirements and the surplus is excreted in the urine. The intake is derived from salt combined in food or added during cooking or as a condiment. Considering the importance of salt, it is odd how often official or authoritative publications omit definition of sodium and chlorine requirements from recommendations regarding dietary allowances, and also leave out of nutritional tables the amount of these elements present in various foods. This is even true in tropical countries, where salt deficiency is perhaps the commonest of all deficiency states. A most important practical point of difference between water and salt, in regard to balance maintenance, is that, whereas water intake is safeguarded by thirst, there is no similar insistent sensory warning when salt is deficient.

If neither water nor food is taken, the effects of water depletion dominate the picture because unavoidable water losses continue while salt loss, assuming no abnormal losses are occurring, is relatively slight. The body economizes salt more efficiently than water. If only intake of food ceases and water continues to be taken it is a considerable time, in the absence of abnormal salt losses, before serious salt depletion occurs. The kidneys practically stop excreting salt as soon as plasma levels fall below normal—that is, sodium, 320 to 350 mg. per 100 ml. or 139 to 152 m.eq./litre; chlorine, 340 to 385 mg. per 100 ml. or 97 to 110 m.eq./litre. Benedict (1915) in his study of Levanzin, who fasted and drank only distilled water for 31 days, found sodium and chlorine in the urine to be as follows:

Period	Sodium	Chlorine
	g.	g.
First 10 days	5·96	8·44
Second 10 days	0·89*	2·13
Third 10 days	0·59	1·57
Total	7·44	12·14

* Benedict's figures for sodium were incomplete for 4 days of the middle period. I have assumed an average for these 4 days.

This represents a total loss of less than 20 g. of salt in 30 days.

Abnormal Salt Balance

Deviations from normal balance may be negative or positive. In the former salt depletion arises from abnormal losses of salt in alimentary secretions, sweat, or urine (Addison's disease). Half, or even slightly more, of the total body salt may be lost. The salt of extracellular fluid may fall to one-third or even one-quarter of normal; this statement is not based on direct measurement but on deductions from data regarding the amount of salt needed to restore normal balance (Marsh, 1937; Bartlett *et al.*, 1938; Sanchez-Vegas and Collins, 1946; Marriott, 1946). Such depletion in a 70-kg. man represents 3 oz. (85 g.) of salt, or the amount in 10 litres (18 pints) of isotonic saline. The causation and effects of salt depletion will later be more fully discussed.

Some consideration of positive deviation from balance (salt retention) is necessary because it has a bearing on the treatment of salt depletion. It occurs from excessive administration of saline or from inefficient renal excretion of salt. It also arises, still more commonly, when imbalance of hydrostatic and osmotic pressures causes a relative shift of fluid from the vascular to the interstitial compartment. This may be due to rise of intravascular hydrostatic pressure, as in congestive cardiac failure or venous obstruction, or to decrease of plasma protein osmotic pressure from hypoproteinaemia (albumin less than 3 g. per 100 ml.: Bruckman and Peters, 1930; Weech *et al.*, 1931, 1933; Himsworth, 1946) due to starvation, insufficient absorption, inadequate hepatic synthesis, or abnormal protein loss in urine or exudate. Frequently an important part is played by increased capillary permeability, permitting escape of protein, due to mechanical, thermal, anoxic, or toxic damage (Landis, 1937). Whenever salt is retained water is also retained to the extent of 1 litre for every 6 or 7 g. of sodium chloride (De Wesselow, 1924). The body tolerates a gross excess of extracellular fluid far better than it does any change in its salt concentration (Stewart and Rourke, 1942). In severe generalized oedema there may be more than 100 lb. (45.3 kg.) of additional extracellular fluid, and the extra salt within the body may cause the body's total to be three times as much as normal; for example, a man normally weighing 70 kg. may contain over 1 lb. (453.6 g.) of salt instead of 6 oz. (170 g.).

