MEDICAL PRACTICE

Clinical Problems

Pathogenesis of Cardiac Oedema*

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Summary

When the heart ceases to meet the requirements of the body for oxygen, the sympathetic-adrenal system is activated. This occurs in people with a healthy heart when the demands for oxygen are excessive—for example, in heavy muscular work—and in subjects with a failing heart when the demands are normal or small. Eventually, when the heart is unable to meet even the ordinary requirements of everyday life, the sympathetic activity becomes more or less continuous. It may lessen during rest at night, but with a further failing of the heart its output may become inadequate even in complete rest.

The sympathetically-mediated renal vasoconstriction, with reduction of the glomerular sodium load, redistribution of the blood flow in the renal cortex to the juxtamedullary glomeruli, and the mobilization of the renin-angiotensin-aldosterone system, is responsible for the salt and water retention which will ultimately become clinically manifest as oedema—especially when it is no longer counteracted by the tidal output of water and sodium at night. A by-product of this continuing dehydration reaction is a cumulative potassium loss which may lead to disastrous consequences if untreated.

Dynamics of Heart Failure

The definition of heart failure is still a matter of controversy. The best one seems to be that it is an inability of the heart to satisfy the requirements of the body for oxygen under ordinary conditions, even if the meaning of the word "ordinary" may be questioned.

Heart failure must obviously start within the heart itself. The consequence, however, is not a simple slowing down of the circulation. Adaptive reactions occur which lead to the clinical picture of heart failure, the most important manifestations of which—dyspnoea and oedema—are due to a retention of sodium and water in the body.

The accumulation of water in the extracapillary tissue spaces was until recently thought to be due to a disturbed Starling equilibrium of hydrostatic and osmotic pressures in the lungs and the systemic circulation resulting from the damming of blood above the failing ventricle. But this view is untenable. Firstly, in a circulatory system where the pump is transferring fluid from a pond (the entire capillary bed) into the same pond, failure of the pump can only slow the circulation down. It cannot possibly cause a rise of pressure (venous pressure) above the pump.[1] Secondly, a rise in the capillary hydrostatic pressure—a passive consequence of the raised venous pressure—can only shift the extracellular fluid out of the capillaries into the tissue spaces but cannot itself cause an accumulation of fluid in the system, which may amount to many litres. For this a positive fluid and electrolyte balance is necessary. The kidneys must obviously play a key part in this fluid and electrolyte accumulation.[2]

It has been observed[2-4] that the administration of sodium chloride will increase the weight of patients with chronic congestive heart failure without raising their venous pressure. There may be a fallacy in these observations, however, since venous pressure was measured only at rest. It has been shown[5] that the venous pressure in dogs with severely damaged heart muscle remains normal at rest but rises at once on exercise. On the other hand it has been found that the renal blood flow in cases of congestive heart failure is decreased out of proportion to the decrease (if any) in the resting cardiac output, and it was thought that this might account for the electrolyte and fluid accumulation in the body.[6 7]

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Role of Renal Blood Flow

From those studies it was impossible to decide whether renal dysfunction is the primary cause of cardiac oedema or whether it is merely a reflection of the disturbance in the tissues. Further observations of the sequence of events when water and electrolytes were being either retained or spontaneously released from the system were needed.

Such a spontaneous release of sodium and water occurs at night in patients with heart failure and is known as nocturia. If the raised venous and capillary pressure is the primary cause of the sodium and water retention, a drop in the venous pressure and an influx of the retained tissue fluid into the blood, with subsequent haemodilution, should precede the nocturia. If on the other hand a decrease in renal blood flow is the reason for water and sodium retention, an increase in renal blood flow must result in a tidal flow of urine followed by at least a transient haemoconcentration, since the flow is initially derived from the plasma perfusing the kidneys.

Measurements of cardiac and renal function in one of the cases previously reported by myself and Fejfar[8 9] are given in Fig. 1. The patient was a woman aged 61 with hypertension, pulmonary emphysema, and a moderately severe left-sided and right-sided heart failure. The flow of urine, which averaged some 0·5 ml/min, started to rise at 11 p.m. to reach a level of 3 ml/min in the early hours of the morning, and this rise was unrelated to cardiac output, which, with the exception of the last measurement, remained the same throughout. But the rise in flow of urine ran parallel with the change in renal plasma flow and to some extent with the change in glomerular filtration rate. The disappearance curve of Evans's blue (and also the plasma protein concentration) pointed to a haemoconcentration soon after the onset of the diuresis.

These observations support the notion that a reduction in renal blood flow is primarily responsible for the fluid and salt retention. The right auricular pressure, however, averaging at first almost 20 cm H_2O, started to drop slightly even before the nocturia began, and the Evans blue disappearance curve had a slight downward trend below the 5% theoretical disappearance line, indicating haemodilution. The difficulty in interpreting a single observation such as this is obvious.

