The Distribution of Body Fluids In Congestive Heart Failure

I. Theoretic Considerations

By J. R. Elkinton, M.D., and R. D. Squires, M.D.

The pathogenesis of congestive heart failure is discussed. Experimental evidence is cited to support the thesis that abnormalities in the distribution of body fluids may affect circulatory and renal function, and hence may be a cause as well as an effect in the complex sequence of events leading to the congestive state. Emphasis is placed upon alterations in cellular metabolism which may lead to such disturbances in body fluids and so through various mechanisms, cellular, humoral, and circulatory, may modify the volume regulation of the body.

During the past few years the clinical entity, congestive heart failure, has been subjected to a great deal of physiologic reinterpretation. This reinterpretation has been due for the most part to the development of new techniques for the study of circulatory dynamics, of renal dynamics, and of transfers of body water and electrolytes. It is now appreciated that this syndrome is one involving a complex series of events often occurring over a considerable period of time between the initiating factors and the final condition of venous congestion and edema of many tissues. Indeed, the lack of correlation between immediate and measurable abnormalities of cardiac function and the congestive state have led some writers to challenge the importance of the factor of "cardiac damage" and to speak of the state as "congestive circulatory failure" or simple "congestive failure." Nevertheless, as Starr points out, "congestive failure occurs with great frequency in persons with damaged hearts," and this fact strongly supports the conclusion that disease of the heart is either an initiating factor, or at least an important contributory factor, in the etiology of this syndrome. Our problem, therefore, is the elucidation of the events which lead from cardiovascular dysfunction on one hand to the edematous state on the other.

From new data many investigators have emphasized especially the role of the kidney in the development of congestive failure, and impaired glomerular filtration has been considered by some to be the principal renal abnormality. Yet much evidence points as well to abnormal function of the kidney tubules, and this in turn suggests the possible involvement of the several endocrine glands which normally share in the regulation of renal tubular transfers of salt and water. The problem, therefore, devolves in part on ascertaining how the kidney operates in the regulation of the fluid balance of the body and how this regulation is disturbed in the condition of congestive failure.

Evidence is accumulating from the study of normal organisms that variations in the volume and composition of fluids in tissues other than the heart or kidney affect the fluid balance of the body. Intake (thirst and appetite) and renal output of water and electrolytes are so adjusted to each other that the volume of body fluids is maintained in a steady state. The means by which changes in the water and solute content of various tissues help to effect this homeostatic control of total body fluid volume are essentially unknown. Yet such knowledge would appear to be of paramount importance to the study of congestive failure. Furthermore, it is now recognized that the differential distribution...
of solutes, and therefore of water, between cells and their surrounding mediums, are maintained by energy derived from metabolic processes within the cells. Any role which may be played by the state of fluid distribution in particular tissues, or in tissues in general, in the fluid balance of the body, is inevitably linked to reactions which take place in the intracellular phase.

For these reasons it seemed advisable, in undertaking an investigation of the distribution of body fluids in congestive failure, to consider in the light of present experimental evidence the various relationships which may obtain between the circulation, the kidney, and the fluid content of other tissues, especially as related to cellular metabolism. Such theoretic consideration is undertaken in the hope that it might place in proper perspective the role of abnormal fluid distribution as a cause as well as an effect in the chain of events leading to the accumulation of edema.

The discussion of this complex problem is perhaps best accomplished by considering the evidence bearing on the following four questions: (1) What are the abnormalities of body fluid distribution in congestive failure which are due to (a) the disease itself, or (b) attempted therapy (for example, mercurials)? (2) To what extent are these abnormalities in congestive failure due (a) to changes in circulatory dynamics directly, (b) to changes in renal function, (c) to modifications of cellular metabolism? (3) Do these abnormalities in body fluid distribution in turn affect (a) circulatory function, (b) renal function? (4) If so, in what ways? Although the experimental evidence bearing on these questions is fragmentary, it is extensive enough to justify the opinion that, in addition to circulatory and renal dynamics, factors of cellular metabolism and tissue fluid distribution must be considered in the pathogenesis of congestive heart failure.

In view of these questions certain observations were made on patients with heart disease and edema. These observations are reported in the succeeding papers. The data which are presented by no means provide the answers, but they do again emphasize that the questions outlined above are pertinent to the problem of congestive failure.

**Distribution of Body Fluids in Congestive Failure**

*Expansion of the extracellular fluid is the predominant abnormality.* The edema of cardiac failure has usually been considered to be an isotonic expansion of extracellular fluid (fig. 1A). Evidence for this rested upon the observation that the products of diuresis are mostly water, sodium, and chloride in the same relative proportions as in extracellular fluid. Various deviations from this simple pattern have been reported. It has been reported that in congestive failure sodium is retained by the kidneys to a greater degree than is chloride; if the disparity in clearances of these two ions is not due to the simultaneous administration of ammonium chloride, an increase in the extracellular concentration of bicarbonate should ensue. Indeed, many patients with congestive failure have been found to have an elevated concentration of serum bicarbonate, indicating that some type of disturbance in acid-base equilibrium occurs in relation to the disease or to its treatment. If more sodium were reabsorbed in order to retain water as part of the dehydration reaction, as suggested by Peters, the concentration of sodium in serum and extracellular water should tend toward or beyond the upper limits of normal, depending on the relative rates of water ingestion and
sodium reabsorption. Conversely, if water is retained in excess of sodium, the serum and extracellular sodium concentration should be depressed. Hyponatremia has been reported or implied from the existence of hypochloremia in congestive failure, but such hyponatremia (and hypochloremia) are almost always observed to follow prolonged courses of treatment with mercurial diuretics. Since water shifts across cell membrane when the sodium concentration is changed in extracellular fluid in normal subjects, such a phenomenon immediately implicates the intracellular phase in the fluid abnormality of edema at least under certain circumstances of therapy (figs. 1B and 1C).

