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## Some Aspects of Circulatory Stability

N. C. H. Stott

B.Sc., M.B. Ch.B.

### Abstract

Based on a dissertation read before the Society on 11th February, 1966.

The secrets of the circulatory system taxed the imaginations and resources of workers in every field of medicine long before even William Harvey produced his classical treatise in 1628 . Now , in 1966, the basic anatomy of the circulatory system is widely accepted but the relative importance of various homeostatic mechanisms in the patho-physiology of this system is still the subject of constant debate; this is no mere 'academic exercise', for the disorders of the circulatory system are becoming major problems throughout the world and they merit careful consideration. Nevertheless this dissertation is not a review. I attempt to outline a few aspects of the subject which are of particular interest, and so well accepted and established concepts are included along with some more recent work.

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# **SOME ASPECTS OF CIRCULATORY STABILITY**

**N. C. H. STOTT, B.Sc., M.B.Ch.B.**

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The secrets of the circulatory system taxed the imaginations and resources of workers in every field of medicine long before even William Harvey produced his classical treatise in 1628. Now, in 1966, the basic anatomy of the circulatory system is widely accepted but the relative importance of various homeostatic mechanisms in the patho-physiology of this system is still the subject of constant debate; this is no mere 'academic exercise', for the disorders of the circulatory system are becoming major problems throughout the world and they merit careful consideration. Nevertheless this dissertation is not a review. I attempt to outline a few aspects of the subject which are of particular interest, and so well accepted and established concepts are included along with some more recent work.

One of the most remarkable facts about the human body is the day to day stability of its total weight (Robinson and Watson, 1965). This stability implies a relative stability of our fluid volume, and especially our extra-cellular fluid volume which bears a fairly constant relationship to total body weight in normal man (Moore, 1965). A patient's weight is therefore a sensitive indicator of his fluid balance and, to the clinician, it usually reflects the state of his extra-cellular fluid.

The extra-cellular fluid is normally an isotonic solution with an osmolality of  $283 \pm 11$  m. osmols/litre in which the principal ions are sodium, chloride and bicarbonate. The trans-capillary exchange of this fluid is governed by the balance of differential hydrostatic pressure, colloid osmotic pressure, tissue pressure and capillary permeability, so an adequate extra-cellular fluid volume is fundamental to the maintenance of a circulating blood volume.

## **OSMO-REGULATION AND VOLUME REGULATION**

The mechanism of osmolar regulation of the extra-cellular fluid is better understood than volume regulation and it is a process students are familiar with. Osmo-receptors somewhere in the distribution of the internal carotids are sensitive to a 2% change in osmolality (Pitts, 1964). Afferent neural impulses are co-ordinated centrally and anti-diuretic hormone is released by the neuro-secretory mechanism of the hypothalamo-hypophysial system. The kidney is the effector organ and excretion of free water is varied by the action of anti-diuretic hormone on the distal tubules and collecting ducts. Thus in this system we have recognised a stimulus, a receptor, a central controlling mechanism, a humoral effector agent and the effector organ. The details need not concern us but it is worth remembering that thirst is part of the osmolarity controlling complex. Haemorrhage, emotion, tobacco, alcohol and many other factors can also influence anti-diuretic hormone output.

The osmolarity of the body is controlled very largely by alteration of intake and excretion of water, but sodium is the predominant ion in the extra-cellular fluid and the following three experiments illustrate how its homeostasis can influence osmolarity and volume regulation in the body:—

1. *Hypertonic saline* injected into the carotid artery induces an acute thirst and anti-diuresis associated with anti-diuretic hormone output (Best and Taylor, 1961). Here, in the interests of maintaining normal osmolarity, the body retains water to dilute the saline and thereby increases its extra-

cellular fluid volume. Re-establishment of normal extra-cellular fluid volume is achieved by subsequent excretion of the excessive salt and water. Thus volume regulation of body fluids is an integral part of the regulation of sodium excretion and clearly a derangement of this system will cause oedema or dehydration.

2. *Salt excess.* Normal man can cope with about 10 grams of salt per day in his diet, as any excess is excreted in the urine, but man is relatively intolerant of high salt intake; 30-40 grams of salt per day causes an elevation of body weight of 5-15 lbs. above normal. This weight increase is due to extra-cellular fluid expansion, and if the high sodium intake is maintained, the body weight stabilizes at this level, the kidneys just managing to excrete the excessive intake when the extra-cellular fluid volume has expanded a little (*vide infra*). Thus, even with normally functioning kidneys, man has been described by Pitts (1959) to be, 'but a salt-shaker away from incipient oedema'.