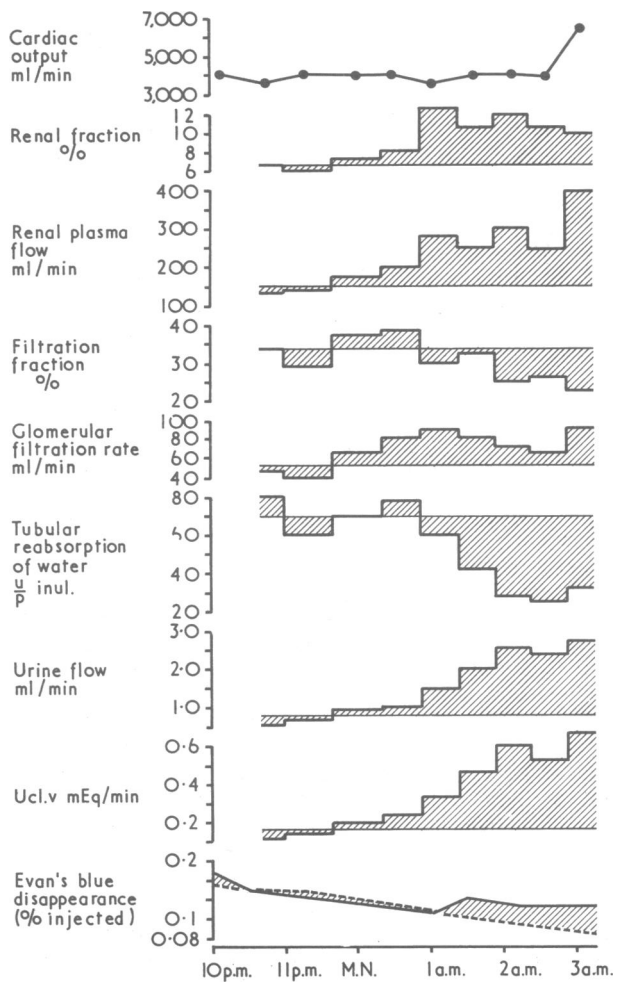

FIG. 1—Changes in cardiac output, right auricular pressure, and renal function in a patient with hypertensive heart disease, pulmonary emphysema, and left-sided and right-sided heart failure. Plasma concentration of Evans's blue should drop along dotted line if there are no water shifts from or into plasma. $U_{Cl}V$ = Excretion of chlorides. U/P inul. = inulin concentration index. Reproduced by permission of *Quarterly Journal of Medicine*.

RELATION TO WATER CONTENT IN BLOOD

An analysis of our studies of 25 patients with heart disease (22 with signs of heart failure) and 10 healthy controls,[8 9] however, showed the following. (1) Whereas the correlation between the nocturnal spontaneous release of water (and salt) from the body and the rise in renal plasma flow was good (Fig. 2), the correlation between the change in urine flow and the change in right auricular pressure was poor, and in several cases the changes ran contrary to expectation (Fig. 3). (2) A

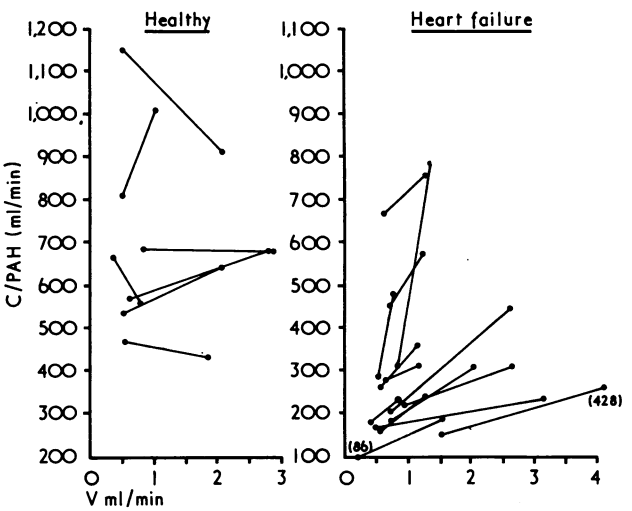

FIG. 2—Correlation between nocturnal change in urine flow and in renal plasma flow in healthy subjects and in patients with heart failure. There is close correlation between these two functions in patients with heart failure. C_{PAH} = Clearance of para-amino hippuric acid.

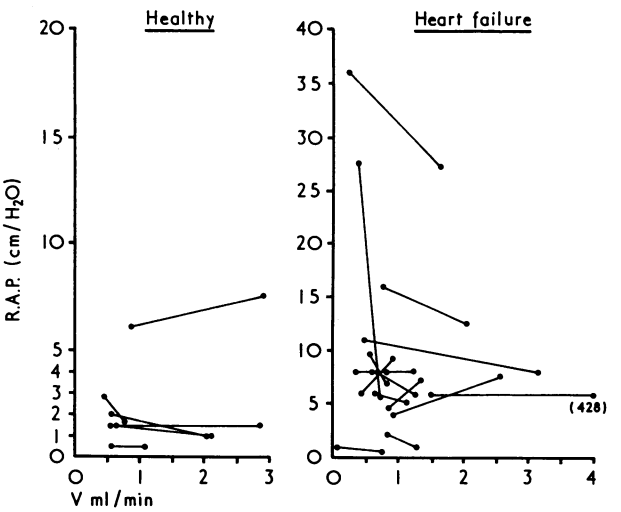

FIG. 3—Correlation between nocturnal change in urine flow and changes in right auricular pressure (R.A.P.) in healthy subjects and in patients with heart failure. The correlation in both healthy subjects and in patients with heart failure is poor.

slight nocturnal haemodilution occurs regularly in normal subjects,[10] and it occurred in most of our healthy subjects with a regular diurnal rhythm of urine flow and also in subjects with heart failure whose urine flow either did not change or fell at night.

