WATER AND ELECTROLYTE METABOLISM IN CONGESTIVE HEART FAILURE

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The Volume of Body Fluids in Congestive Heart Failure

One of the main features of congestive heart failure is a retention of fluid, which at times may be striking in amount. It accumulates in all tissues of the body and for many years the term dropsy has been used to describe it.

Dropsy has more than nuisance value, for in the lungs and pleural cavities it contributes to the predominant symptom, shortness of breath, by altering the mechanics of respiration and lowering the vital capacity. It is possible, too, that the functioning of the heart is also impaired by it. Certainly the removal of oedema is followed by much clinical improvement and prognosis in chronic heart failure improved by the routine use of diuretics.

The fluid retained is not just water, as even today many patients think, but water and salts. This seems to have been appreciated by Paracelsus, for he wrote, 'It is not simply a collection of water, but bodily substance liquified, more precisely it is salt liquified by astral action' and elsewhere, 'Mercury is the remedy for it wields the power of expelling the dissolved salt and of promoting the appropriate salt.'⁷⁶ Dropsy is in fact largely made up of the fluid present outside cells, and the 'salts' therefore are those which predominate in this extracellular fluid, sodium and chloride.

In living organisms, structure and composition are maintained dynamically, by means of an interchange of materials and energy with the environment. The volume of fluid and the amounts of salts in the body are maintained in this way. Sodium, chloride and potassium are derived entirely from the diet; water from dietary intake and an additional amount as a by-product of metabolic reaction. If one is to understand the problem posed by the accumulation of fluid in congestive heart failure, it is therefore necessary to think dynamically in terms of balances between these gains and losses, and

the beginnings of such an approach are to be found in the writings of Avicenna where we find '... if the amount (of urine) is less than the fluid consumed, it points to great loss by diarrhoea or to a tendency to dropsy.'³ And early Caelius Aurelianus, when writing on dropsy¹¹ commented on 'relatively little urine in comparison with the amount of fluid drunk.'

Water is not retained by itself in heart failure and so it is not necessary to restrict fluids, although this is a practice which often commends itself to patients and their attendants. Its lack of theoretical soundness and perhaps also its streak of Calvinism could be forgiven, were it not in fact potentially dangerous. This was appreciated by Withering, who warned against it in his monograph on digitalis¹¹¹ published in 1785. The dangers often stem from the fact that retention of salt appears to be the primary event in the accumulation of fluid and so, unless its intake is restricted salt will be retained *and with it fluid*. If drinks are severely curtailed, then some of the water of this fluid will be obtained from other sources, some losses of water are obligatory and hence prior call on the gains of water to the body. Unless intake can also accommodate the sodium retained, water will therefore be extracted from cells, and with it potassium. This results in impaired cellular metabolism and tissue function; there may also be intolerable thirst.

Some 1 to 2 litres of fluid may accumulate before being detectable as pitting oedema. In a while the accumulation is progressive and in more florid cases this phase is prolonged, although there comes a time when accumulation virtually ceases. No one as yet has seen a patient build up even though the skin may split locally.

Several problems are raised by this accumulation of fluid. Why and how does accumulation take place? What determines for how long the accumulation shall be progressive? What is the me-

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nism whereby it ceases and a new steady state is maintained? And, of course, how may the process be set into reverse?

The fluids of the body are both cellular and extracellular, and the regulation of total fluid volume, which occurs in health, therefore subsumes regulation of both the component volumes. Clearly changes could occur in the volume in either compartment at the expense of the other; changes could also occur in the volume of either compartment independently or in both simultaneously. The accumulation of fluid in heart failure belongs to the last category, since there is an overall gain of fluid reflected in a gain of body weight.

The osmotic pressures of the fluids inside and outside cells are equal and changes produced in either cause shifts of water and solute negating the differences. In health these shifts are not usually permanent, since the osmolality of body fluids is kept fairly constant, largely by adjusting urinary losses in the light of dietary intake. The osmotic pressure of extracellular fluid is derived largely from the contribution made by sodium and its accompanying anions. Similarly the osmotic pressure of cellular fluids is largely due to potassium and associated anions, potassium being the main intracellular cation. Although sodium can and does enter cells, the amount in most healthy cells is very small, for it is continually extruded or baled out. The functioning of this 'sodium pump' requires energy.

It follows, from this partition of sodium and potassium, that, provided the sodium pump is working, any gain of sodium will remain almost entirely in the extracellular fluid, the volume of which will expand. If there is also a gain of water, the volume of intracellular fluid will not change; if not, then this volume will fall. Similarly, gain of potassium will cause an increase of extracellular fluid volume, as all but about 2% of the body potassium is in cells. Gain of both sodium and potassium, together with water, causes expansion of both fluid compartments. Gain of water alone would expand both, but a fall, of course, also cause a fall in the osmotic pressure of all body fluids.*

The regulation of body fluids is therefore secondary to the regulation of their content of sodium, and the maintenance of a normal volume of extracellular fluid largely a matter of the regulation of sodium excretion by the kidneys.

That the oedema fluid which accumulates in congestive heart failure is largely extracellular is supported by evidence from several sources. Thus

the total amount of sodium in such patients is increased,^{2, 8, 24, 30, 68, 75, 102, 103} whilst the total amount of potassium in the body shows no increase. For the most part the loss of weight accompanying recovery from congestive heart failure is that to be expected from the measured loss of sodium. Finally, the measurements of total body water and body sodium also suggest that increase in the former is due largely to accumulation of extracellular fluid.²⁴

This failure to maintain a normal volume of extracellular fluid does not, however, imply a complete breakdown of the process of regulating this volume, since the accumulation of fluid is progressive for only a finite period. Is then the retention of fluid a normal response to stimuli which in health serve to maintain the volume within normal limits, and which in heart failure are more persistently present, or present in greater measure; is it an aggravated response to normal stimuli, or is it, indeed, an abnormal process occasioned by altered renal function or initiated otherwise than in health?