3. *Salt depletion.* Normal young men on salt free diets, but encouraged to drink plenty of water, undergo progressive weight loss for 4-5 days and remain in negative salt and water balance, indicating an isotonic contraction of their extra-cellular fluid. During the subsequent week the subjects stop excreting salt and start retaining water. Their weight stops falling so rapidly and during the latter phase water is retained despite increasing hypo-osmolality of the extra-cellular fluid. An explanation is that initially osmo-regulation dominates, causing an isotonic contraction of the extra-cellular fluid, but latterly the volume of fluid in the body is so depleted that another mechanism dominates, to cause water retention, despite the extra-cellular fluid dilution. Anti-diuretic hormone is probably the mediator hormone but it appears that osmo-regulation is sacrificed in this circulatory emergency and volume regulation dominates. (McCance, quoted by Borst et al, 1961).

Two points from these experiments should be emphasised. a) Men may vary in their ability to excrete a chronic salt load but in general this is limited to a few grams more than the average daily intake. b) The volume control mechanism seems to be an extremely powerful one — teleologically one could sug-

gest that this is necessary to maintain vital circulation of blood in the face of osmolar and metabolic derangements.

These experiments each represent a considerable challenge to the internal milieu of the body and it may be argued that this detracts from their value as physiological experimental models. Nevertheless it is recognised that any procedure which causes a minor reduction in the effective blood volume also causes salt and water retention, and vice versa. Tight tourniquets to exclude venous return from the legs, a change in posture from recumbency to standing, an acute haemorrhage or the sudden opening of an arterio-venous fistula all induce salt and water retention. On the other hand, release of the tourniquet, assumption of recumbency, infusion of plasma expanders or closure of the arterio-venous fistula each induce a measurable salt and water diuresis in normal man (Pitts, 1959; 1964). In each of these instances the water diuresis and anti-diuresis is determined by anti-diuretic hormone. This can be demonstrated by blocking anti-diuretic hormone release with alcohol, e.g. when thigh tourniquets are applied the usual anti-diuresis is diminished by the absence of anti-diuretic hormone, but the natriuresis persists (Borst et al, 1961). It is believed that volume (stretch) receptors in the thorax send afferent impulses via the vagus to initiate anti-diuretic hormone release during volume depletion. This reflex has been established in animals by abolishing it after vagal section or freezing (Welt, 1964), and it is possible that the vagal afferents stem from stretch receptors in the left atrium (Pitts, 1964).

#### SODIUM HOMEOSTASIS

The mechanisms of salt retention are poorly understood. Aldosterone from the zona glomerulosa of the adrenal cortex causes sodium retention, and in recent years it has been shown that renin, through its conversion product angiotensin, stimulates the secretion of aldosterone (Bartter et al, 1961). There is good evidence for increased serum levels of aldosterone in many salt retaining states, e.g. haemorrhage, congestive cardiac failure, cirrhosis, thigh tourniquets (Borst et al, 1961) and prolonged standing (Mills et al, 1960; Gowenlock et al, 1959). However the natriuresis of recumbency or released tourniquets is not prevented by exogenous aldosterone and spironolactone (an aldosterone antagonist) does not block the anti-natriuresis of standing or application of tourniquets (Gowenlock et al, 1969; Mills et al,

1960). Also adrenalectomised or Addisonian patients on steroid maintenance, in whom increased aldosterone output is impossible, have normal responses to these stimuli (Borst et al, 1961; Pitts, 1964). Furthermore, aldosterone has a latent period of about 40 minutes before it is physiologically active (Pitts, 1964), whereas the salt retention which follows acute volume depletion is immediate. These findings suggest that acute salt retention is mediated by some mechanism other than aldosterone and the renin-angiotensin system.

Recently Brown et al (1965-66) have produced more evidence for the view that changes in sodium balance are the cause rather than the result of variations in renin output. These workers reached this conclusion after assaying the plasma renin and electrolytes in a series of 253 hypertensive patients, in whom they demonstrate an inverse relationship between plasma renin and plasma sodium. However, the sodium ion does not necessarily affect the juxta-glomerular apparatus directly because body sodium may exert its influence by affecting the blood volume, renal plasma flow, filling of the arterial system or some other circulatory parameter; and some workers do believe that haemodynamic factors mediate the more acute changes in sodium excretion, whereas the overall day to day balance of sodium intake and output is determined by aldosterone (Pitts, 1964).