In oedematous states the restriction of water intake, so long practised, tends merely to cause the extracellular fluid to become hypertonic because the kidneys are provided with insufficient water to excrete the excess of salt. In consequence water tends to be sucked out of the cells. Hence the patient, though massively oedematous, may actually suffer from cellular dehydration (Schemm, 1942, 1944) and complain of thirst and dry mouth, which are symptomatic of cellular desiccation (Dill, 1938). Every clinician of experience has seen such cases, in which the water in the great pool of tissue fluid is not available to the kidneys and thus a policy of water restriction has

little influence on the oedema but causes oliguria and may produce uraemia. Such patients are better regarded as "brine-logged" (Schemm, 1942) rather than water-logged. The really important consideration in their treatment, apart from rectification of the fundamental cause of the oedema, is restriction of daily intake of sodium chloride to not more than 1.5 g. The kidneys will not, save in exceptional circumstances, retain water in the absence of salt, for they obey their fundamental law, as chief regulators of the internal environment, that extracellular isotonicity is the prime consideration. For example, it is very difficult under experimental conditions to produce oedema from hypoproteinaemia if salt is restricted (Kerkhof, 1938). In patients suffering from cardiac failure, and on a regimen of severe salt restriction, daily water intake may exceed 6 litres (Leevy *et al.*, 1946) and even reach 10 litres (Schemm, 1942) without increase of the oedema. Actually in such cases it would seem that the right course is neither to restrict nor to force water intake but to allow the patient whatever water he desires (Leevy *et al.*, 1946).

Salt in Alimentary Secretions and Sweat

The salt content, with the relative sodium and chlorine ratios, in the alimentary secretions and sweat is shown in Fig. 7 (after Gamble, 1923, 1942; and McCance, 1936).

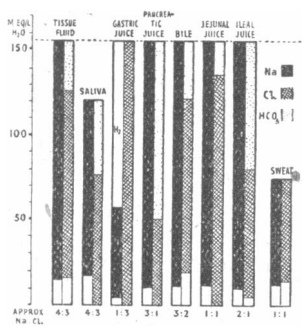

FIG. 7.—Salt content of alimentary secretions and sweat, with relative sodium and chlorine ratios.

The great predominance of these ions should be noted. The quantity of the various secretions daily secreted into and reabsorbed from the alimentary tract is shown in Table III (Rowntree, 1922; Gamble, 1942; Abbott, 1946). So far as sweat is concerned, it needs to be appreciated that there are two kinds—insensible and sensible. Insensible sweat (Sanctorius, 1614; Newburgh and Johnston, 1942) vaporizes continuously and invisibly from the body even under cold atmospheric conditions. Its average amount is about 600 ml. daily. Its sodium content is said to be negligible, and it may be regarded as practically distilled water (Nadal, Pedersen, and Maddock, 1941). Sensible sweat is secreted when the body becomes heated. In the Tropics its volume may reach 3 gallons (13.5 litres) a day

TABLE III.—*The Alimentary Secretions*

	ml.
Saliva	1,500
Gastric juice	2,500
Pancreatic juice	700
Bile	500
Intestinal juices	3,000
Total	8,200 *

* Approximately 2 gallons, with 2 oz. of sodium chloride.

(Hunt, 1912). It is virtually hypotonic saline, since sodium and chlorine are its main constituents. The concentration of sodium chloride varies from 1 to 5 g. per litre in different individuals (Moss, 1923; Kuno, 1934; McCance, 1936; Dill, 1938; Ladel, Waterlow, and Hudson, 1944). The average concentration for Europeans is usually around 2.5 to 3.0 g. per litre, or 1/3 to 1/2 oz. per gallon.

Under normal conditions in Britain nearly all salt excretion is by way of the urine, and individuals lose only a very small proportion of their daily salt intake from the alimentary tract or from the skin.

Physiological Functions of Salt

As already shown, sodium and chlorine are the chief components of extracellular fluid (tissue fluid + plasma), the alimentary secretions, and sweat. In the extracellular fluid the main function, already discussed, of these ions appears to be to supply osmotic pressure so that isotonicity with intracellular fluid is preserved. Another function is that sodium and chlorine play principal parts in the acid–base balance of extracellular fluid. As is well known, the general tissue cells require an environment of constant slight alkalinity, and the various acid–base regulating mechanisms work to preserve it. In Figs. 2 and 7 basic and acid radicals occupy respectively the left and right columns of each diagram. Reference to Fig. 2 shows that in extracellular fluid more than 90% of the total base is represented by sodium and more than 70% of the total acid by chlorine.