These are difficult questions and are made more difficult in view of the little we know of the regulation of extracellular fluid volume in health. Several mechanisms have been proposed, all suggesting that change in sodium excretion is caused by the altered production and release of a sodium-retaining hormone by the adrenal cortex;† the possibility of a neurological enhancement of tubular reabsorption of sodium has also been suggested. They differ, however, in the stimuli proposed to initiate such changes. These include a change in the volume of interstitial fluid, change in blood volume, change in stroke output of the heart and an assessment of the parity or disparity between the volume of blood and of the functioning vascular system.

It has been suggested that these changes are monitored by stretch receptors in the interstitial space, on the venous side of the systemic circulation, in the right auricle or diffusely from many parts of the vascular bed, arterial as well as venous.

Some years ago it was held that in congestive heart failure the kidney retained more salt and water than usual, due to a more complete reabsorption from the lesser quantity filtered at the glomerulus, in turn caused by the lower blood flow through the kidneys resulting from an impaired circulation. Tubular reabsorption was held to proceed normally, but since less was filtered, less was excreted. Whilst sometimes filtration may be lowered, in fact the cells of the

*The possibility of variation in production and release of a salt-excreting adrenal hormone has now to be considered following the recent isolation of such a steroid⁷¹.

renal tubules are reabsorbing water, sodium and chloride more avidly than normal; this may be due in part to an increased production and release of aldosterone by the adrenal cortex, for which there is some evidence,²⁵ and in part also to an increase in filtration fraction.

It seems likely, therefore, that retention of sodium, accompanying anions, and water, results from a normal response to stimuli which in health serve an homeostatic function. Is the progressive nature of oedema accumulation due to a faulty shut-off mechanism, or does the stimulus in fact persist and, if so, why? If it does persist, why does it not persist indefinitely; and why does it persist longer in some than in others? Clearly complementary studies of circulatory dynamics and fluid retention are needed if this point is to be elucidated. This means defining closely the stimuli promoting retention of sodium, chloride and water in health and the mechanism whereby it is stopped. Changes in circulatory dynamics, the operation of shunts, alteration of vessel tone, etc., may also be called into play by the same circumstances, inducing change in excretion, and the possible interplay of these two sets of responses requires further consideration and observation.

It is tempting to speculate that 'recognition' of a lack of fullness on the arterial side of the systemic vascular bed, due to a redistribution of blood (more on the venous side, more in the pulmonary circuit, more in the dilated heart), may initiate the accumulation of fluid in congestive heart failure.⁴⁰ If this is correct, then one would anticipate an increase in blood volume to accompany gain of extracellular fluid. This has been shown to occur by Funkhauser, Pritchard and Little.³⁷ However, because retention of sodium and water, initiated via the system outlined, is homeostatic in health, it does not follow that this is also the case in congestive heart failure. One needs to know, therefore, whether it is always or indeed ever beneficial.

Clinically it is abundantly apparent that most patients benefit from *removal* of their oedema, and prognosis is improved if its reaccumulation can be prevented. This might be thought to demonstrate that fluid accumulation in congestive heart failure is never homeostatic. There are, however, patients whose condition is worsened by the complete removal of oedema. Clinically they appear to suffer a marked fall in cardiac output, manifest as a fall in blood pressure and feeble pulse. Their condition improves if they are allowed to accumulate some oedema, presumably because of the associated increase in blood volume and hence venous return and so cardiac output. Soloff and Zatzuchni⁹² pointed out that it would be incorrect to assume that a normal

blood volume is optimal for persons with heart disease. It would seem, then, that the accumulation of oedema can serve an homeostatic function even in frank cardiac failure with oedema.

This prompts the suggestion that *some* retention of fluid, with consequent expansion of blood volume, may be helpful, but that beyond a certain critical level, individually determined, *further retention is harmful*. That patients with chronic heart disease have increased volumes of extracellular fluid and blood even before congestive failure is manifest clinically, or can be detected by catheterisation studies,⁶⁴ is in accord with this view. These volumes are also raised above normal in patients who have recovered from an episode of congestive heart failure.²⁶

The deterioration which results when fluid retention exceeds a certain level may perhaps be due to an increase in venous return to the heart to a level at which cardiac output falls rather than increases, or which causes significant tricuspid incompetence.⁶³ Possibly, too, myocardial efficiency is impaired as a result of increase in tissue water content.

Fluid retention in heart failure is thus seen as serving an homeostatic function—compensating for pooling of blood on the venous side of the systemic circulation and in the heart resulting from myocardial inefficiency, leading to inadequate filling of the arterial tree. Further deterioration of the heart's pumping efficiency will thus occasion further retention of fluid. Sooner or later a vicious cycle will result—increased fluid retention aggravating the congestive failure, in turn causing increased fluid retention.

In such a concept the persistence of a lack of fullness of the arterial vasculature is responsible for the progressive nature of fluid retention. Whether arterial lack of fullness persists longer in some and what eventually limits oedema formation is not known.

The Composition of Body Fluids in Congestive Heart Failure

If the accumulation of oedema is attributed to a process directed at expansion of the extracellular fluid, one would not expect to find an abnormality in the composition of this fluid, nor indeed earlier studies failed to reveal any. However, with a study of a larger number of patients including those in *severe* cardiac failure, abnormalities have been seen. Mostly these have been regarded as complications caused by treatment rather than consequences of the congestive heart failure.

Hypochloraemic Alkalosis has been described and attributed to a greater loss of chloride than sodium from the body, occasioned by the actual

mercurial diuretics.^{17, 89, 96} Once established it is associated with a poor or absent diuretic response. Its reversal by supplements of chloride followed by clinical improvement and enhanced responsiveness to diuretics. This condition is by no means as common as one might gather from perusal of the literature. In a series of 397 patients in congestive heart failure it was seen in only 7% of the patients.²⁹

It is, nevertheless, true that the diuresis caused by mercurials in congestive heart failure is often accompanied by a greater loss of chloride than sodium in urine. However, this is not usually accompanied by a fall in extracellular concentration of chloride. Partly this is because gains of chloride from the diet exceed those of sodium, and partly because over several days (including days when diuretics are not given) the cumulative loss of chloride from the body may not actually be greater than that of sodium. However, even where loss of chloride *does* exceed loss of sodium, hypochloraemia may not supervene. We shall return to this enigma later.