The amount of haemodilution, as indicated by a lowering of the plasma protein concentration, packed cell volume, or Evans's blue disappearance curve in decompensated heart patients was similar to or less than that in subjects without nocturia. The descending trend of the plasma protein concentration, however, was sharply stopped and gave way to haemoconcentration after the nocturia had set in (Fig. 4). Thus the nocturnal rise in urine flow occurred at the expense of the plasma water, whereas the nocturnal influx of water from the tissue spaces into the blood was unrelated to nocturia and so also was the nocturnal change (if any) in right auricular pressure. The increased renal plasma flow at night, closely linked with nocturia in patients with heart failure, was independent of any change in cardiac output (Fig. 5).

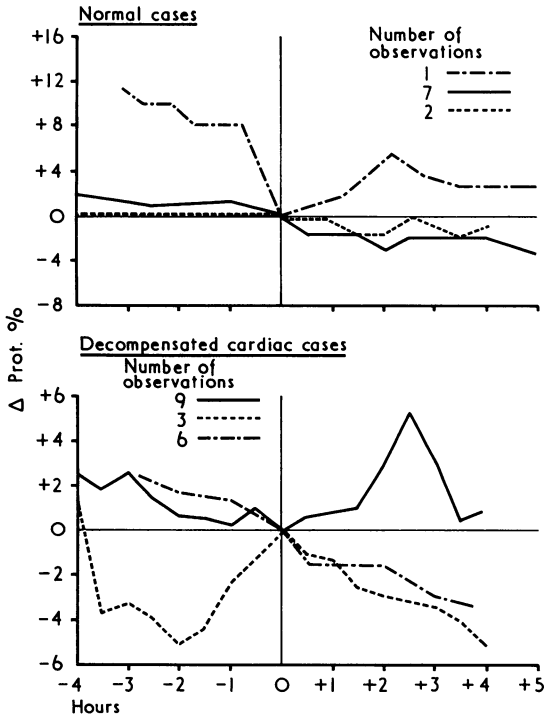

FIG. 4—Composite diagram showing percentage changes in plasma protein concentration related to change in urine flow at zero hour. In patients with no change in urine flow zero hour was fixed arbitrarily at 7 p.m. Δ protein % = Deviation of plasma proteins from value at zero hour. Solid line indicates patients with nocturia, and dashed and dotted lines patients without nocturia. Reproduced by permission of *Quarterly Journal of Medicine.*

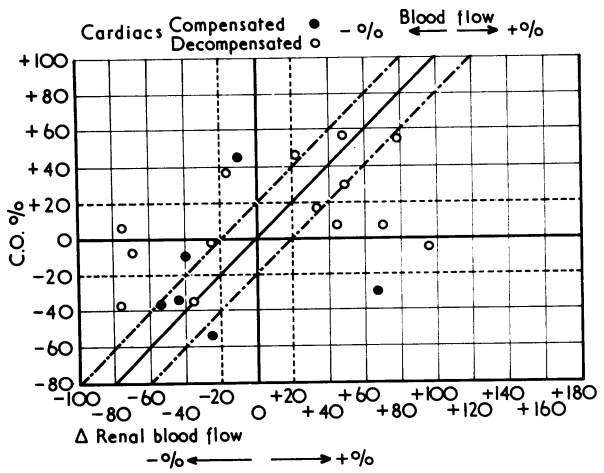

FIG. 5—Correlation between nocturnal changes in renal blood flow and cardiac output (C.O.) in compensated and decompensated heart patients. Lack of correlation is obvious. Reproduced by permission of *Quarterly Journal of Medicine.*

Renal Vascular Resistance

Since the mean blood pressure of most patients with congestive heart failure is normal or raised and the renal blood flow diminished the renal vascular resistance must be high. A patchy ischaemia of the renal surface was noted in dogs with an experimental valvular heart lesion and heart failure, and it was beautifully demonstrated in injected specimens of kidneys from normal dogs and dogs with heart failure.[11] Injection of ^{85}Kr as an indicator into the renal artery in dogs[12] has established that most of the blood is directed to the deeper layers of the renal cortex with a flow rate similar to that of the outer renal medulla.

This pattern of intrarenal redistribution of blood flow is typical of various conditions, such as muscular exercise or haemorrhage, in which the sympathetic nervous system is overactive, and it can also be produced by an infusion of noradrenaline. On the other hand it can be counteracted in the experimental animal by an intrarenal injection of the alpha-adrenergic blocking agent Dibenyline (phenoxybenzamine).[13] Similarly, we significantly lowered the high renal vascular resistance in practically all the cases of congestive heart failure we investigated by an intravenous infusion of the alpha-adrenergic blocking agent Dibenamine (Fig. 6).[14] Thus the high renal vascular resistance in patients with heart failure is at least partly mediated by the sympathetic nerves.

