The definition of hypertension is arbitrary and its occurrence therefore depends critically upon the arterial pressure selected as a cut-off point for normality. Nevertheless, using conventional clinical criteria, between 10% and 20% of the adult population will be classified as "hypertensive". In every adult specialty therefore, hypertension is encountered frequently as an incidental disorder. In the majority of patients no cause for hypertension is discovered even if patients are investigated intensively for renal, endocrine or neurological disease. Any abnormalities discovered (such as an increased blood urea or focal neurological lesions) are likely to be a consequence of hypertension rather than its cause. Whilst a high prevalence of renovascular hypertension or primary aldosteronism amongst hypertensive patients has been reported frequently in the past, this reflects almost certainly the selective referral of patients with secondary hypertension to specialist units. Excluding women with hypertension caused by the contraceptive pill, the true frequency of all forms of secondary hypertension amongst unselected hypertensive patients is probably not more than 1–2%. This review therefore will focus on the possible mechanism responsible for arterial pressure increase in patients with essential hypertension; secondary hypertension will be introduced where it helps to throw light on these mechanisms.

**Essential hypertension**

In unselected populations, arterial pressure is distributed as a unimodal curve with a skew causing a tail in the higher pressure ranges. The concept of essential hypertension as a quantitative rather than a qualitative deviation from the norm first proposed by Pickering (1960) has now been generally accepted. The corollary of this hypothesis is that arterial pressure is determined by at least several factors: as Pickering pointed out, there is a close analogy with body stature which is also determined multifactorially and which forms a unimodal curve.

A role for genetic factors has been demonstrated conclusively in patients with essential hypertension. Thus it has long been known that essential hypertension tends to occur in families (Platt, 1947). More detailed studies have shown that arterial pressure tends to be similar in first degree relatives across the spectrum of pressure values. Thus, in a population study carried out in South Wales, there was a highly significant correlation between diastolic arterial pressure of first degree relatives (Miall and Oldham, 1958, 1963). This finding is particularly impressive as single measurements of arterial pressure inevitably impose a random error which may result in an understatement of true resemblance. Allowing for this, for every 50 mm by which systolic arterial pressure of the propositus exceeded the expected value for an individual of that age, the first degree relative's arterial pressure was 12 mm higher. Studies of monozygotic and dizygotic twins have also supported the concept that genetic factors are important determinants of arterial pressure (Pickering, 1968). On the other hand, it is difficult to assess the precise importance of genetic factors since some of the resemblance between blood relatives may be attributed to shared environmental influences. Nevertheless, there is little doubt that genetic factors play a role. As there is no tendency for the offspring of hypertensive patients to group into identifiable normotensive or hypertensive populations (Pickering, 1968) it seems likely that the inheritance of arterial pressure is polygenic rather than the manifestation of a single gene. This is consistent with the fact that arterial pressure control is the result of a number of physiological processes involving several tissues; under these circumstances single gene inheritance would be extremely unlikely.

The complexity of genetic influence upon arterial pressure has been demonstrated by the development of hypertensive strains of rat by selective inbreeding. One of the earliest attempts in this direction was that of Dahl who was able to develop a strain of rat which became hypertensive when given a very high

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intake of salt (Dahl, Heine and Tassinari, 1962). In this strain, arterial pressure remained increased even when animals were given a normal salt diet after earlier exposure to a high salt intake. The factor concerned appeared to reside in the kidneys, since it could be transmitted by transplanting a kidney from the salt sensitive to the salt resistant strain (Dahl, Heine and Thompson, 1974). By contrast, arterial pressure increases when another laboratory strain of rat (Sprague-Dawley) is given a low salt diet (Seymour et al., 1980). The Okamoto-Kyoto strain of rat does not require excessive salt in its diet and hypertension appears to be associated with increased sympathetic nervous activity (Folkow, 1976) (see below). The way in which genetic and environmental factors interact may therefore differ in different clinical and experimental situations. Since in almost every form of hypertension, arterial pressure is maintained by an increased peripheral resistance, factors acting at this site are particularly relevant.