Hypokalaemia has been reported^{5, 87, 90} and is sometimes associated with an hypochloraemic alkalosis secondary to cellular potassium deficiency. Usually the fall in serum level of potassium follows the use of diuretics (most commonly chlorothiazide and its analogues) which may promote its loss in addition to that of sodium, chloride and water. In our experience a lowering of serum potassium is not common.

A high urinary loss of potassium is perhaps less common consequence of mercurial diuretics than a loss of chloride in excess of sodium. This may be relevant to the rarity of hypochloraemic alkalosis which perhaps only supervenes in the presence of a potassium deficiency brought on in this way.

Hyponatraemia. Low serum levels of sodium have been reported^{14, 16, 17, 27, 35, 36, 77, 95, 100} mostly in seriously ill patients, and a good deal of confusion has arisen from the use of the term 'low salt syndrome,' which suggests that the lowering is due to a total shortage of sodium. This, of course, cannot be reconciled with the presence of oedema, which signifies an increased body content of sodium. It is difficult to tell from the original account by Schroeder⁸⁸ whether such an absolute shortage was implied, or whether that was implied was a relative loss of sodium from the body. However, even the suggestion that the lowering of the level of sodium in extracellular fluid is attributable to *loss from the body* is made merely by *analogy* with the lowering seen in severe experimental salt deficiency. Indeed, the term is still more confusing in view

of the looseness of the original definition which permits diagnosis in the *absence* of a low serum sodium level, a liberty Schroeder himself took in no less than 14 of the 18 cases put forward to demonstrate the syndrome. In fact, his definition was so loose that *any* severe case of congestive heart failure automatically qualifies.

In a series of 397 patients in congestive heart failure,²⁹ low serum levels of sodium were often found and not only in those patients seriously ill and resistant to treatment. Indeed the frequency with which low levels have been encountered (62%) was much greater than had previously been suspected. *Serum levels were determined as a routine on all these patients on admission and at intervals of not more than one week thereafter.* The serum level of chloride was also often found to be lowered, whilst that of potassium commonly was raised.

FIG. 1.—The lowest serum levels of sodium obtaining in 397 episodes of congestive heart failure with oedema. These episodes have been grouped by known duration of a failing heart (judged by dyspnoea of effort), by grade of failure (Classification of the American Heart Association) and by speed of response to treatment (see reference 29). The shaded bands enclose the 95% confidence limits for serum sodium obtaining in 157 healthy individuals.

TABLE I
SERUM SODIUM AND PROGNOSIS. PERCENTAGE MORTALITY FOR THE PATIENTS
GROUPED BOTH BY SERUM LEVEL ON ADMISSION AND BY THE LOWEST LEVEL
ATTAINED DURING THE ADMISSION
Serum level of sodium—mEq/l

	> 135	135—132	131—126	125—121	≤ 120
Level on admission ..	11	20	38	42	100
Lowest level	7	16	28	35	90

Significance of Hyponatraemia

Clinical Significance

Low values for serum sodium occur even in patients in mild congestive heart failure, although *very low values are more often found* in those patients in severe episodes. Neither the duration of heart failure, nor the grade of the failure, bear much relation to the level to which serum sodium may fall during an episode of congestive heart failure (Fig. 1).

This level, however, affords a good index of the immediate prognosis; the lower it is the greater the likelihood of a fatal outcome (Table 1). But it must be emphasised that patients die whose serum levels have been normal throughout or whose serum levels have returned to normal from low values. Clearly the situation is complex, suggesting that there is no single cause for the lowering of sodium encountered in congestive heart failure. This conclusion is further supported by the facts that, in some, the serum level of sodium falls insidiously over months and years, whereas in others it is attained acutely, over a period of days. As would be expected, prognosis is worse in the latter group.²⁹

Is a low serum level the cause or a consequence of clinical deterioration or resistance to treatment? This is difficult to answer, although often it has been assumed that the abnormal concentration is a complication of treatment and a cause of further deterioration. However, there may be more than one cause for the lowering of the serum level. Indeed, it is not improbable that several causes may operate in any one patient, e.g. the patient with a moderately low serum sodium level for many months or years in whom an acute lowering supervenes. Whilst, therefore, it is possible that sometimes the lowering may be a cause and sometimes a consequence of deterioration, the clinical impression is strong that a low sodium level more often reflects, rather than determines, the severity of the underlying condition. Certainly a fall in the serum level may be an effect of deterioration, for instance following a pulmonary embolus.

Therapeutic Significance

It has been suggested that the lowering of the

FIG. 2.—Lowest serum levels of sodium, the highest of chloride obtaining on the same day, the highest serum levels of potassium from patients in congestive heart failure with oedema who have been given mercurial diuretics. Ninety-seven patients were admitted who had not been given diuretics. The levels presented for these patients are the lowest (Na), and highest (K) obtained before diuretics were started.

serum level of sodium is due not to the process involved in congestive cardiac failure but to treatment. Two widely used therapeutic measures have been indicted—mercurial diuretics and a diet low in sodium^{17, 36, 47, 95, 96, 100}—and it has been claimed that adherence to a few arbitrary rules regarding their use prevents a fall.⁹³

Patients may, however, have low levels of sodium (also low chloride and high potassium levels), whether or not mercurial diuretics have ever been given (Fig. 2). This same pattern of disturbance of serum electrolytes has also been seen in a smaller number of patients who have had chlorothiazide and a number who have been on a diet supplying only 10 mEq. of sodium, or less per day (Fig. 3). Subsequent experience with chlorothiazide, hydrochlorothiazide and Furosemide confirms this pattern. It is concluded that the altered pattern is caused by the condition of congestive heart failure, not

FIG. 3.—The lowest serum levels of sodium, the levels of chloride obtaining on the same day and the highest serum levels of potassium are presented for 26 patients treated with chlorothiazide and 58 patients receiving a diet prescribed to contain 10 mEq. of sodium, or less, per day.