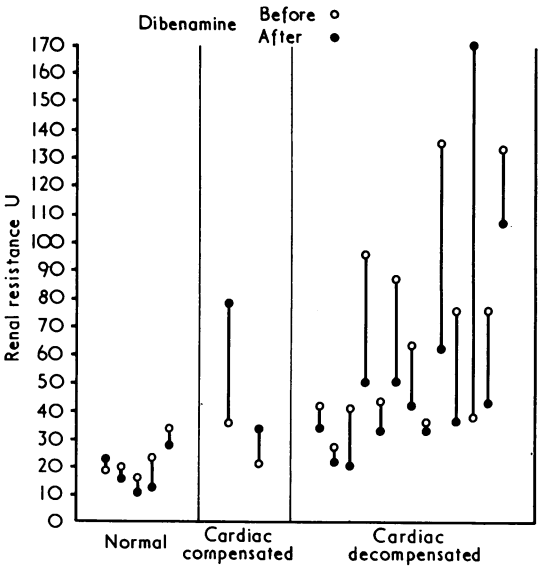

FIG. 6—Effect of alpha-adrenergic blockade with Dibenamine on renal vascular resistance in normal subjects and in patients with heart disease.

ADRENERGIC ACTIVITY

Activation of the sympathetic-adrenal system in healthy subjects also produces, of course, a vasoconstriction in parts of the body other than the kidneys[15] (Fig. 7); that in the splanchnic area[16] and in the skin[17] are the best documented. The venous tone is also raised.[18-22] Similarly, in subjects with heart failure vasoconstriction has been found in the splanchnic area[23] and in the skin and an increased venous tone has also been reported.[19 20 25-27]

The vascular bed in the skeletal muscles is less sensitive to adrenergic vasoconstrictor impulses, as may be seen from Fig. 7. Also in subjects with decompensated heart disease vasoconstriction occurs less often in the muscles than in other regions. It has been reported in severely decompensated patients,[28] whereas we[29] and others[30] have found the vascular resistance in the forearm muscles rather on the lower side of normal in these cases (Fig. 8). The controversy seems to have been resolved by dividing the subjects into those who were more and those who were less severely decompensated.[31] A raised muscle resistance was found in the former and a normal one in the latter group.

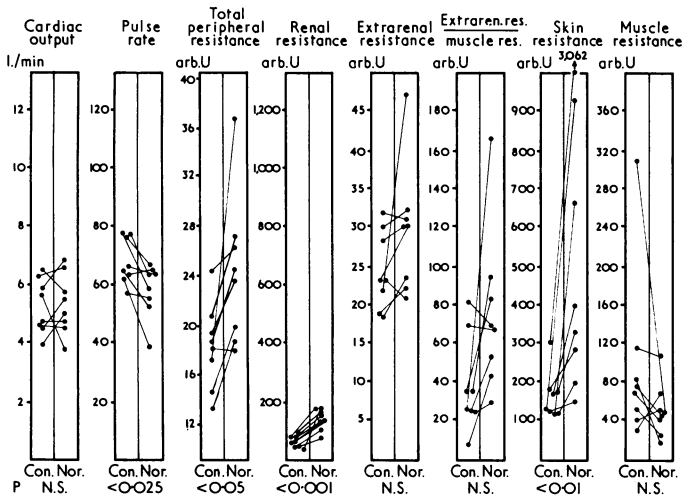

FIG. 7—Haemodynamic effects of mildly pressor infusion of noradrenaline in healthy subjects. Ratio of extrarenal vascular resistance to muscle resistance indicates changes in splanchnic vascular resistance. N.S. = Not significant. CON = controls NOR = noradrenaline. Reproduced by permission of *Clinical Science*.

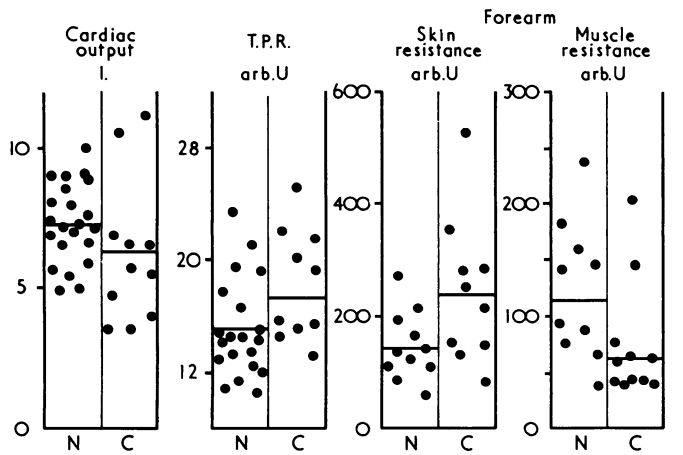

FIG. 8—Changes in vascular resistance in skin and muscle of forearm in subjects with decompensated heart disease. N = Healthy controls. C = Patients. T.P.R. = Total peripheral resistance. The two patients with high muscle resistance are those with the lowest cardiac output. Reproduced by permission of *Kardiologia Polska*.