**Intracellular content of water and of certain electrolytes may also be abnormal.** Disturbances in intracellular fluid have been found in many disease states, including water deprivation and dehydration, starvation, gastrointestinal fluid loss, metabolic alkalosis, acidosis due to diabetic coma and renal insufficiency, and in diseases involving hypo- and hyperfunction of the adrenal cortex. In most of these states the fluid abnormalities described have been depletion or excess of intracellular sodium and intracellular potassium. In considering intracellular fluid disturbances, other components in addition to these must be taken into account. With present methods of study it should be possible to describe changes in the following: (1) transfers of water across the cell boundary according to the dictates of variations in the effective osmolar concentrations in the two phases, (2) transfers of potassium into and out of cells, (3) transfers of sodium into and out of cells, (4) transfers into and out of cells of other anions, particularly phosphate and possibly chloride, and (5) changes in osmotic activity of solutes within the cells (fig. 2). Abnormal transfers of some of these constituents have been described in congestive failure. Newman and co-workers found that potassium was retained in excess of nitrogen in a number of cardiac patients during diuresis of edema fluid. Fox and co-workers have reported the occurrence of diuresis following the administration of hypertonic solutions of sodium and potassium and have postulated that in congestive failure there is a hypotonic overhydration of the intracellular phases. Other workers have also described the uptake of potassium in cardaces, but more complete information has yet to be obtained concerning abnormalities in the major fluid constituents of the intracellular phase in patients with congestive heart failure.

**There are regional differences in fluid distribution in congestive failure.** This statement needs no further support than the common observation that the edema is usually greater in the dependent portions of the body. This disparity of distribution presumably is due to the effect of gravity on the hydrostatic pressure in veins and capillaries in these regions, although other factors such as local anoxia may play a role.

![Fig. 2. Diagram of transfers of certain constituents of the body fluids between cells, extracellular fluid and environment. Arrows between the several phases indicate only the directions of movement of the individual constituent; no quantitation of rate or magnitude of transfer, or of concentration, is implied. The cross-hatched area on the right represents fractions of intracellular solute that are osmotically inactive and as such may be considered to be transferred out of the aqueous phase of cellular fluid.](http://circ.ahajournals.org/)

**In summary,** from this brief review it appears that the evidence in regard to the first question may be stated as follows. The common fluid abnormality in congestive failure is retention of extracellular electrolytes and water. Intracellular disturbances in respect to volume of water are suggested by the occurrence of an abnormally low electrolyte concentration (hyponatremia) but this phenomenon is probably the result of therapy rather than of the congestive failure per se. Intracellular disturbances in content of electrolytes, especially potassium, have been documented, but the relationship of these abnormalities to the disease or to the state of nutrition has not been established. Finally, abnormalities in the regional distribution of body fluids are present in this condition.
Given these disturbances of body fluid distribution in congestive heart failure, we turn to the second question, namely, how are they initiated by cardiovascular and renal dysfunction.

**Circulatory and Renal Factors in Edema**

This discussion deals with the type of congestive failure which develops over a prolonged period of time in patients with heart disease. It is recognized that congestive failure may develop acutely: (1) in cardiac patients as a result of a sudden redistribution of fluids without an increase in total body weight, for example, acute pulmonary edema; and (2) in patients without heart disease who in various ways acquire abruptly a large increment of total body water and salt. However, we are concerned with the patient with a damaged heart who accumulates edema more slowly, that is, who over a protracted period has a total output that fails to equal the total intake of fluids. In some manner this must result from a functional impairment of the damaged heart.

"Backward failure" and "forward failure" have both been proposed to account for congestive heart failure. For many years the sequence of events as deduced from Starling's original hypothesis was held to describe adequately the development of edema. Essentially, this sequence was as follows: cardiac failure with diminished output, elevation of venous and capillary hydrostatic pressure, transudation of fluid from plasma to interstitial spaces causing edema, diminution of plasma volume, and reduction of sodium and water excretion by the kidney. In 1943 Starr and co-workers and subsequently Warren and Stead proposed another sequence of events: cardiac failure with diminished output, decreased renal blood flow and rate of glomerular filtration, decreased excretion of sodium and water, increased plasma volume, increased venous and capillary pressure, transudation and edema. This hypothesis rests in part on evidence that fall in cardiac output, expansion of blood volume, and the development of edema may precede the rise in venous pressure in congestive failure, and in part on the demonstration of changes in renal hemodynamics. However, Peters has questioned the validity of the evidence for high blood volumes in this condition. He points out that in any case Starling's theory in regard to the distribution of fluid across the capillary membrane must obtain and challenges the primary place of the renal dysfunction in the sequence of events. Thus, the role of the changes in renal hemodynamics is still the subject of considerable controversy.

Neither "backward failure" nor "forward failure" accounts for the lack of correlation between the output of the heart and the development of congestive failure. These two theories have been based on the assumption that an absolute diminution in cardiac output to below the average normal range is the critical impairment of function in the diseased heart. Yet signs and symptoms resembling congestive failure are known to occur in the presence of abnormally high levels of cardiac output, as in beriberi and thyrotoxicosis. Decompression and recompensation may occur in a patient with very little change in the level of cardiac output. For these reasons other factors would appear to be involved which relate the output of the heart to demands which the body places upon it.