#### HAEMODYNAMIC FACTORS

A reduced cardiac output and renal plasma flow are usually associated with sodium retention (Thompson & Pitts, 1952). Therefore the hypovolaemia of salt depletion will, by Starling's Law (Pickering, 1960), induce a reduced cardiac output and sodium retention. The mechanism of this salt retention has been the source of some controversy, but Selkurt (1949; 1951) has dissociated glomerular filtration rate from sodium excretion and demonstrated that the haemodynamic factor which correlates best with sodium excretion is the pressure in the renal arterial system. Moreover it has been observed that increased tone in the afferent arterioles of the kidney induces sodium retention, whilst elevation of blood pressure without alteration of arteriolar tone produces a rapid natriuresis. It is likely that a pressure-receptor site in the kidney exists downstream from the afferent resistance but upstream from the efferent resistance (De Bono and Mills, 1965), and there is a little evidence for a locally acting

humoral mediator which causes the rapid variation of sodium reabsorption (De Bono and Mills) in response to pressure changes at this site. This theoretical pressure-receptor site is remarkably near the juxta-glomerular apparatus but it remains to be seen whether this organelle is the receptor involved in these haemodynamic changes.

If this hypothesis is correct, factors which alter pressure at the receptor site should alter sodium output profoundly. Two such factors are afferent arteriolar tone, and the blood pressure. A great reduction of arteriolar tone occurs clinically in an iatrogenic postural hypotension because, on standing up, no vascular reflexes are functioning to maintain the peripheral resistance, and cardiac output also diminishes due to a reduced venous return from peripheral pooling of blood; under these conditions sodium and water retention occurs. Return to the supine position is associated with a salt and water diuresis, which is probably due to improved cardiac output and exposure of the pressure sensitive area in the kidney to higher arterial pressure (De Bono and Mills, 1965). It is unlikely that these phenomena are initiated by pressure changes in the venous system as, in attacks of paroxysmal tachycardia, a sudden rise of arterial pressure is always associated with a diuresis of salt and water despite reduced central venous pressure, whilst high venous pressure in patients with congestive cardiac failure is associated with salt retention.

In a normal subject, movement from recumbency to standing results in sympathetic reflexes which prevent a fall in blood pressure and cardiac output by increasing peripheral resistance (Wang et al, 1960). However, despite the constant blood pressure, a reduction in the excretion of sodium and water occurs when we assume an upright posture, because the increased arteriolar tone induces the kidney to retain sodium and water. This expands the extracellular fluid and permits some relaxation of arteriolar tone. A more perfect co-ordination of rapid acting and slow acting homeostatic mechanisms can hardly be conceived (Borst and Borst-de-Geus, 1963).

The concept helps to explain many unexpected phenomena in medical science, e.g. angiotensin, which has a controlling influence on aldosterone secretion, is known to cause salt retention if administered in small doses but in large doses it has a powerful pressor effect and it causes a natriuresis. Ames et al (1965) have explained this paradoxical situ-

ation by pointing out that even small doses of angiotensin, which have no pressor effect, result in a natriuresis if given for a long time. The initial salt retention expands the extra-cellular fluid, improves the cardiac output and increases the vascular reactivity to pressor agents. This exposes the kidney to pressures which are high enough to precipitate a natriuresis. These workers believe that a large initial dose of angiotensin has a pressor effect large enough to overcome the salt retaining action of the drug, by exposing the receptors to higher arterial pressures immediately.

#### CLINICAL APPLICATIONS

In congestive cardiac failure the poor cardiac output results in reduced pressure at the theoretical receptor site in the kidneys. This occurs either as a direct result of failing cardiac output or as a result of protecting afferent arteriolar spasm which occurs reflexly when systemic blood pressure falls. Salt and water retention results, and the extra-cellular fluid volume increases venous return to a heart which cannot respond by improving its performance. The patient in cardiac failure is thus conserving salt and water in an attempt to increase the plasma volume and thereby obey Starling's law. In this situation the therapeutic measure of greatest value is improvement of cardiac output and hence the diuretic effect of digitalis in many of these patients.