**Structural changes**

Resistance to blood flow occurs mainly in small arteries and arterioles. According to Poiseuille's law, this resistance is proportional to the fourth power of the radius of the vessel lumen. Small changes in luminal diameter therefore have a major effect upon resistance. The pre-capillary resistance vessels are particularly well-designed to modulate resistance since, in common with the more proximal vessels, they have a high wall-to-lumen ratio with a proportionately greater volume of smooth muscle. Vasoconstriction is initiated from the adventitial side of the muscle layer where the neuroeffector junctions lie, with subsequent activation of the inner layers by myogenic spread of excitation. Thus the wall mass is pushed inwards on contraction to narrow the luminal diameter. As a consequence, the thickening of the wall with increased wall-to-lumen ratio amplifies the increase in resistance produced by vasoconstrictor stimuli (Folkow et al., 1973; Folkow, 1982). Because of this relationship of structure and function, measurement of flow provides a much more sensitive index of resistance vessel hypertrophy than direct measurement.

In classic experiments (Folkow et al., 1973) Folkow demonstrated the importance of resistance vessel hypertrophy in essential hypertension. Vascular smooth muscle relaxation was produced by exercise, ischaemia and warmth. Although resting forearm blood flow was normal or even slightly increased in patients with essential hypertension, forearm resistance was increased at maximal vasodilatation.

The second cardinal feature of vascular hypertrophy was also demonstrated. Pressor dose-response curves are steeper in the presence of hypertension since, for any given degree of vascular smooth muscle shortening induced by agents (such as noradrenaline), a greater increase in resistance to flow is produced (fig. 1). This type of analysis makes it possible to differentiate between the consequences of hypertrophy and specific hypersensitivity to pressor agents such as noradrenaline and angiotensin II.

The stimulus for hypertrophy of the resistance vessels is an increase in load imposed by increased perfusion pressure. The subsequent narrowing has three components. First, there is an immediate protective vasoconstriction to normalize tissue blood flow—"autoregulation" (see below); second, there is smooth muscle hypertrophy; and third there is increase of collagen and interstitial material (Ooshima et al., 1974). Whilst the first is instantaneous, the second occurs in experimental animals within 1 or 2 weeks, whilst the last follows more gradually.

Regression of smooth muscle hypertrophy occurs with restoration of a normal arterial pressure in experimental animals over a 2- or 3-week period (Lundgren, 1974). When hypertension is longstanding however, the process is slower and incomplete (Lundgren et al., 1974). The same process of regression of structural resistance vessel changes may be
shown in man with medical treatment (Sivertsson and Hansson, 1976).

There is little evidence that resistance vessel hypertrophy precedes increased arterial pressure in patients with essential hypertension. It cannot, therefore, be an initiating mechanism, but it may be of importance in maintaining arterial pressure. Thus, when spontaneously hypertensive rats are treated with antihypertensive medication during the period in which arterial pressure would normally be expected to increase, the pressure remains substantially lower even when the medication is discontinued, suggesting that a vicious circle is normally established by which hypertension induces changes which maintain hypertension (Freis et al., 1972).

On the other hand, the effect of hypertrophy can be overcome by some circulatory control mechanisms. Thus when experimental renovascular hypertension is corrected (by removal of a constricting clip applied to the renal artery or by unilateral nephrectomy of the ischaemic kidney), peripheral resistance decreases within 24 h to normal values even when hypertension has been present for many months (Russell et al., 1981). In addition to structural changes, it is also possible to demonstrate increased sodium and fluid content of the arterial wall in some forms of clinical and experimental hypertension. This gave rise to the hypothesis that waterlogging of the resistance vessel walls plays a role (Tobian, 1956). It seems more likely, however, that electrolyte changes at this site are a consequence of hypertrophy and not a cause of hypertension (Johnsson, Ludgren and Wennergren, 1975; Folkow, 1982).