In the alimentary secretions the chief functions of sodium and chlorine again appear to be concerned with osmotic pressure and acid–base adjustment. As regards osmotic pressure, the cells lining the alimentary tract, particularly in its upper part, are adapted to withstand non-isotonic fluids. Nevertheless, isotonicity appears to be an important consideration, since, with the exception of saliva, these secretions are all approximately isotonic with tissue fluid (see column heights in Fig. 7). As regards acid–base adjustment, the various digestive enzymes need widely differing conditions of acidity and alkalinity. In consequence sodium and chlorine are secreted in the varied ratios shown in Fig. 7.

In sensible sweat sodium and chlorine seem almost accidental constituents and not to have important functions. The reason for this statement is that there is such a wide individual difference in the salt concentration of the sweat of different persons that it seems hard to believe that any particular concentration matters. In tropical countries the salt content of the sweat of natives or long-time residents appears to be much lower than that of new arrivals (Dill, 1938; Lee *et al.*, 1941).

Renal Regulation of Extracellular Sodium and Chlorine

As Gamble (1937) has said: "The kidney is very inadequately described as an organ of excretion. Were removal of waste products its only function, a much simpler mechanism would suffice. Its complexity of design and intricacy of function are required for the construction and accurate defence of extracellular fluid on the chemical constancy of which depends the successful operation of intracellular processes." Renal conservation of the constancy of the internal environment is achieved by selective reabsorption of the components of the glomerular filtrate. First in importance among them are water, sodium, and chlorine. In normal adults the maximum attainable urinary concentration of chlorine is about 0.33 N (Davies, Haldane, and Peskett, 1922). Expressed as NaCl this concentration equals approximately 2% of salt in urine. The concentration of chlorine and HCO_3 equals 0.33 N of either or of both together. The maximum for sodium seems to be of the same order or a little higher. The ability of the kidneys to excrete sodium and chlorine, together or separately, has an important bearing on the administration of saline. In adults the renal concentrating power may be damaged in the common conditions mentioned in the section on minimum urine volume, and in these conditions patients may be unable to excrete salt in concentrations exceeding 0.4% (approximately 1/2 isotonic saline). In normal infants the ability to excrete salt is much less than in adults (McCance and Young, 1941, 1942; McCance, 1946); this explains why they so readily become oedematous if given even small excesses of saline. McCance

and Young found the sodium and chlorine clearances in full-term babies aged 7–14 days to be about one-fifth of the value they would be likely to acquire in later life. Still lower clearances were found in premature babies (Young, Hallum, and McCance, 1941).

As is now well known, the cortex of the suprarenal glands plays an important part in regard to renal excretion of salt. In experimental adrenalectomy or in Addison's disease there is an excessive excretion of sodium chloride, and in consequence the plasma level falls. Excretion may continue in Addison's disease even when the plasma chloride, expressed as NaCl, is below 500 mg. per 100 ml. (Anderson and Lyall, 1937). The subject has been reviewed by Loeb (1941), whose own work in this field has been of such importance. Detection of the tendency to excessive salt excretion, under standard conditions of salt restriction, is the basis of the well-known test for Addison's disease which has been devised by Cutler *et al.* (1938a, b). There is similarity in failure of hormonal control causing excessive excretion respectively of water and salt in diabetes insipidus and in Addison's disease. However, in the former the body is saved from very serious consequences by the protective mechanism of thirst, while in the latter there is no equivalent salt-craving. In passing it should be observed that in diabetes insipidus there is no increase of salt excretion or fall in plasma chloride level; this was the finding of Blotner (1941) in 22 cases of that disease.

(Part II will be published in the next issue.)

THERAPEUTIC POSSIBILITIES OF RADIO-PHOSPHORUS

BY

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Radio-phosphorus (P^{32}) has been used since 1936 in the treatment of patients with chronic myeloid and lymphatic leukaemia, polycythaemia vera, lymphosarcoma, and various related diseases. Most of this work has been done in the U.S.A. Important summaries of the American results have been given by Low-Beer, Lawrence, and Stone (1942); Kenney (1942); and Reinhard, Moore, Bierbaum, Moore, and Kamen (1946). Of great interest is a paper from Stockholm by Lindgren (1944).