Disparity between the output of the heart and the metabolic demands of the body may be the basic cause of the signs and symptoms of congestive heart failure, including edema. This concept, stated by Altschule, is suggested to explain the lack of correlation between the absolute level of cardiac output and the degree of congestive failure. Such a concept receives further support from the observation that recompensation of the failing heart can occur when an unchanged or falling cardiac output is associated with a lowering of the basal metabolic rate. This demand on the heart by the body can be stated in terms of oxygen requirement, although other metabolic factors conceivably may be involved. Evidence has been presented by Little of inverse correlations between the degree of congestive failure and the ratio of oxygen supply to oxygen consumption, and also between central venous pressure and mixed venous oxygen tension. Briggs and associates found that oxygen A-V differences decreased with recompensation. These observations sug-
gest that lack of oxygen (hypoxia) in one or more areas of the body is a next step in the sequence leading to congestive failure. Whether or not hypoxia may influence directly at the cellular level the retention of fluid in tissues (see below), it at least has an effect on the general and regional dynamics of the circulation. Regional changes in circulation are known to result when the blood volume and oxygen supply are inadequate for the entire body. These regional differences in circulation may influence the accumulation of edema in a variety of ways, as set forth in the last section of this paper. But diminished blood flow to the kidney with consequent impairment of glomerular filtration has been considered by the proponents of “forward failure” to be the major factor in the development of congestive failure.

Diminished glomerular filtration and a fixed rate of tubular reabsorption of sodium do not alone explain the retention of salt and water. The studies of Merrill, Mokotoff, Ross and Leiter, and others, have shown conclusively that renal blood flow and glomerular filtration are markedly reduced in many patients with congestive failure. Leiter and Wesson, Anslow and Smith have used these findings to support the hypothesis that a constant maximal rate of reabsorption of sodium obtains in the distal renal tubule and hence, when filtration of sodium diminishes, the excretion rate of the ion falls. This hypothesis is difficult to substantiate or refute since the amount of sodium rejected by the tubule and excreted is such a minute fraction of the amount filtered and reabsorbed that it falls well within the error of measurement of the latter. However, considerable evidence has accumulated that tubular transfers are likewise important in determining the abnormally low rate of sodium excretion in heart failure. In the patients studied by Merrill and Mokotoff and associates the correlation was very poor between excretion rate and filtration rate, and other workers have found that the excretion rate may vary considerably with the loss or gain of edema without much change in the rate of glomerular filtration. In normal subjects, when renal plasma flow has been varied independently of filtration, the excretion rate of sodium has been found to correlate more closely with the former than with the latter. It would appear, therefore, that abnormalities of renal tubular transfers are integral to the pathologic function of the kidney in edema.

Tubular transfers are abnormal in congestive failure and may be influenced by circulatory, humoral and cellular factors. The relationship of circulatory insufficiency to glomerular function in the kidney is much more easily understood than its relationship to that of the tubules. To what extent is there a direct effect of circulatory factors on the renal tubules and to what extent is there an indirect effect mediated through one or more endocrine glands? Hormonal regulation of such transfers in the normal kidney is well established. The antidiuretic hormone (ADH) of the posterior pituitary gland regulates water reabsorption, and at least one of the adrenal cortical steroids, closely resembling, if not identical with, desoxycorticosterone acetate (DCA), affects the reabsorption of sodium and potassium. Abnormal amounts of antidiuretic substance and of adrenal cortical steroids have been found in the urine of patients with congestive heart failure but it has not yet been shown conclusively that the failure of the kidney to excrete water or salt is mediated primarily through either of these hormones. A variety of circulatory factors have been investigated for their effects, direct or indirect, on renal tubular function in this condition. Renal venous hypertension has been shown experimentally by Blake and co-workers to result acutely in increased renal tubular reabsorption of sodium. The importance of the time factor in this phenomenon was emphasized by Hwang and associates who demonstrated that with prolongation of the renal venous hypertension over a period of a week or more, the rate of sodium excretion returned to control levels. Wilkins and colleagues have found a decreased excretion of sodium following venous congestion of the limbs. The observations of Blake and co-workers suggest a direct effect of renal circulation on the tubule, those of Wilkins and his associates suggest a humoral as well as a direct circulatory effect. Anoxia might logically be thought to be a factor but the experiments of
Berger and colleagues indicate that in the normal subject systemic anoxia accelerates rather than retards the excretion of sodium and water. However, these also were acute studies; protracted anoxia in certain cases has been associated with the accumulation of edema, which in turn was relieved by the administration of oxygen. In fact, both the degree and the duration of anoxia must be considered before a clear cut idea can be entertained as to its effect on sodium metabolism. Again, the immediate receptor of this stimulus may be in the kidney or elsewhere. Perhaps alterations in the fluids of various tissues are shared by the tubular cells of the kidney and so directly effect tubular transfers of electrolytes and water. Thus, despite the many possibilities which have been considered, one of the key questions remaining unanswered is how the kidney tubular cells know how to regulate their transfers of electrolytes and water in terms of the distribution of fluids in tissues at a distance, and how this process functions abnormally in the patient with congestive heart failure.

In summary, it is apparent that much remains to be learned concerning the relative roles of cardiac and renal dysfunction in congestive heart failure. The absolute level of cardiac output does not correlate with the degree of edema, and cannot explain it on either a “backward” or a “forward failure” theory. An output of the heart which is inadequate in relation to metabolic demands would appear to be a primary factor leading to secondary changes in circulatory dynamics in several regions of the body. Renal retention of salt and water results from more than a circulatory disturbance causing a diminished glomerular filtration; tubular transfers are involved and these are conditioned by humoral and cellular, as well as by circulatory, factors.