**Autonomic nervous system**

Rapid adaptive changes of arterial pressure are necessary for survival. Activity of the vascular efferent pathways of the sympathetic nervous system supplying the heart and vessels is critically important for this response. It is possible, therefore, that resetting of autonomic activity may be responsible for a sustained increase of arterial pressure. Such resetting may be the result of alteration at the baroreceptor level or central changes in vasomotor control. It is also possible that vascular smooth muscle is more responsive to efferent nervous activity. However, this will be discussed in relation to postulated changes in smooth muscle activity.

The carotid and aortic baroreceptors reset to the higher arterial pressure fairly rapidly when, for instance, renal hypertension is induced (McCubbin, Green and Page, 1956). Similarly, resetting of the baroreceptors at the baroreceptor level occurs in both essential and genetic hypertension so that afferent neural activity is similar to that observed in normal patients and animals. Thus the baroreceptor response to sustained arterial pressure increase is different from the increased neural activity produced by acute increases in arterial pressure (Pickering and Sleight, 1977). Resetting takes place within hours and is associated with a reduction in distensibility of the baroreceptor (Angell-James, 1973). The rapidity of resetting suggests that hypertensive damage cannot be the cause. On the other hand, experimentally induced stiffening of the arterial wall by means of, for instance, vitamin D or cholesterol administration, impairs baroreceptor sensitivity and is associated with slight increase of arterial pressure (Angell-James, 1974; Angell-James and George, 1980).

Denervation of arterial baroreceptors causes a great increase in minute to minute variability in arterial pressure, but in one careful study in dogs there was no overall increase in mean arterial pressure (Cowley, Liard and Guyton, 1973). This has not, however, been the universal experience with baroreceptor denervation and moderate hypertension has been reported following denervation of the carotid sinus in man (Pickering and Sleight, 1977). In such procedures the aortic baroreceptors are intact and the effects of complete baroreceptor denervation are unknown in man. In addition, it is possible that increased arterial pressure variability, whilst without effect on mean arterial pressure in the short term, may lead to vascular hypertrophy and so produce long-term effects. There is, however, no convincing evidence to implicate baroreceptor dysfunction in essential hypertension in man.

It is conceivable that increased arterial pressure variability induced by impaired baroreceptor reflexes produces structural hypertrophy.

There is more evidence for changes in the central mechanisms which govern sympathetic nervous system activity. This is demonstrated most easily in the genetically hypertensive strain of rat which has been used extensively as a model of essential hypertension in man (spontaneously hypertensive rat SHR (Yamori, 1982)). Young SHR, even in the prehypertensive phase, show an exaggerated response to alerting stimuli in the environment: this is manifested through an increased arterial pressure, stroke volume and heart rate response. The resting circulation of these animals is also slightly hyperkinetic.
Increased cardiac noradrenaline turnover has been demonstrated and, in some studies, increased plasma concentrations of noradrenaline and dopamine beta hydroxylase (Yamori, 1982).

Folkow (1982) has integrated these observations with his analysis of the consequences of resistance vessel hypertrophy. He suggests that exaggerated responses to environmental stimuli set up structural changes in resistance vessels, thus giving rise to sustained hypertension. Left ventricular hypertrophy and renal vascular changes may also contribute.

A fascinating model of the way in which environmental and genetic factors may interact has been produced in rats of the SHR strain by subjecting them to deprivation of environmental stimulation. The normal increase in arterial pressure to acute stress was delayed and reduced, although it was still possible to demonstrate sympathetic hyperresponsiveness. In contrast, in SHR exposed to chronic environmental stress, the arterial pressure increase was accentuated (Folkow, 1982).