Thus the cardiac output in heart failure is redistributed in the same way as it is after an intravenous infusion of noradrenaline. The vasoconstriction is expressed as a *raised total peripheral vascular* resistance found regularly in subjects with heart failure, and the increased venous tone is responsible at least partly for the raised venous pressure. Both can be decreased by an intravenous infusion of Dibenamine, the decrease being proportional to the original increase (Figs. 9 and 10).[25]

An increased activity of the sympathetic nervous system in subjects with heart failure has been corroborated by the finding that their urinary excretion of noradrenaline (but not of adrenaline) exceeded that of healthy controls by, on average, about 2·5 times,[32] despite the fact that the heart muscle in failure is depleted of catecholamines.[32] The increased excretion of noradrenaline in subjects with heart failure is due no doubt to an enhanced sympathetic neurotransmitter activity in the peripheral vascular bed, as is seen in the increased response of the vessels of the legs to tyramine.[28]

Thus the renal vasoconstriction in cardiac failure, which correlates with the tendency to water and salt retention, is part of a sympathetically-mediated redistribution of the inadequate cardiac output in the same way as in healthy subjects the cardiac output is redistributed when the oxygen requirements are greater than the heart can supply. In fact, it is probably the same reaction.

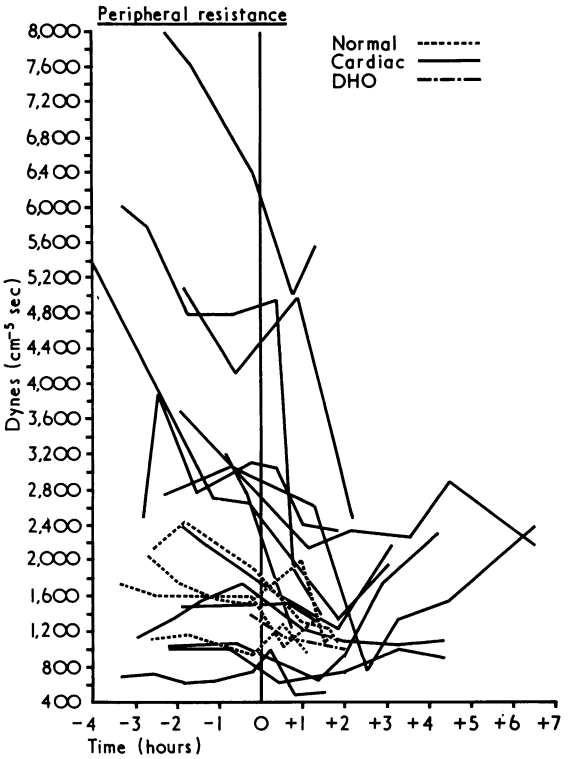

FIG. 9—Effect of adrenergic blockade with Dibenamine on total peripheral vascular resistance in normal subjects and patients with heart disease. DHO = Dehydroergotamine (used instead of Dibenamine). Each line indicates changes in one patient. Dibenamine was administered at 0 hr. Reproduced by permission of *Acta Medica Scandinavica*.

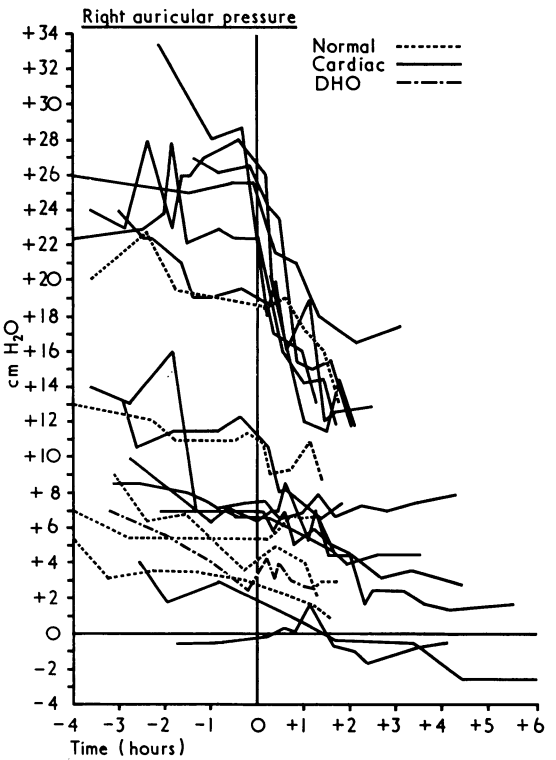

FIG. 10—Effect of alpha-adrenergic blockade with Dibenamine on right auricular pressure. Reproduced by permission of *Acta Medica Scandinavica*.

Sodium Excretion

A decreased renal blood flow lowers the glomerular filtration rate, and this in its turn diminishes the glomerular sodium load. The linear correlation between the filtered sodium load

and the amount of reabsorbed sodium is preserved in subjects with heart failure[7 25] and was believed[7] to be the reason for the inadequate sodium and water excretion in these cases. The spontaneous nocturnal change in urine flow runs parallel to the nocturnal change of the glomerular filtration rate and this correlation was as close as the correlation we found between nocturnal urine flow and the renal plasma flow,[9] but a glance at Fig. 11 shows that with a changing glomerular filtration rate the changes in urine flow were approximately tenfold.