treatment, and it is emphasised that neither diuretics nor a diet containing little sodium should be stopped merely because the serum sodium is found to be low. This is stressed because it is frequently urged that treatment be so modified, *in spite of the clear indication of an excess of body sodium presented by overt oedema.*⁷⁷ This paradox of dearth amidst excess is confirmed by measurement of the total mass of sodium in the body (which will exchange with its radioactive isotope ^{22}Na). Clearly the serum level of sodium is an unreliable index of body content (Fig. 4) and the presence of a low level of sodium should not in itself provoke the administration of sodium, as is sometimes counselled. To give sodium where there is already an excess in the body may be dangerous as well as illogical. In fact, measures for the removal of the excess should be persisted in; successful, clinical improvement usually results and the serum sodium level will often rise. This has also been the experience of others.⁸³ If diuretics are persisted in *after complete removal of oedema*, signs of a lowered cardiac output may develop, and attention was drawn to this shortly after the introduction of the organic mercurial diuretics.⁷⁸ Instances have been reported from time to time subsequently.^{9, 23, 44, 50, 92} The peripheral circulatory failure which occasionally follows the rapid stripping of an ascites or drainage of oedema fluid⁴⁹ belongs to this category too, for it is likely that some reaccumulation occurs at the expense of extracellular fluids elsewhere, and that in particular results in a fall of plasma volume. For this

FIG. 4.—Serum levels of sodium and total exchangeable masses of sodium in patients with congestive heart failure.

reason some prefer to apply firm crepe bandages to the abdomen or legs after removal of fluid to prevent or minimise such re-accumulation and its sequelae,¹⁰⁵ a practice which dates back at least to Græco-Roman times.¹¹ As already mentioned, there are some patients who manifest signs of a falling cardiac output before the removal of oedema is even complete. In them the sequence of events is reversed if they are allowed to retain some excess fluid, as also is the case when circulatory deterioration is associated with a fall in serum level of sodium. It seems very probable that this is secondary to the circulatory impairment and is not the cause of the immediate deterioration. Their improvement when allowed to retain some oedema and the rise in serum sodium is likely to be due to the coincident increase of plasma volume and improvement in cardiac output. It seems very probable that they would be better treated with a transfusion of packed cells or of salt-free albumin. *It is regrettable that both this clinical sequence and hyponatraemia have been linked with terms such as 'low salt syndrome,'⁸⁸ 'electrolyte depletion'¹⁰⁰ and 'salt depletion'⁹ with their definite and at times misleading causal implications.*

No more can be said of the therapeutic implications of a low serum level of sodium until its possible causes have been discussed.

Causal Significance

Much that is confused or even meaningless has been written about hyponatraemia. A fall in the level of sodium implies either loss of sodium from, or gain of water by, the extracellular fluids but not necessarily a change in the total amounts in the body of either, although of course there may be. Thus sodium could shift into cells or bone matrix, and water might be gained from

cells. Alternatively sodium could be lost from the body in sweat or urine, whilst water could be gained from the dietary intake.

When these various possibilities are examined more closely, it becomes obvious that each can arise in several ways. Thus *loss of sodium to cells* could follow:

- (1) A lack of potassium in cells.
- (2) An impairment of the mechanism ('sodium pump') whereby sodium is extruded from cells as fast as it normally enters.
- (3) Alteration of the permeability characteristics of cell membranes leading to a greater entry of sodium than normal, overwhelming the 'sodium pump.'

An increase in the sodium within cells has been shown and, as will shortly be mentioned, there is evidence of a cellular deficiency of potassium in congestive heart failure. Evidence will be presented elsewhere which suggests that at any rate in muscle either the 'sodium pump' is impaired or else the permeability characteristics of cell membranes are altered, *in patients in a severe episode*.³³ Anoxia has been shown *in vitro* to cause these two changes,^{15, 54, 82, 107} but there is other conflicting evidence. Thus acutely, *in vivo*, it causes not a fall but a rise in serum sodium⁴ and *chronic exposure* to low oxygen tension leads, in rats, to an *increase* in tissue potassium.⁵¹ The possibility that adrenal cortical hormones may affect permeability characteristics or the 'sodium pump' is raised by work on yeast cells and erythrocytes,^{15, 108} changes following adrenalectomy¹⁹ and the effect of cortisone in patients with low sodium levels following operations.³⁹ It has been suggested that there may be an excess of aldosterone, and a dearth of glucocorticoids in congestive heart failure has also been considered. Again cardiac glycosides have been shown to affect influx and efflux rates to and from cells.¹⁰⁸

The simplest way in which a *loss of sodium from the body can arise* is from profuse sweating with replacement of water and only partial replacement of sodium loss. This can occur in congestive heart failure,³⁴ but it is rare. An increase in urinary sodium loss might follow a fall in cellular osmotic pressure thus lowering the osmotic pressure of extracellular fluids and so maintaining osmotic equality in the two fluids. A fall in the osmotic pressure of cell fluids could arise in many ways, among them:

- (1) An enhanced permeability of cell membranes leading to a loss from cells of solutes, which normally are unable to diffuse through the membranes. If these solutes have a greater number of negative than positive charges, then some potassium too will leave cells.

FIG. 5.—Hyponatraemia and serum albumin. Admission sodium levels and the lowest obtained during an episode of congestive heart failure, plotted against serum albumin levels.

- (2) Metabolic change leading to a decrease in the number of organic molecules within the cells, e.g. polymerisation.
- (3) Inactivation of some cell cations, through binding.

How these circumstances might arise is another matter; tissue anoxia and/or hormonal factors might be implicated. Moreover where the fall in intracellular osmotic pressure takes place insidiously, the secondary urinary loss of sodium would be difficult to document; where the fall is acute we have observed such losses.

An increased loss of sodium in urine could also be due to a primary change in renal function and it has often been loosely suggested that mercurial diuretics might lead to such a loss of sodium unaccompanied by water and so produce a fall in extracellular sodium concentration, but evidence for this is inconclusive.