Essential hypertension is another problem which may prove to be a disorder of homeostasis if the concepts described above are correct (Borst & Borst-de-Gues). It is an intermittent disease in its early stages, the blood pressure fluctuating between normal and hypertensive levels, due to alteration of peripheral resistance and not cardiac output (Brod et al, 1959). There is a tendency for the blood volume of these patients to undergo greater than normal fluctuations initially (Jones et al, 1964), but in established hypertensive disease the cardiac output and extra-cellular fluid volumes are believed to be normal (De Graeff, 1957).

Tobian (1960) has reviewed many relationships between electrolyte disturbances and the development of hypertension, and the evidence is strongly suggestive of a direct association between disturbances of sodium and/or potassium homeostasis and hypertensive disease. Furthermore, epidemiological evidence from cross-cultural surveys reveals that there is an almost linear relationship between salt intake

and the incidence of hypertension in various population groups (Isaacson et al, 1963).

#### EXPERIMENTAL HYPERTENSION

Borst and Borst-de-Gues (1963) produced an experimental model of essential hypertension in man which is in keeping with the hypothesis outlined above. These workers gave low doses of liquorice, which has a deoxycortone like action and causes salt retention, to patients every day for three months. Initial salt and water retention expanded the extra-cellular fluid volume causing rapid rise in central venous pressure and cardiac output. The arterial pressure began to rise slowly and after several weeks it attained hypertensive levels. The authors attributed this slow increase to reflexes initiated by baro-receptors in an abortive attempt to drop the rising blood pressure by increasing the renal excretion of sodium. They also postulate cardiac hypertrophy in the face of continued sodium retention and greater demands on the myocardium. Eventually a salt and water diuresis commenced and after three months the extra-cellular fluid volume and central venous pressure had returned to normal, but the subject was left with high diastolic and systolic blood pressure, i.e. a state equivalent to essential hypertension. Borst and Borst-de-Gues explain the diuresis of sodium and water by suggesting that the cardiac output and blood pressure rise, until a point is reached at which the salt retaining action of liquorice is less than the natriuretic effect of a very high renal perfusion pressure. In terms of the above hypothesis this exposes the receptor site to high pressures, and excessive extra-cellular fluid is then excreted, as occurred in this experiment. The patient is left with a hypertrophied heart which is capable of greater work at the same or lower central venous pressure than a normal heart (Borst & Borst-de-Gues). It is likely that carotid baro-receptors become adapted to the higher pressure and thus sodium excretion also requires greater arterial pressures than were previously needed.

This is a thought-provoking experimental model which puts forward a possible explanation for many of the clinical and experimental features of hypertensive disease. It explains essential hypertension as a disorder of homeostasis, and if it proves to be a correct interpretation many cases of essential hypertension should be preventable.

In conclusion I need to quote one more

experiment. Normal young men on a standardized diet have been shown to have significantly elevated extra-cellular fluid volumes and blood volumes on Saturday morning after a hard week's work. On Monday morning after a restful weekend these volumes are back to normal (Gerbrandy, quoted by Borst, 1961). Is it possible that a combination of repeatedly busy weeks and hectic weekends, in subjects with a high salt intake and a limited capacity to excrete a salt load, could place them into the first stage of essential hypertension, as illustrated in Borst's experimental model. Here a genetic factor (ability to excrete a salt load) and environmental factors (salt intake and stress) could be operating together. These questions have not been answered and it would be presumptuous of me to speculate further. However I can refer to the conjectures of two

well known workers who suggest that essential hypertension may be an inborn error of sodium metabolism conditioned by environmental factors (Knudsen and Dahl, 1966).

#### SUMMARY

1. Aspects of salt and water metabolism have been described with particular reference to the relationship between osmo-regulation and sodium homeostasis in the body.
2. Man's limited capacity to excrete a salt load has been emphasised and its possible pathological implications discussed.
3. Some recent hypotheses and experiments in the field of circulatory stability have been described.
4. Congestive cardiac failure and essential hypertension are discussed in the light of these findings.

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## Of Opium

Two hundred years ago William Patten, an undergraduate member of the Society, gave his dissertation on the subject of opium. He described how the drug might cause rarefaction of the blood, with consequent distension of the arterioles (especially in the brain) so that they "must obviously compress the nervous tubules, in a ratio of their distensions, and the nerves being too much compressed will permit a smaller quantity of animal spirits to be sent to the several parts of the body; hence all their actions must be weakened and numbed." How much nearer the truth are we today?