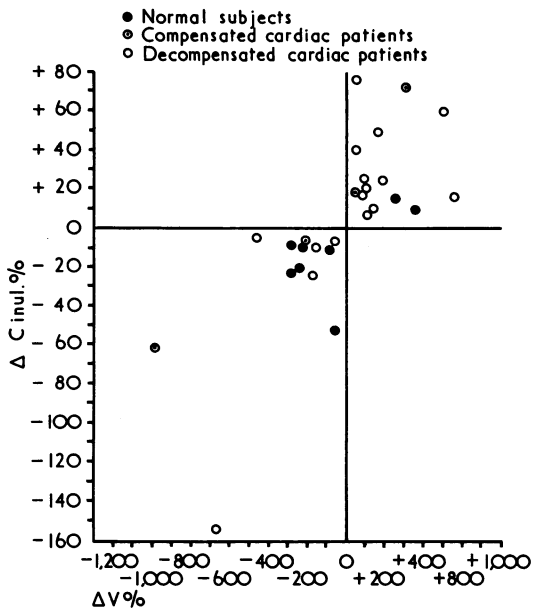

FIG. 11—Changes in urine flow (Δ V%) in relation to changes in glomerular filtration rate (Δ C inul. %) in normal and cardiac subjects. The change, irrespective of its direction, is expressed in each case as a percentage of the lower value in order to make the percentage conform to the absolute change. For example, an increase in urine flow from 0·1 to 1·0 ml/min is a change of +900%; but a decrease of urine flow from 1·0 to 0·1 ml/min if expressed as a percentage of the original value would be a change of only −90%. The changes in urine flow accord with those in glomerular filtration rate but are of a higher order. The divisions of the ordinate are therefore 10 times smaller in value than those of the abscissa. Reproduced by permission of *Quarterly Journal of Medicine*.

In a few of our patients, however, sharp increases in the chloride (which in these cases parallels sodium) excretion occurred during the nocturnal tidal flow of urine despite an almost unchanged glomerular filtration rate. A similar lack of close relationship between changes in the sodium excretion and the glomerular filtration rate were noted in animals with experimentally-induced heart failure. Thus a diminished sodium reabsorption is responsible for the increased sodium release at night and, conversely, an enhanced tubular sodium reabsorption is responsible for the retention of sodium and the oedema in patients with heart failure.

The close correlation between the increased nocturnal sodium excretion and the nocturnal change in the renal plasma flow naturally raised the question of a possible link between the two. Micropuncture studies[33] produced evidence of the existence in rats of at least two populations of glomeruli in the renal cortex, the glomerular function shifting on a low-salt diet to the fewer juxtamedullary nephrons, whose individual glomerular filtration rate amounts under these circumstances to 58·2 ± 13·6 mμl/min compared with 23·5 ± 6·4 mμl/min in the superficial glomeruli. On a high sodium intake the more superficial glomeruli predominate, with an individual glomeruli filtration of 38·1 ± 11·3 mμl/min compared with 16·5 ± 6·6 mμl/min in the juxtamedullary nephrons.

That sodium is almost totally absent from the urine of people on a sodium-free diet is well established, and it is believed[11] that the above-mentioned shift of blood to the deeper layer of the cortex leads to a perfusion mainly of the deeper glomeruli, whose nephrons form long loops of Henle, which may be responsible for a more complete reabsorption of sodium. That such a shift of renal cortical blood occurs also in human subjects with heart failure is suggested by the high filtration fraction (due to the higher individual glomerular filtration rate in the juxtamedullary nephrons) in these cases which drops when nocturia begins (Fig. 12). This, then, may be one factor underlying the retention of sodium and water in cases of heart failure.

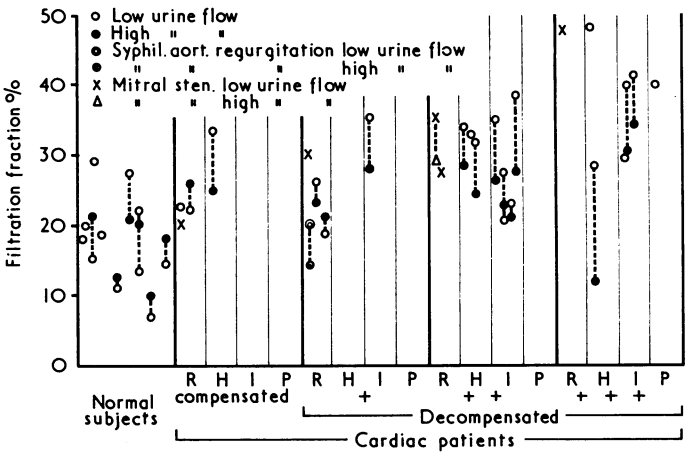

FIG. 12—Filtration fraction in normal and cardiac subjects. The latter are divided into four groups according to their state of compensation assessed clinically. Each group is further subdivided into rheumatic (R), hypertensive (H), ischaemic (I), and pulmonary (P). Patients with predominant mitral stenosis and one with aortic regurgitation of syphilitic origin have distinctive mark. In remaining patients of rheumatic group aortic regurgitation was predominant. Dotted lines connect individual subjects at high and low urine flows. Reproduced by permission of *Quarterly Journal of Medicine*.