A *gain of water from cells* might follow a fall in the osmotic pressure of cell fluids, and ways in which such a fall might arise have been outlined already. Conceivably it might follow a 'shrinking' of cellular 'scaffolding' were such to occur. It might also follow destruction of some cells. Undernutrition can realise both of these possibilities and undernutrition is a prominent feature of congestive heart failure.⁶⁹ It has indeed been suggested that undernutrition will cause a hyponatraemia,^{21, 65, 69} although this has not been confirmed in rats.^{22, 45} It is, of course, difficult to assess this point without a rigorous definition of undernutrition; there may well have been differences in the patients and animals considered under this heading.

At any rate, using the serum albumin as an index of 'undernutrition' in congestive heart failure, the extent of hyponatraemia appeared unrelated to it (Fig. 5).

A greatly enhanced water intake has been shown to cause a *gain of water by the body* post-operatively. However, even that intake advocated by Schemm (1. per day) did not lead to dilution of body fluids; indeed, serum chloride often rose.⁸⁴⁻⁸⁶ An enhanced production of anti-diuretic hormone (ADH) or an inhibition of the osmoreceptor-ADH mechanism would result in a greater gain of water than sodium.

It has been suggested that the therapeutically induced loss of sodium and water from the body, by causing a lowering of some part (blood volume) of the whole of the extracellular fluids, promotes further retention of salt and water to effect expansion. If the intake of sodium is limited, it is suggested that the 'ADH mechanism' is over-arranged, or that more ADH is produced resulting in a retention of water which is sufficient to effect a significant dilution of all of the body fluids. Observed weight gains, however, are rarely as much as would be anticipated on such a basis, but it must be allowed that the discrepancy could be due to a loss of fat from the body simultaneously. Evidence has been presented that cellular water may at times be increased in congestive heart failure,^{2, 12, 57, 66, 94} but it cannot be regarded as conclusive.²⁴

We have already referred to instances where the blood volume may be lowered. It has been suggested that where peripheral circulation is already poor, an induced diuresis will be effected solely or predominantly at the expense of the plasma volume. However, convincing evidence of such functional sequestration of oedematous regions of the body is lacking. *These various possibilities are however not commonly realised.* Moreover, the lowering of the sodium in these patients may well be secondary to deterioration accompanying a fall in cardiac output rather than to retention of water induced by the fall in blood volume. Certainly a fall in serum sodium can accompany clinical deterioration from many causes. This has been noted also by Weston *et al.*¹⁰⁶ But these workers have attributed the fall which accompanies deterioration to this single cause—a greater retention of water than sodium. Their data are not convincing however; and moreover, it is hard to believe that all deterioration is followed by a greater retention of water than sodium, *for often a diet containing a normal amount of sodium is being consumed.* Certainly the body weight does not always rise under these circumstances as would be expected.

Whatever the cause of a lowered level of sodium in the extracellular fluids, its persistence implies that processes, which in health intervene to raise it, are not doing so.^{54a}

In the absence of hyperlipaemia or hyperglycaemia, the lowering of sodium implies a lowering of the osmotic pressure of extracellular fluid, and so far as we know at present, a lowering of the osmotic pressure of cell fluid. Correction of the lowering of sodium requires either loss of water from the body or a gain of sodium and potassium. This latter is needed to increase the osmotic pressure of cell fluids which otherwise must be effected at the expense of a significant lowering of their volume. The studies of McCance first showed that ingestion of water does not effect the usual diuresis where extracellular fluid volume is sufficiently low, and the poor or absent diuretic response to water, by patients in congestive heart failure with hyponatraemia³⁶ suggests that in them too the osmoreceptor-ADH mechanism is deranged. It may be that the stimulus responsible for oedema formation is also responsible for this failure. But, of course, other factors might be responsible. For example, a water diuresis besides increasing the concentration of sodium and lowering the volume of extracellular fluids would also lower the volume of cell fluids, and *this may be prohibitive.*

When sodium is given by mouth or parenterally and retained, it repeatedly fails to effect a permanent rise in the serum level, which suggests that the mechanism for volume expansion is not dominant; or else that the sodium has entered cells. A permanent rise in extracellular sodium concentration would demand a parallel increase in the osmotic pressure of cell fluids. The failure of this response would therefore be attributable to an inability to effect such an increase in intracellular osmotic pressure. This might betoken a 'reluctance' to lower the volume of intracellular fluids, or might be attributable to an inability of the kidneys to retain potassium, or it might mean that an increase in solutes other than potassium is needed to raise the osmotic pressure of cell fluids and that this was not realizable.

It is perhaps worth noting that although in these patients the ADH mechanism is faulty or 'set' to maintain a new steady-state level of osmotic pressure, no benefit results from restricting fluids; for the fault is responsible only for the *persistence* of hyponatraemia; fluid restriction cannot promote the loss of water and, in these patients, retention of sodium is accompanied by a gain of water, not a rise in the level of sodium.

It will be clear that it is important to define the mechanisms involved in the lowering of serum sodium before treatment can be directed at the hyponatraemia. At present, however, it is difficult or impossible to differentiate between possible causes or to assess their relative con-

tribution, so that treatment is not usually directed at the hyponatraemia unless it is very marked. Then it is usually associated with a failure to respond to the usual treatment and in view of the therapeutic urgency in severely ill patients, quite reasonably, various additional therapeutic measures are tried, although the mechanisms involved in the hyponatraemia are not known.

Potassium salts may be given in view of the possibility that a cellular shortage of potassium causes a gain of sodium. Laragh⁵³ reported an increase in serum sodium following this measure which we have confirmed in studies in 125 patients.³¹ However, this increase, although significant, may not be so great and some degree of hyponatraemia may persist. Moreover, extreme degrees of hyponatraemia are usually not improved.

Alcohol has been tried with some success^{52, 70} in an attempt to depress the production and release of antidiuretic hormone. Experience with its use is, however, limited at present and we have also seen instances of a worsening of hyponatraemia whilst alcohol was being taken.