Clinical trials of the therapeutic possibilities of radio-phosphorus have not yet been carried out in Great Britain, although tracer studies with P^{32} made by cyclotrons are in progress. However, it now seems reasonably certain that within the next year we shall be fortunate enough to obtain adequate and regular supplies of P^{32} made by means of a "pile." The isotope P^{32} is produced in the pile from ordinary phosphorus (P^{31}) by slow neutron capture and is used in the form of isotonic Na_2HPO_4 solution (15 mg. per ml.), with initial radioactivity of about 300 microcuries per ml. The pile can produce a specific gravity of one-third curie of P^{32} per g. of phosphorus. The P^{32} given therapeutically should be accompanied by the smallest possible amount of P^{31}.

Dosage

The radioactivity of the phosphate solutions used can be determined by means of a Lauritsen electroscope calibrated with a uranium standard, but for clinical investigations a Geiger counter is essential. It appears most satisfactory to give the radioactive phosphate solution intravenously, usually in unit doses of the order of 0.5–2 millicuries. However, oral administration is possible, and it is stated that "it is the practice of most workers who give P^{32} orally to assume that 75% of any given dose is absorbed."

The physical properties of P^{32} are well known. This isotope has a half-life of 14.3 days and emits only beta particles. The maximum energy of the beta particles is 1.71 mev.; the mean energy of the beta particles is of great importance in clinical applications and has the approximate value of 0.70 mev.

Although as yet most of the clinical dosage of P^{32} has been necessarily empirical, it seems highly desirable to correlate the dose of radioactive isotopes with the roentgen unit. An important paper on this subject was published by Marinelli (1942). It can be shown that 1 microcurie of P^{32} per g. of tissue delivers 43 r. per day, 1 g. roentgen corresponds to 1.13 microcuries destroyed per kilogram of tissue, and if 1 millicurie is retained for 24 hours by a patient weighing 70 kg., approximately 0.6 roentgen equivalents of whole body radiation are delivered. In radioactive isotope therapy it is useful to measure the differential absorption ratio for the isotope, which may be defined as the ratio of the concentration of the radioactive material in a particular tissue to the mean concentration in the body as a whole. The possibility of delivering useful doses of radiation in any particular case may be determined by measuring the differential absorption ratio by means of tracer studies (Kenney, Marinelli, and Woodard, 1941). In this way it was found impossible to deliver therapeutically useful doses of beta radiation from P^{32} to the primary tumour or metastases in cases of carcinoma of the breast and of osteogenic sarcoma. The present tendency in all diseases except polycythaemia vera appears to be to follow the "fractional method" of dosage of P^{32} outlined by Low-Beer, Lawrence, and Stone (1942). It seems that one can treat a typical case of chronic myeloid leukaemia with an initial dose of perhaps 1 millicurie of P^{32}, followed by five doses of 0.5 millicurie at three- to four-day intervals, and then doses of 0.5 millicurie weekly until the total white cell count has fallen to about 30,000 per c.mm. Then one or two fractions may be given subsequently at longer intervals. The whole clinical and haematological picture must obviously be taken into account. It seems likely that the above unit doses can be safely doubled in some cases, with reduction of the over-all time of treatment. The average treatment for the 39 cases of chronic myeloid leukaemia reported by Reinhard *et al.* (1946) corresponds to 11.8 millicuries of P^{32} administered in 78 days. In the treatment of polycythaemia vera it is recommended that the initial dose is 3.5 to 4 millicuries of P^{32}. This may suffice, but in some cases it is necessary, after waiting three months, to give a second dose of 1 to 3 millicuries; ancillary venesection is often advisable.

Therapeutic Value

It is not yet possible to assess with confidence the therapeutic value of radio-phosphorus, but it is evident that the earlier optimism is not yet justified. The conclusions reached by Reinhard *et al.* (1946) may be summarized as follows:

1. Radio-phosphorus is probably the best therapeutic agent available at the present time for polycythaemia vera.

2. The results of treatment by radio-phosphorus of patients with chronic myeloid leukaemia are probably comparable with those of the usual *x*-ray therapy but are not substantially better. With P^{32}, "freedom from radiation sickness is a practical advantage which patients who have had previous *x*-ray therapy appreciate." Great care appears to be necessary in treatment with P^{32} to avoid serious damage to the bone marrow.

3. "In the treatment of chronic lymphatic leukaemia radio-phosphorus is probably as satisfactory as, but not better than, roentgen radiation."