Effects of Abnormalities of Body Fluids on Circulatory and Renal Function

What are the properties of the body fluids and their component parts which effect their regulation by the kidney? It is perhaps stating the obvious to say that changes in the volume and composition of body fluids produce effects on renal function. Yet, as indicated above, little is known as to just how renal regulation of body fluid volume takes place. Wolf has recently reviewed this problem and points out that most of the emphasis in the past in investigation of renal function has been placed upon the regulation of concentration of solute rather than of volume of solvent. Clearly the regulation of body content of electrolytes is intimately tied up with that of water, but there is some evidence that such renal regulation is more than a function of concentration, ionic or total osmolar, in circulating plasma. Warren and Stead, Borst and Dock have related the renal regulation of body fluid volume to maintenance of an adequate cardiac output. Aside from the problem of how these two factors act upon one another, there are other difficulties involved in this concept which have been reviewed by Lewis and co-workers. These include the observation referred to above, that there may be no correlation between the level of cardiac output and the degree of edema in congestive failure, and that alterations of cardiac output in other conditions are not associated with corresponding changes in the renal excretion of water and electrolytes. Therefore, in addition to cardiac output, it is necessary to look for certain characteristics of the body fluids, such as regional composition and volume, which may influence their regulation by the kidney.

Cellular hydration, interstitial volume, and intracranial volume appear to condition the renal excretion of water and electrolytes. Under conditions of water deprivation and dehydration, sodium and chloride are increasingly reabsorbed by the renal tubule despite rising concentrations of these ions in the plasma. Peters has termed this the “dehydration reaction” and suggests that in congestive failure a similar stimulus mistakenly occurs. The precise nature of the stimulus is not apparent, although it may be related to a contraction of the effective circulatory volume; in any case it is certainly not the concentration of electrolytes in the extracellular fluid and plasma. Seldin and Tarair have shown in normal subjects that the increased excretion of sodium which occurs during certain types of osmotic diuresis occurs...
only following the injection of solutes which are essentially excluded from cells, such as free glucose and mannitol, and not following the injection of urea which is freely diffusible and does not cause cellular dehydration. These authors interpret these data to indicate that the excretion of sodium under these circumstances is conditioned not merely by the total osmolar concentration of solute in the tubular urine but also by the effects of the specific solute injected on cellular hydration of tissues elsewhere in the body. It should be pointed out that in these experiments expansion of extracellular fluid volume was an invariable accompaniment of the contraction of the intracellular fluid and hence may be a significant variable. Green and Farah,\textsuperscript{24} in experiments on the renal effects of sodium loading in dogs, have presented evidence that the rate of tubular rejection of this ion is more closely related to the rate of cellular dehydration produced by the load imposed, than to the concentration or absolute amount of sodium in the extracellular fluid. Welt and Orloff\textsuperscript{14} studied the effect on water and sodium excretion of variations in plasma volume, plasma colloid osmotic pressure, and interstitial fluid volume, as produced by injection of human albumin in various concentrations. They found that elevation of plasma volume without elevation of the colloid osmotic pressure led to an increased rate of excretion of water and possibly sodium, whereas a decrease in sodium excretion resulted from raising the colloid osmotic pressure as well. The data were interpreted to indicate that the renal excretion of water and sodium is influenced by not only plasma volume and colloid osmotic pressure but possibly also by interstitial fluid volume. Harrison and co-workers\textsuperscript{31} have found evidence that compression of the neck veins is associated with increased excretion of sodium by the kidney, indicating that some attribute, possibly volume, of the intracranial fluids may condition the renal excretion of electrolytes. The experimental manipulations in normal subjects, cited above, of Seldin and Tarail and of Welt and Orloff lead to different results in edematous patients.\textsuperscript{45, 46} This suggests that in the edematous state additional factors influence renal function. But, nevertheless, experimental evidence of this kind indicates that in some way, directly or indirectly, changes in the distribution of fluids in the body, including expansion of plasma and interstitial volumes and contraction of intracellular volume, effect changes in renal function.

Body fluid distribution and circulatory system are closely interrelated because of the role of the latter as the “mixing apparatus.” There is an interrelationship between body fluid distribution and circulatory dynamics as well as between the former and renal function. Primary changes in the circulation may induce secondary changes in the distribution of body fluids, and vice versa. This is best understood if one considers the multicompartmental character of the body fluids. It is an error to conceive of the extra- and intracellular fluids as single homogeneous solutions contained, so to speak, in a beaker (fig. \textsuperscript{1}4.1). The extra- and intracellular fluids are parts of many different tissues widely separated throughout the body, and are connected by extended lines of communication, the circulation (fig. 3). The circulation is the “mixing apparatus” and its efficiency determines the constancy of composition, or homogeneity, of the fluid phases (the extracellular directly and the intracellular indirectly). It is not surprising, therefore, that disturbances in circulatory function may lead to differences in composition and distribution of fluid in various parts of the body. It is, perhaps, less obvious, but nevertheless true, that disturbances in the composition and distribution of body fluids may affect the function of the circulation.