Urea has been advocated as an osmotic diuretic on the grounds that it may cause loss of water unaccompanied by sodium and hence a lessening of the hyponatraemia.⁶ We have found it to be successful at times and, similarly, it was found useful to allow a considerable glycosuria in a patient with diabetes mellitus in addition to congestive heart failure.

Steroids (cortisone, hydrocortisone, prednisolone) and ACTH have been used in such circumstances and they are undoubtedly at times valuable.^{12, 13, 18, 41, 42, 73, 81, 87} It has been our experience, however, that even when successful, hyponatraemia does not always regress; moreover they may be effective therapeutically in the absence of hyponatraemia. Many grounds for their use have been propounded (replacement therapy, promotion of 'free water clearance,' inhibition of aldosterone production) but none established.

The non-specific adrenal inhibitor, *amphenone*, has been tried but has unpleasant side effects^{80, 98, 112} and more recently *specific anti-aldosterone compounds, spiro lactones*, have been used.^{55, 56, 91} Undoubtedly these latter compounds can be useful but again in our experience hyponatraemia does not always regress.

We have found¹⁰ that 50g. glucose three times a day, preceded by insulin (10 units soluble) is at times followed by rapid improvement and it is interesting to note that Macchioro had reported favourably on the value of sugar combined with insulin in states of cardiac insufficiency in 1931.⁵⁸ How this measure takes effect is conjectural. It may be noted that glucose and insulin are both known

to increase the number of non-diffusible organic phosphate compounds within cells which attract more potassium into cells. Insulin may affect the permeability characteristics of cell membrane⁷ and alter the membrane potential of muscle cells.¹¹³⁻¹¹⁸

The practice of discontinuing diuretics and low salt diets, of supplementing the dietary intake of sodium and even of giving hypertonic saline intravenously has already been referred to. Usually it is ineffective; and supplements of salt, particularly intravenously, can be disastrous.

Of course successful response to any of the measures outlined, with regression of the hyponatraemia, is not proof that the appropriate mechanism was in fact responsible for the lowered levels of sodium; a rise in sodium may be secondary to general improvement, for these measures may be useful therapeutically in patients responding poorly or not at all to treatment and in whom hyponatraemia is not present. Again, none is always successful in effecting a rise in the level of sodium; this we feel is further suggestive support for the diversity of origin of hyponatraemia.

It is appropriate to ask whether a low sodium level, however induced, or the general lowering of osmotic pressure of body fluids that it implies, can cause further deterioration. Claude Bernard alerted us to the importance of the regulation of the internal environment. But the hag fish¹ and some euryhaline fishes (salmon, eel) tolerate considerable variations in osmotic pressure of their body fluids.¹⁰¹ Whether a fall in the osmotic pressure of body fluids *per se* affects the functioning of tissues in man is uncertain, one suspects that it may depend on the cause of the fall. For as Elkinton has put it, many patients exist quite 'comfortably adjusted to their state of hypotonic sin.'²⁰ There is, however, some evidence that a lowering of the level of sodium may impair function of heart and kidney.²⁰ On the other hand McDowell and colleagues have shown that lowering the sodium level of the perfusing fluid improves contractile efficiency of isolated rat ventricles or diaphragm subjected to periods of anoxia^{43, 61 62} and have suggested that this may be because a low level of sodium in the extracellular fluids diminishes the work of the sodium pump of cells. No clear answer therefore can be given at present to our question; it is probably conditional on the cause of the fall in sodium level, and also the speed of onset.

It would seem then that what was said earlier, before possible causes of hyponatraemia were discussed, is perhaps the safest generalization that can be made. Where there is hyponatraemia, and oedema is clinically evident, measures directed at effecting removal of oedema fluid should be

FIG. 6.—Serum levels of sodium, and the levels of chloride obtaining on the same days, in patients in congestive heart failure with oedema. Two groups of patients are presented; one receiving mercurial diuretics and one consisting of patients who have never had any diuretics. Each group is subdivided into those receiving supplements of chloride and who have had at least 1 g. ammonium chloride three times a day for 10 or more days, and those who have not had supplements of chloride.

The shaded bands enclose the 95% confidence limits for serum levels of sodium and chloride in 157 healthy individuals. The oblique continuous line is the average ratio of serum sodium to chloride in these 157 individuals; the dotted lines are two standard deviations above and below this ratio.

persisted in, unless there is evidence that this is further impairing circulation.

Hypochloraemia

It has already been mentioned that chloride is usually lowered proportionately with sodium (Fig. 6). In consequence the same significance attaches to the lowering of both levels. It has also been mentioned that mercurial diuretics often cause a greater loss of chloride than sodium in

urine and yet may not induce disproportionate lowering of serum concentration of chloride. Balances between gains and losses of both sodium and chloride drawn up during recovery from congestive heart failure, and which show greater losses of chloride than sodium without either a fall in serum chloride or a rise in serum sodium have been reported by several groups.^{32, 46, 48, 59,}

What is the explanation of the enigma?

It is submitted that the extra chloride has been mobilized from cells, and evidence from several lines suggests that the amount of chloride inside cells is increased. Burch and his colleagues present evidence from studies with the isotope ³⁶Cl.^{79, 99} Chloride space in the same muscle obtained by biopsy was considerably greater than inulin space in the same muscle and indirect evidence that intracellular chloride was abnormally raised was also derived from theoretical considerations of the relation between the total exchangeable mass of potassium and the product of the concentration of potassium and chloride in extracellular water.³² This evidence of an increase in cellular chloride is in keeping with evidence from *in vitro* studies which show that chloride enters cells where tissues are subjected to anoxia^{15, 54} and with evidence of an increase in cell chloride in ischaemic heart muscle.¹⁰⁴ There is also evidence that under other circumstances the amount of chloride present in cells can increase.^{1, 19, 60}

It is a corollary of this view that the action of mercurial diuretics in effecting a greater loss of chloride than sodium must be non-specific, and indeed this is so, for it may be encountered when other diuretics are used or when a natural diuresis occurs (Fig. 7). Moreover, diuretics do not always cause a greater loss of chloride than sodium. This suggests that perhaps the increase in cellular chloride is not always greater than the increase in cellular sodium and on theoretical grounds one might expect cellular chloride at times to be equal to or less than sodium.³³