Sodium Reabsorption

The high venous pressure in heart failure is still suggested by some as a possible explanation for the increased tubular reabsorption of sodium. The poor correlation referred to above, however, between the nocturnal changes in right auricular pressure and

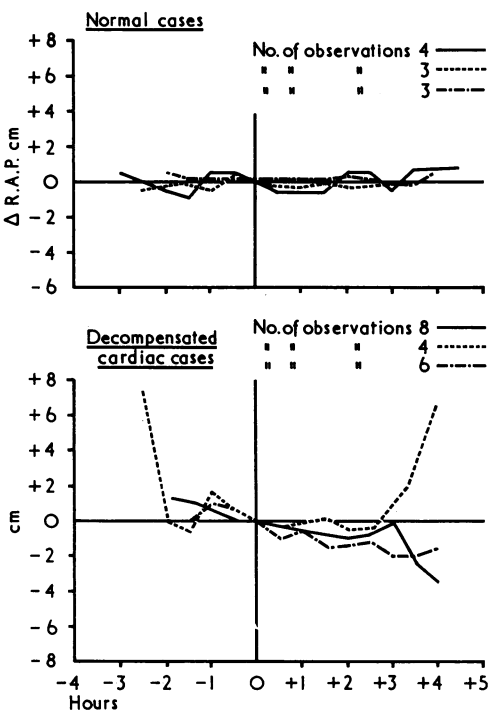

FIG. 13—Composite diagrams showing absolute changes in right auricular pressure (R.A.P.) in cm/H_2O from its level at 0 hr, when a change occurred in the renal plasma flow, in normal and cardiac subjects. In patients in whom there was no change in renal plasma flow 0 hr was fixed arbitrarily at 7 p.m. Lines are classed as in Fig. 4. Reproduced by permission of *Quarterly Journal of Medicine*.

the appearance of nocturia disproves this, as also does the lack of any correlation between nocturnal changes in right auricular pressure and renal plasma flow (Fig. 13).

One of the most important factors in the control of tubular reabsorption of sodium is aldosterone, the release of which from the adrenal cortex is controlled in the first place by the renin-angiotensin system. Even brief increases in sympathetic activity —for example, in mild orthostasis—mobilize the renin-angiotensin system.[34] Sodium retaining activity of the urine of patients with heart failure is increased [35]and this was found to be due to the urinary content of aldosterone,[36] whose secretion rate was found increased in dogs with experimental heart failure[34 38] and whose increased urinary excretion of aldosterone has been found[39] in the majority of patients with right-sided heart failure, whereas it was within normal range in most of the patients with left-sided heart failure. Bilateral adrenalectomy induces a diuresis in these dogs and relieves their ascites.

A raised plasma aldosterone level has been reported[40] in patients with heart failure (though to a lesser extent than in patients with the nephrotic syndrome or with liver cirrhosis).

Apart from an increased secretion by the adrenal cortex found in some patients[41] the raised plasma aldosterone level in these circumstances may be due to a decreased metabolic clearance rate, since in severely decompensated patients there is in addition a correlation between the splanchnic extraction of aldosterone and hepatic blood flow.[42 43] An inverse correlation between the plasma aldosterone level and the urinary sodium excretion has been established.[42]

CAUSE OF HYPERALDOSTERONISM

The increased secretion rate of aldosterone in dogs with experimental heart failure can be greatly lessened by bilateral nephrectomy,[37] and this points to the kidneys as the origin of the aldosterone-stimulating activity in heart failure. In fact, a raised plasma renin activity has been shown in dogs with experimentally-induced heart failure[44] and in patients with heart failure.[45 46] In such patients a raised plasma angiotensin level has also been found.[47]

In healthy animals and man continuous administration of mineralocorticoids produces only a transient retention of sodium and water. After four or five days the well known "escape" takes place. Whether a suppression of renin secretion, which is known to occur at that moment,[44] the activation of a hypothetic natriuretic factor, or a redistribution of renal blood flow is responsible for this is so far unknown. Why such an escape does not take place in subjects with heart failure and why the secondary hyperaldosteronism eventually leads to a large sodium and water accumulation remain problems for further study.

In dogs with heart failure experimentally induced by an arteriovenous fistula the administration of desoxycorticosterone acetate led to the formation of ascites despite the fact that the plasma renin activity was diminished, as in intact animals. Can it be that the shift of the intrarenal blood flow to the juxtamedullary glomeruli, already referred to, is the sought-for extra-adrenal factor?