Primary changes in the circulation may cause secondary disturbances in the fluid content of tissues, for example, “prerenal deviation.” Changes in the circulation which affect fluid distribution are many and some may be enumerated. Increased venous pressure due to obstruction or gravity leads to local transudation of fluid from plasma to interstitial spaces.\textsuperscript{37} Diminished cardiac output, arterial occlusion, or peripheral vascular collapse may produce tissue anoxia and so disturb electrolyte equilibria which are maintained by oxidative reactions; for instance, potassium may leave and sodium enter cells.\textsuperscript{50–61} Under such circumstances cellular water may or may not be re-
leased, according to the dictates of the changes in the effective osmolar concentration of solutes in the two phases. Collapse of the circulation may result in the retention of water and solutes in the body because of the simple failure of transport of such substances to the organ of excretion. Borst and Wolf have inveighed against the validity of this concept of "pre-renal deviation." Wolf states that there is little evidence that all parts of the body fluids are not readily accessible to renal regulation. Yet in the instances just set forth it appears to the authors that the integrity of the circulation stands between the fluids of peripheral tissues and the action of the kidney upon them. Hence circulatory dysfunction may lead to "pre-renal deviation," at least in the sense that the time that is required for their regulation by the kid-

ney is greatly increased. Such a concept is easily understood by the clinician who observes, for instance, certain effects of transfusion on a patient in shock, such as absorption of subcutaneous pools of fluid (hypodermoclyses, for example), reestablishment of urinary flow, correction of acid-base disturbances (for instance, chloride acidosis) and excretion of accumulated metabolites.

Primary changes in the body fluids may affect the circulation; for example, sodium depletion causes diminution of cardiac output and renal blood flow. Changes in the body fluids which affect the circulation are also numerous and not completely understood. Obviously, alteration in the volume of that portion of the extracellular fluid contained within the vascular system, the plasma, is intimately related to circu-
ulatory function. Expansion of blood and plasma volume, as when whole blood or concentrated albumin is administered, may result in an increase in cardiac output in patients in shock and in renal blood flow in normal subjects. Contraction of the blood and plasma volume may lead to diminution of cardiac output, arterial pressure, renal blood flow, or generalized peripheral vascular collapse. Abnormalities in the extra- and intracellular fluids as a whole, are less well understood in regard to their effect on the circulation. Diminution of extracellular fluid volume resulting from dehydration, and especially from sodium depletion, is closely associated with collapse of the circulation. That this relationship is not due alone to the concomitant fall in plasma volume is suggested by the following experimental evidence obtained in dogs by one of the authors and his associates. Shock due to sodium depletion was more profound than that due to dehydration alone; in the initial phases of sodium depletion the cardiac output and arterial pressure fell abruptly well before the drop in plasma volume; restoration of extracellular fluid and plasma volume alone, by the infusion of isotonic glucose solutions, did not restore the cardiac output. From these data it appeared that changes in total electrolyte concentration, and therefore in intracellular fluid volume, had some effect on the circulation, peripheral or central, other than that mediated through the plasma volume. Changes in the volume or composition of intracellular fluid have effects on the circulation under a few other circumstances. Depletion of intracellular potassium, and excess of cellular sodium in the myocardium, as produced by overdosage of desoxycorticosterone, has been reported to produce lesions which might result in acute congestive heart failure. The same phenomenon has been suggested to occur in other types of clinical potassium deficiency.

In summary, from these observations it would seem that the third question asked in the introduction can be answered in the affirmative; that is, that body fluid distribution can affect both circulatory and renal function. The question remains, does this occur in congestive failure, and if so, how?

Various Ways in Which Abnormalities of Fluid Distribution May Play a Role in the Pathogenesis of Congestive Failure

Abnormalities of fluid distribution in many tissues may modify, secondarily, the circulatory and renal factors in congestive failure. Circulatory factors must be primary in the etiology of congestive failure in patients with heart disease, at least in a temporal sense; the place of such factors in the more immediate sequence of events is still open to discussion. Factors of fluid distribution which may modify secondarily the circulatory disturbances have received less attention from investigators. From the preceding discussion, however, it should be apparent that some of these possible modifications occur on the cellular level. Accordingly, in the discussion which follows, particular emphasis will be placed on disturbances in cellular metabolism and fluid composition of various tissues, as they may play a role in the pathogenesis of congestive failure.

For purposes of discussion some of these hypothetic relationships are listed in table 1. Primary Relationships are concerned with cardiac dysfunction and its immediate sequelae. Cardiac dysfunction may be defined as a cardiac output which is inadequate in relation to the demands of the body. A and B are the essential relationships of “forward” and “backward” failure. C introduces the possibility that a relatively inadequate output of the heart may modify cellular metabolism by failing to maintain an adequate supply of oxygen and other nutrients or to remove completely the products of catabolism. Given this last result of an inadequate cardiac output, a series of secondary relationships is postulated. In the first place, such a state of modified cellular metabolism may lead to alteration of effective blood flow and effective blood volume between various regions of the body. And in the second place, it may disturb the exchanges of electrolytes and water between the cells and extracellular fluid in various tissues. Such disturbances in turn may promote the edema of congestive failure by direct effect on the cardiovascular system and on the peripheral tissues, or indirectly by humoral effects on the kidney. Some of the possible sites of these cellular disturb-
ances are diagrammatically indicated by the letters a to e in figure 3. Obviously we are dealing with a set of complex interrelationships in which secondary effects may further aug-

**Table 1.—Hypothetical Relationships of Circulatory, Renal, and Body Fluid Factors in the Production of Edema in Congestive Heart Failure.**

I. Primary relationships
   - Relatively inadequate cardiac output and:
   1. Diminished glomerular filtration
   2. Venous congestion
   3. Modified cellular metabolism
      - Failure to supply oxygen and other nutrients, failure to remove products of catabolism, etc.