In view of this infrequency of hypochloraemia alkalosis is it then wise to give supplements of ammonium chloride routinely with mercurial diuretics? The danger of inducing a hyperchloraemia is perhaps not so great, for when supplements are given the urinary losses of chloride increase still further (Fig. 8) (see also Fig. 6). But ammonium chloride solutions are unpleasant and may induce nausea or vomiting or at least further impair appetite. Moreover, in cirrhotic patients ammonium chloride may precipitate hepatic coma—a possibility worthy of consideration in severe congestive heart failure too, for in such cases the so-called 'liver flap' may be met and the electro-encephalographic changes as-

FIG. 7.—Daily losses of sodium and chloride in patients recovering from congestive heart failure. All were at rest in bed and were having digitalis. In addition one group was receiving injections of a mercurial diuretic, one chlorothiazide and one FT 9 (hydroflumethiazide). None was having supplements of chloride. The continuous oblique line, in all, is the average ratio of serum sodium to chloride (from 157 healthy individuals, reference 29) and the dotted lines are two standard deviations above and below this average.

FIG. 8.—Daily losses of sodium and chloride in a group of patients given mercurial diuretics and also having supplements of chloride. The shaded band indicates the excretion found in the similar group (Fig. 7) not having such supplements.

FIG. 9.—This figure presents the highest serum levels of potassium in 397 episodes of congestive heart failure with oedema. The episodes have been grouped by known duration of a failing heart, by grade of failure and by speed of response to treatment. The shaded bands enclose the 95% confidence limits for serum potassium obtaining in 157 healthy individuals.

associated with hepatic coma or pre-coma. Comfort may perhaps be drawn from the reflection that ammonium chloride is often given as enteric coated tablets and it has been found that many of these are not absorbed.

Significance of Hyperkalaemia Clinical Significance

Raised serum levels of potassium were found in about one-third of our patients²⁹ and were common in two other series.^{47, 95}

In our series the highest levels were most

FIG. 10.—Impact on immediate mortality of an increase in serum potassium. This has been considered separately, in the left-hand diagram, for patients whose lowest serum sodium levels were from 135-132 mEq/l, 131-126 mEq/l and 125-121 mEq/l. The potassium levels considered are those obtaining on the day of the lowest serum sodium. The heavy line presents the mortality obtaining for the combined group of patients (serum Na 135-121 mEq/l).

The right-hand diagram presents this line and for contrast the mortality obtaining for the group of patients whose lowest serum sodium level was 120 mEq/l or less.

commonly encountered in patients responding less quickly to treatment, although high levels were found in all groups (Fig. 9). There was no obvious relation either to grade of failure or to the known duration of a failing heart and it is our impression that raised levels of potassium reflect the severity of the patient's condition.

Thus while serum potassium usually falls with clinical improvement it remains high or rises preterminally, and there is a good correspondence between the ranking of the levels of potassium in two successive admissions and that of the severity of the episodes.²⁹ Moreover, prognosis correlated well with the level of potassium; the higher the level, the greater the likelihood of a fatal outcome. This is not just the other side of the sodium penny for this relation is still seen among patients grouped according to the level of sodium; to have a raised level of potassium as well as a low sodium is worse than to have a low sodium level only (Fig. 10).

Therapeutic and Causal Significance

It is our impression that raised potassium levels are not attributable to treatment with diuretics for they are met in patients who have not been given any. Raised levels do not imply that cells and tissues are in a state of satiety; in fact there may be a dearth of potassium (Fig. 11). This paradox of excess amidst dearth again emphasises the unreliability of serum levels as indices of body potassium content. Moreover, raised serum levels should not preclude the giving of supplements of potas-

FIG. 11.—Serum levels of potassium and total exchangeable mass of potassium in patients with congestive heart failure.

sium, for they are not the result of an impaired ability to excrete potassium in the urine, as urinary losses may be above normal. It has been our experience that supplements may safely be given; indeed, serum levels have fallen whilst supplements were given.³¹

It is possible that raised levels of potassium are a consequence of an altered handling of sodium and potassium by cells, and it has been suggested that they may facilitate the functioning of the sodium pump.¹⁰⁹

Dearth of Potassium

The dearth of potassium so often found may be due to a loss of lean tissue, a loss of potassium from cells or both. In the first instance the remaining tissues would not be short of potassium.

In practice the two causes are not distinct as a cellular deficiency of potassium often induces a secondary loss of lean tissue. Again, as lean tissue is restored, potassium requirements are increased and if not met in the diet, potassium will be taken from other tissues on the principle of robbing Peter to pay Paul. This will lead to some overall cell shortage.

There is good evidence that the dearth of potassium in congestive heart failure is not solely due to loss of lean tissue; it is part of a true cellular deficit. Thus during recovery potassium is retained in excess of that 'required' for the tissue restoration made possible by nitrogen retention; studies of muscle composition based on biopsy material have indicated a cellular deficit and the lowering of body potassium is more than calculated loss of lean tissue would entail.²⁸ However, not all tissues or indeed all muscles need share in the depletion. It is convenient to group the causes of such a deficit under the headings of simple and complex.

Simple. Here the cells may be thought of as parting 'reluctantly' with potassium, as losses

from the body exceed gains and one may note that intake in congestive heart failure is often low.

Losses are enhanced by diuretics and may be an indirect consequence of sodium retention since the anions produced by metabolism demand cationic accompaniment in the urine.

Complex. Here the cell's metabolism is so impaired that a gain of sodium and loss of potassium results. The potassium so lost will mostly be excreted in urine. This possibility has already been considered as a cause of the low sodium serum levels.

Then again potassium may be evicted as it were by hormonal action; an increased production and release of aldosterone might be expected to have such an action. However, it has been reported that whereas aldosterone (or deoxycortone) when given to patients in congestive heart failure with oedema causes further retention of sodium, it does not promote a loss of potassium.