Dehydration Reaction

There is evidence supporting the view that apart from causing renal vasoconstriction the sympathetic nervous system can also activate by some mechanism not yet fully understood the secretion of renin from the juxtaglomerular cells in the kidney. Sympathetic nerve endings have been detected in the juxtaglomerular apparatus.[48]

The sympathetically-mediated increased output of renin with activation of angiotensin, leading to an enhanced production of aldosterone, forms part of the physiologically important dehydration reaction (Fig. 14). The sequence of events in this is as follows: decrease in volume of extracellular fluid, decrease in plasma volume, diminished mean systemic pressure, diminished venous return of blood, decreased stroke volume, lowered pulse pressure, stimulation of baroreceptors (and possibly volumoreceptors), reflex activation of the sympathetic nervous system, vasoconstriction in the kidneys, decrease in glomerular filtration rate and less sodium delivered into the tubule, increase in sympathetically-mediated production of renin-angiotensin, increased secretion of aldosterone, increased tubular reabsorption of sodium and increased tubular secretion of potassium, secondary activation of posterior pituitary lobe (by the tendency to hypertonicity of the internal environment from increased sodium tubular reabsorption) and increased secretion of antidiuretic hormone, oliguria with disappearance of sodium from the urine, and increased potassium excretion.

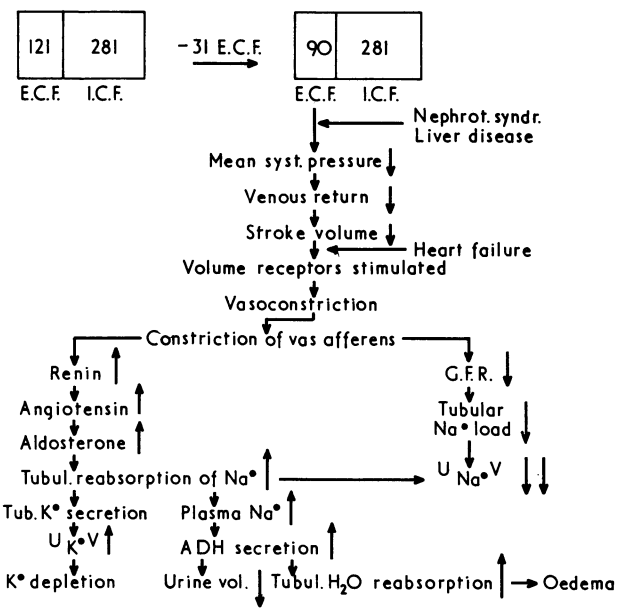

FIG. 14—Schematic representation of dehydration reaction (see text).

It seems that the mobilization of this reaction, which usually occurs with a loss of extracellular fluid (haemorrhage, burns, large abrasions of skin, intestinal losses), can also be stimulated at one of its further steps—for example, by a decrease in stroke volume or a lowering of pulse pressure. In these circumstances the retention of sodium by the kidneys would start from a normal and not from a negative sodium balance and would lead to an accumulation of sodium and water in the system and thus to the main manifestations of heart failure—pulmonary and peripheral oedema.

The increased plasma volume thus produced may contribute in the later stages of heart failure to the rise in the venous and mean systemic pressures. This could eventually bring the cardiac output to the falling branch of the Starling curve and explain why giving salt to patients with heart failure may increase their aldosterone secretion[41] and why they may respond to sodium depletion by a decrease in plasma renin activity.[47] On the other hand the increase in mean systemic pressure will help to re-establish an adequate cardiac output in patients with a failing heart,[49] and this might explain why under the new equilibrium the plasma renin activity and aldosterone secretion may fall to normal[39 50] Disturbing the equilibrium by giving a diuretic agent without first strengthening the failing heart with digitalis would again raise plasma renin activity and renew the hypersecretion of renin and aldosterone.[51]

A consequence of this continuing activitation of the dehydration reaction might be a cumulative loss of potassium and a serious potassium depletion. Apart from its major symptoms it may be one of the reasons for digitalis intolerance. It

should therefore be taken into account in all cases of heart failure (and other oedematous states), and should be prevented by potassium replacement or by giving spironolactones.

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Scientific Basis of Clinical Practice

Violence: A Clinical Viewpoint

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Much confusion surrounds the closely related concepts of aggression and violence. Most authors agree that they are not synonymous and find it helpful to regard violence as an end point in a continuum of aggressive behaviour. Aggression has been defined as the determined pursuit of one's own interests. Violence, on the other hand, is the pursuit of such interests by force or the threat of force. If violence is to be interpreted as one of the ways in which aggressive drives are expressed, one has to distinguish violence from force. Force may be seen as controlled aggression which is limited in degree and appropriately directed to a specific goal. Violence, on the other hand, is more unpredictable in its course and mode of onset and is characterized by its more extreme nature and its more irrational patterns, so that the stimulus which provoked the violence and its goal orientation may be lost. Violent behaviour is frequently without obvious motive, apparently spontaneous, self-perpetuating, and capricious in nature.

The approach to violence varies with the particular discipline involved. The clinician's main concern is with the victims of violence. The social scientist usually focuses on measurement of violence in terms of its departure from normally accepted behaviour and will, for example, emphasize social class differences showing that wealthy and better educated people tend to have a less tolerant attitude to violence, whereas lower socioeconomic groups tolerate a much wider variety of violent behaviour. Anthropologists are concerned with cultural differences in violent and non-violent tribes, while ethologists and other behavioural scientists argue the pros and cons of the biological and environmental schools of aggressive behaviour.

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