II. Secondary relationships
   A. Modified cellular metabolism and regional alterations in effective blood flow and blood volume:
      1. Relatively decreased renal blood flow
         [IA]*
      2. Relatively decreased peripheral blood flow [IIIB4]
      3. Relatively decreased cerebral blood flow and volume
         Stimulation of a blood and interstitial volume receptor [IIIB2]
   B. Modified cellular metabolism and alterations in cellular electrolytes and water:
      1. Impairment of myocardial and peripheral vascular function (a), [I].
      2. Increased tubular reabsorption of Na and H2O [II]
         a) DCA from adrenal cortex (d)
         b) ADH from posterior pituitary (e)
         c) Local stimuli in renal tubular cells (c)
      3. Fluid intake increased in relation to output (thirst and appetite) (f) [IB]
      4. Direct effect on peripheral tissues (g)
         a) Cellular depletion of potassium
         b) Cellular overhydration due to increased cellular osmolarity.

III. Tertiary relationships
   A. Modifications of I and II by therapy.
      1. Mereurials, acting on IIIB:
         2c, 2b, 73, 74

* Figures in brackets indicate possible interrelationships.
† Letters in parentheses refer to cellular loci diagrammatically represented in figure 3.

Alterations in regional blood flow may promote edema. Anoxia is known to result in changes in blood flow between various regions of the body. The stimulus presumably is initiated on the cellular level and is effected in part through reflex vasomotor activity and in part through direct local action. Diminution of renal blood flow may cause a further fall in glomerular filtration rate and so promote retention of salt and water. Diminution of peripheral blood flow should lead to increased excretion of salt and water by the kidneys. On the basis of their experimental work they postulate a “volume receptor” in the cranial cavity which conditions the renal excretion of salt and water. These workers suggest that in congestive heart failure intracranial blood volume is diminished by redistribution of blood to other parts of the body, and so stimulates the receptor to initiate the renal retention of salt and water. To such a receptor changes in blood volume or in interstitial fluid volume are more likely to be the stimulus than are changes in cell volume. In either case, alterations in the circulation in this region of the body may be a critical factor.

Aside from influencing the blood flow to various regions of the body, modified cellular metabolism leading to disturbances in water and electrolyte content of the cell may be a secondary factor in the pathogenesis of congestive failure by a variety of mechanisms.

**Secondary tissue fluid changes may affect directly function of the heart or peripheral vascular system** (fig. 3, a and b). This possibility is supported by the hemodynamic response cited above to the experimental depletion of sodium leading to hyponatremia and intracellular overhydration. Potassium depletion of the myocardium has also been reported to lead to acute congestive failure. However, it has not been established that such a vicious cycle occurs in the congestive failure attendant upon chronic valvular disease of the heart; coronary occlusion with myocardial infarction is a special case in this regard.

**Increased renal tubular reabsorption of sodium**
and water is probably the result of secondary changes in the cells of the receptors of certain endocrine glands, or of changes in the renal tubular cells themselves (fig. 3, c, d, e). Evidence has been presented above for humoral factors which influence tubular transfers of water and electrolytes in congestive heart failure. If adrenal steroids are involved, their secretion requires a stimulatory mechanism, whether the pathway goes from the sympathetic nervous system through the secretion of epinephrine to the production of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, or whether the latter receives its stimulus from the central nervous system via the hypothalamus. In either case a receptor tissue (fig. 3, d) is probably stimulated in the normal subject by changes in the distribution of its water and electrolytes; in the subject with congestive failure the response may be altered by metabolic changes in the receptor tissue or by stimuli of a different nature, perhaps associated with stress. Antidiuretic hormone production by the posterior pituitary is initiated not only by central nervous system stimuli but by certain hypothalamic osmoreceptors as well (fig. 3, e).\textsuperscript{71} This is a clear example of fluid distribution in a remote tissue modifying renal function. The functions of these osmoreceptors and how they may be involved in congestive failure, at least under certain circumstances of therapy, are discussed below. Finally, in the light of present knowledge one can believe that renal tubular transfers are conditioned by factors present in the renal tubular cells themselves (fig. 3, c). These cells may share with those of peripheral tissues changes in volume and electrolyte composition resulting from altered metabolic processes. That such is the case in congestive failure, however, has not been demonstrated.

The physiologic regulation of intake of water and electrolytes (thirst and appetite) is probably effected through certain tissue factors, such as cellular hydration (fig. 3, f). These regulating mechanisms appear to function in an abnormal way in congestive failure since the normal relationships of intake to output are maladjusted during the period of edema formation. Such may also be the case following prolonged administration of mercurial diuretics (see below).