Implications for Treatment

Whatever its cause potassium deficiency leads to impaired functioning of cells and complications. It may even predispose to or actually cause cardiac arrhythmias and certainly a lower toxic threshold of digitalis. Every effort therefore should be made to achieve an adequate intake of potassium. Where the cause is complex this may not result in repletion, which is dependent upon an improvement in cell function in turn dependent upon increased circulatory efficiency. Here what is wanted is a cell tonic—unfortunately one has not yet been found but digitalis and bed rest are good *cardiac* tonics and help indirectly.

The balance of evidence is in favour of complex causes being foremost, particularly in those patients with a high serum level, and it is not possible always to avoid potassium depletion by the routine use of supplements as has sometimes been claimed.⁶⁷ However, supplements should be given, for the simple causes still operate and if not countered will surely complicate the issue.

It has been the experience of all, that supplementing the dietary intake is difficult; all potassium salts induce some degree of epigastric discomfort, nausea or even vomiting. We have found that gastric irritation is lessened if the salts are given in a solution of 10 or 50 per cent. glycerine and that potassium glutamate is often tolerated where others are not. This may possess other advantages too for glutamic acid has been found to enhance potassium intake of tissues *in vitro*^{97, 98} and to be preferable to many other salts when given to digitalis intoxicated dogs.¹¹⁰

Summarizing, we may say that a central feature of congestive heart failure is an abnormality of volume regulation, leading to the accumulation of

FIG. 12.—Serum levels of sodium and potassium in patients admitted in three or more episodes of congestive heart failure with oedema. Values have been plotted twice; once ignoring the time interval between admissions and again taking this into account.

alt and water in the extracellular fluids, including the plasma. Retention of sodium is primary; water secondary. It is possible that intracellular fluids are sometimes increased. Initially this retention is probably homeostatic, but with progressive retention it ceases to be so. The transition usually reached just before oedema is clinically apparent. It follows that oedema should be expelled and kept at bay. This may be achieved directly by increasing the circulatory efficiency with cardiac glycosides and rest, or directly by promoting loss of sodium with diuretics and inhibiting or limiting retention of sodium by giving corticosterone antagonists or a diet containing very little sodium. It is important that attempts to get rid of oedema should not be pursued beyond the point where further loss of fluid will undo the homeostatic value achieved. It is usually best for the patient to mobilize all the oedema; sometimes, however, some must be permitted or else circulatory efficiency is embarrassed.

The heedless pursuit of diuresis will result in circulatory collapse, *but the level of sodium in the serum must not be used as a yardstick.*

There is a dearth of potassium in congestive heart failure, to which there are two components. Firstly, a loss of lean tissue; secondly, a loss of potassium from cells over and above that accompanying the shrinkage of cells underlying lean tissue loss. That lean tissue and fat are lost from the body in progressive heart failure is clinically very obvious. Quantitative evidence of the loss of body weight involved can be derived from consideration of the body weight over a period of years⁷⁴ and also from consideration of the simultaneous total exchangeable masses of sodium and potassium.²⁸

At present one cannot give the cause of this cardiac cachexia; one wonders whether tissue anoxia plays any role and whether cellular potassium deficiency is a factor. Undoubtedly appetite is impaired and the consumption of food lessened in consequence; this must contribute.

Similarly, several factors may be involved in potassium deficiency, some of which cause a drain of potassium from 'reluctant' cells; others impair the cell's ability preferentially to retain potassium, whilst others may evict potassium from cells.

It follows that every attempt should be made to achieve a good diet. At times this consideration may conflict with the need for a low sodium diet, which is less palatable. Further difficulty may be met because of the need for potassium supplements, as these cause gastric irritation. These supplements may not be successful in promoting repletion, but to allow further deficiency by default is surely reprehensible.

Extracellular fluid may be of normal composition in congestive heart failure. However, in severe episodes this is not so and with successive episodes it is even less likely (Fig. 12). *Paradoxically the concentrations of sodium and chloride are often low and again paradoxically that of potassium may be raised.* It follows that the serum levels are misleading as indices of body or cellular content.

The possible causes of low sodium level are many and more than one may occur in individual patients.

Certainly hyponatraemia does not imply a deficit of sodium, nor necessarily that measures to remove oedema have been indulged in excessively. *In the absence of circulatory collapse the measures should be continued.*

Undoubtedly hyponatraemia is a gloomy sign, but it is not certain whether it should provoke any direct therapeutic response. It has been suggested that a low sodium level facilitates the 'sodium pump.' Certainly none of the therapeutic efforts so far made are uniformly successful. Nonetheless, most of them appear to have some value, whether or not by affecting the hyponatraemia is not clear.

The raised levels of potassium are not due to poor kidney function, nor to cellular satiety with potassium. They are not, therefore, a contra-indication to giving potassium salts. Possibly they reflect altered equilibria across cell membranes and may also facilitate the working of the 'sodium pump.' Indeed, the question of raising potassium levels therapeutically has been seriously considered.

The composition of intracellular fluids may also be abnormal. Thus there may be an increase in the concentrations and amounts of both chloride and sodium in cells.

This, too, could arise in more than one way, but it seems likely that in part it may be due to either a change in cell membranes with enhanced sodium and chloride influx 'overwhelming' the sodium pump or to its direct impairment.

Subtle interrelationships exist between the processes underlying these abnormalities in congestive heart failure. But none appears to be direct or obvious and many of the abnormalities can occur independently. Thus

- (1) There is no relationship between the extents of the dearth of potassium and excess of sodium.
- (2) An increase in cell sodium may be present without a cellular deficit of potassium.
- (3) The amount of sodium in cells may fall with recovery from congestive heart failure, whilst lean tissue remains low.
- (4) Lean tissue may have been lost without an increase in the amount of sodium in cells.
- (5) Serum sodium may be low without there being a raised serum level of potassium.

Moreover, most of the abnormalities can appear in the absence of any gross abnormality of volume regulation, for instance, in 'left ventricular failure.'

The causal meshwork needs much unravelling and relationships to the circulatory patterns of progressive so-called 'left, right or total heart failure' should be sought.

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