Secondary changes in the peripheral tissues (muscle) may directly alter the exchange between cells in these tissues and the immediate internal environment, the interstitial fluid (fig. 3, b). Evidence has been presented that transfers of water into and out of cells may be effected without any primary change in extracellular tonicity and without any net transfer of solutes across the cell boundary, that is, by changes in effective osmolar concentration of the solutes within the cell. This evidence is of several kinds. In intact man and animals it has been shown experimentally\textsuperscript{72, 73} that significant discrepancies may exist between the total water balance and the total sodium plus potassium balance of the body, discrepancies that, in the opinion of the authors, could only be explained by changes in the osmotic activity of solutes within the intracellular phase. In another type of experiment based on direct analysis of skeletal muscle before and after certain manipulations of extracellular fluid, a similar discrepancy was found between the observed transfers of water and those predicted from the transfers of base.\textsuperscript{74, 75} Other workers\textsuperscript{76} have observed phenomena that are most easily explained by such a process. Presumably such a change in the osmotic activity of intracellular solutes is due to changes in the degree of dissociation of molecular aggregates. Such changes are most likely conditioned by metabolic processes. Hill\textsuperscript{77} has demonstrated that following stimulation of a frog’s muscle, under anaerobic conditions, there is an increase in its total effective osmolar concentration and when oxygen is introduced into this system, the total osmolar concentration returns to its previous level. More recently, Robinson\textsuperscript{78} has found that transfers of water in slices of rat kidney cortex are dependent upon oxygenation. The “active process” of water transfer which he postulates is probably the process under discussion. Thus the evidence is strong for the view that metabolic processes not only condition differential exchanges of solutes across the cell boundary,\textsuperscript{2} but also changes in osmotic activity of solutes within the cell, and therefore that metabolic processes control the volume of intracellular water.

For these reasons it is not difficult to believe that such a factor as hypoxia, in congestive
failure, might well condition directly the exchanges of fluid in the peripheral tissue (fig. 3, g) without a preliminary effect on either intake or renal output of salt and water. The possibility of such an occurrence is suggested by the observations of mentioned above which related edema formation to anoxemia. Such transfers of fluid in the peripheral tissue would undoubtedly lead to secondary transfers elsewhere in the body but this fact should not detract attention from the possibility that the first transfer took place in the periphery.

Therapeutic measures in congestive failure may further modify the primary and secondary relationships listed in table 1; this is especially true of the prolonged use of mercurial diuretics. The already complex relationships of the physiologic and chemical factors in congestive failure may be further complicated by at least one therapeutic agent. Since mercury is an enzymatic poison because of its ability to combine with sulfhydryl groups, it is reasonable to look for its effects in congestive failure at the cellular level, that is, among the secondary relationships in table 1. The problem posed by the hyponatremic mercury-fast patient in congestive failure exemplifies the extreme complexity of the relationships of the physiologic factors involved. The remainder of the discussion is devoted to a consideration of this special aspect of congestive failure.

“Systemic” sodium depletion following prolonged mercurial therapy (the low-salt syndrome) may augment the circulatory and renal failure. Changes in composition of extracellular fluid with further deleterious effects in the circulation have been recognized for some time to occur in the presence of prolonged administration of mercurial diuretics. Klinghoffer described in four such patients the occurrence of hemococoncentration and azotemia. These findings suggested a contraction of plasma volume and an increased degree of renal insufficiency which probably was the result of a further drop in renal blood flow. Schroeder has reported a series of patients with similar findings and with hypochloremia and hyponatremia, who responded to the administration of hypertonic solutions of sodium chloride. This condition in cardiae he has designated as the “low-salt syndrome.” Presumably these patients have a “systemic” sodium depletion and dehydration in the presence of localized or regional edema. It is easily understood how this paradoxic situation can occur. During the administration of mercury which inhibits the tubular reabsorption of sodium, salt is lost from the only portion of the body fluids immediately available to the kidney, namely, the plasma flowing through it. If the circulation is adequate, edema fluid may be mobilized to replace the salt and water deficits of the circulating plasma, and diuresis ensues. If, however, for such reasons as impaired cardiac action, increased hydrostatic pressure due to gravity, hypoalbuminemia, that is, “prerenal deviation,” the circulation is not able to effect a mass movement of fluid from the segregated pools of edema, then the rest of the “systemic” extracellular fluid is depleted, with further circulatory collapse instituting a vicious cycle. The results of this sequence of events are represented diagrammatically in figure 4.

The hyponatremia of the low-salt syndrome should produce, in sequence: (1) intracellular overhydration; (2) inhibition of antidiuretic hormone production (through Verney’s osmoreceptors) and inhibition of thirst; and (3) diuresis. The hyponatremia described as a cardinal sign of the low-salt syndrome implies a state of intracellular overhydration. This is a condition which in normal subjects is associated with inhibition of the antidiuretic hormone (ADH).
of the posterior pituitary and diuresis. It is pertinent, therefore, to speculate as to how the intracellular fluid may be altered in these circumstances and how such alteration might in turn affect the circulation and renal function.

Evidence is presented in the papers which are to follow that hyponatremia frequently occurs in patients with congestive failure and that it is usually associated with the administration of mercurial diuretics. In addition it is not always associated with the "low-salt syndrome" insofar as the latter is indicated by a successful response to hypertonic sodium solutions. If the removal of sodium from some portion of the body is not the major factor, some other mechanism must be invoked to account for the maintenance of a low concentration of sodium and total electrolyte in the body fluids in the presence of edema.

The osmoreceptors of the posterior pituitary, as described by Verney, represent one intracellular fluid in which changes of composition may materially affect the distribution of fluids throughout the body (fig. 3, e). When Verney injected in the area of the supraoptic nuclei hypertonic solutions of substances which did not readily cross the cell membrane, the diuresis of a standard water load was inhibited. He postulated that the osmotic effect of these solutions on the "osmoreceptor" cells is to reduce intracellular fluid volume with a consequent stimulation of the antidiuretic hormone production by the posterior pituitary. The antidiuretic hormone as a humoral agent then increases the reabsorption of water in the distal tubule of the kidney. If thirst is directly related to intracellular hydration, wherever the receptor of this stimulus is located, the effect of sodium loading on thirst and on antidiuretic hormone production may be represented diagrammatically as in figure 3A. The converse, the effect of water loading, has not been experimentally demonstrated by Verney, but for purposes of discussion may be assumed to hold true: intracellular overhydration results in inhibition of antidiuretic hormone production, and abolition of thirst (fig. 3B). According to this theory, cellular overhydration as the result of sodium depletion should also inhibit antidiuretic hormone production and abolish thirst (fig. 5C). In our previous experiments on sodium depletion, it was found that the abolition of thirst did occur, but diuresis did not occur, apparently because of failure of the general and renal circulation. In the "low-salt syndrome" of systemic sodium depletion, this combination of circumstances should obtain (fig. 4). The administration of hypertonic sodium solution should result in a diuresis of salt and water as the pattern of body fluids moves from that of relative sodium deficit (fig. 5C) in the direction of that of sodium excess (fig. 5A) provided that improvement of circulatory efficiency occurs before the production of antidiuretic hormone becomes too great.

![Diagram](http://circ.ahajournals.org/)

**Fig. 5.** Diagram of the effects of changes in sodium load and water load on the distribution of water between the phases of body fluid; correlated with the expected effects of antidiuretic hormone production and thirst.

The lack of diuresis and the development of thirst in hyponatremic cardiaces suggests an altered response of cellular receptors which sets the total electrolyte concentration of body fluids at a new level; changes in osmotic activity of cellular solutes might produce such a result. For those edematous patients with hyponatremia who develop thirst but do not have a diuresis following the administration of hypertonic sodium solutions, an alternative mechanism may be hypothesized in the light of the above discussion. As already mentioned, indirect evidence has been presented in the past by ourselves and others for the occurrence of changes in osmotic activity, or osmolarity, of solutes within the intracellular phase, changes
which are independent of transfers to and from the extracellular fluid across the phase boundary. If a sufficient amount of intracellular solute, most readily quantitated in terms of the cation or base, were osmotically inactivated, water would pass from the cellular phase. Under these circumstances the total concentration of osmotically active electrolyte would be lowered throughout both phases (fig. 6A), provided the extra water were not excreted from the extracellular phase. But since the intracellular volume is lowered rather than elevated, production of the antidiuretic hormone should be stimulated and the diuresis inhibited. Thus the solutions would be anticipated. Such therapy should raise the extracellular concentration of electrolyte and cause further intracellular dehydration. If a systemic sodium depletion and vascular collapse is not being rectified, the only result should be increased antidiuretic hormone production and thirst—even at hyponatremic levels (fig. 6B). On the other hand, the administration of water or hypotonic sodium solutions would expand the intracellular fluid volume and should so inhibit antidiuretic hormone production (figure 6C). This mechanism may be an important factor in the remarkable diureses reported by Schemm to be the result of the administration of water. Schemm has attributed the response to the reduction of an elevated total osmolar concentration within the cell due to nonelectrolyte solutes. This concept is difficult to accept in view of the experimental evidence that solutes, such as urea, which diffuse freely across cell membranes have no effect on either thirst or on antidiuretic hormone production. In any case, the hazard of the pure water treatment would seem to be that, while the intracellular volume is expanded, the tonicity or total electrolyte concentration of the body fluids is further depressed (figure 6C). Therefore, if this contributes to "systemic" sodium depletion and associated circulatory insufficiency, the benefit of any inhibition of antidiuretic hormone may be negated by collapse of the circulation.

In summary, it has been pointed out that in congestive failure alterations in fluid distribution in various tissues and organs may result from modification of cellular metabolic processes produced by circulatory dysfunction, and that such alterations may in turn affect secondarily circulatory and renal function. These secondary factors may be effective locally in the myocardium, the cells of the peripheral vascular system, the cells of the renal tubule, or the cells of peripheral tissues; they may condition intake and output of water and electrolytes through humoral mechanisms dependent upon stimuli in such tissues as the receptors of the anterior pituitary-adrenal cortex axis or in the osmoreceptors of the posterior pituitary gland. These secondary factors appear to be modified further by the therapeutic adminis-
Summary and Conclusions

In this discussion an attempt has been made to review some of the factors which enter into the chain of events leading from cardiaic and circulatory dysfunction to the congestive state. The relationship of circulatory to renal factors has been discussed; abnormalities of tubular as well as of glomerular function suggest that endocrine and possibly other factors are involved in the sequence. In short, the homeostatic mechanisms which control body fluid volume, unknown in part, may be functioning in an abnormal way in congestive failure.

This consideration directs attention to the relationships of the state of fluid distribution in various tissues to the circulation and kidneys. Evidence has been found that intracellular as well as extracellular fluid abnormalities exist in congestive failure. Since such abnormalities certainly modify circulatory and renal function in other conditions, it is reasonable to consider that they do so in the edematous patient. There are various tissues and cells in which these secondary mechanisms may be initiated, given a primary disturbance in cellular metabolism which is related to circulatory dysfunction. Fluid transfers may be affected directly by changes in the myocardium, the renal tubular cells, and the peripheral tissues, and indirectly through hormonal mechanisms by changes in the receptor cells of the adrenal cortex or the osmoreceptors of the posterior pituitary.

Changes in cellular hydration may be related to altered metabolic processes influencing the transfers of electrolytes and the osmotic activity of the solutes within the cells. Such changes occurring in the osmoreceptors of the posterior pituitary would affect antidiuretic hormone production, and possibly the sensation of thirst. At least following the prolonged administration of mercurial diuretics, some such mechanism appears to set a new level of total electrolyte in body water.

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References


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J. R. ELKINTON and R. D. SQUIRES

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