It is difficult to measure stress in man, but this does not imply that it is not an important environmental factor in the development of hypertension. In one study subjects with a family history of hypertension were exposed to the stress of mental arithmetic under pressure (Falkner et al., 1979). They exhibited an increased heart rate, pressor and catecholamine response compared with subjects without such a family history. In addition, Jonsson and Hansson (1977) demonstrated in man that increased exposure to noise was associated with a sustained increase of arterial pressure.

Further evidence is provided by haemodynamic studies of essential hypertension. The defence reaction in man shows haemodynamic similarities to the early stages of early hypertension with increases in arterial pressure, heart rate, cardiac output and muscle blood flow (Brod et al., 1959).

Such haemodynamic measurements provide only an indirect assessment in man of the role of sympathetic nervous system over-activity in essential hypertension. There are also substantial problems with careful matching of patients and controls. If, for instance, laboratory personnel are used as controls, it is likely that their defence reaction is substantially different from that of patients or their relatives. In addition, only after long-term follow-up of relatives of hypertensive patients is it possible to say that essential hypertension has developed.

Earlier invasive studies which suggested that the first phase of essential hypertension was an increase in cardiac output have not been confirmed by more recent studies using non-invasive methods. This implies that in many patients peripheral resistance is increased ab initio (Lund-Johansen, 1983). Another measurement of sympathetic nervous system activity would therefore be of great value. Early reports suggested that plasma noradrenaline was increased in patients with essential hypertension. This finding aroused great interest and was confirmed in some studies but not others. In a recent review of 32 such studies Goldstein (1981) observed that 28 reported higher concentrations in the hypertensive group, although in only 13 was the difference statistically significant. Curiously, the discrepancy between positive and negative investigations lay in differences in the normotensive and not hypertensive groups. Many of these studies have paid insufficient attention to the source of their subjects, age and other social factors and no firm conclusion is possible on the current evidence regarding sympathetic overactivity in essential hypertension.

In summary, there is good evidence in the genetically hypertensive rat for an early increase in sympathetic responsiveness and this seems to be central in origin. In man, the evidence is much weaker although perhaps suggestive. This does not imply of course that any increased responsiveness is necessarily causal in hypertension. It may, for instance, be a manifestation of a generalized membrane disturbance and if such a disturbance also affected the vascular smooth muscle, this may be the relevant factor determining arterial pressure.

**Sodium excretion in hypertension**

When a bilaterally nephrectomized patient or animal is maintained on dialysis, arterial pressure increase may be produced by sodium loading and relieved by sodium removal. Such hypertension is termed renoprival. When dialysis became a feasible procedure, a prolonged debate developed on whether renoprival hypertension may be attributed solely to sodium retention or to removal of a renal vasodepressor system in addition. The difficulty lay in defining the normal extracellular fluid and sodium content of an anephric patient or animal (Swales, 1975b). With increasing experience of haemodialysis, however, it became clear that arterial pressure in a large majority of anephric subjects could be controlled by withdrawal of sodium and water (Vertes et al., 1969; Brown et al., 1971). Such dialysis-sensitive hypertension also occurs in the
majority of patients with terminal renal disease (e.g. chronic pyelonephritis or glomerulonephritis) and it is a reasonable assumption that these patients have effectively been subjected to autonephrectomy.

How does the sodium ion cause arterial pressure to increase in renoprival hypertension? Two types of hypotheses have been propounded. One group of hypotheses postulates that sodium retention produces a direct effect on peripheral resistance vessels; this will be discussed in relation to smooth muscle responsiveness. The other hypothesis attributes the increase in arterial pressure to increased cardiac output secondary to increased venous return to the heart (Guyton et al., 1974). Increased cardiac output according to this hypothesis leads to "luxury overperfusion" of the tissues. This results in protective autoregulatory vasoconstriction which reduces tissue blood flow to normal, but at the expense of increased arterial pressure. This hypothesis was supported by observations on the effects of sodium loading of partially nephrectomized dogs which produced an initial increase in arterial pressure associated with an increase in cardiac output which was followed subsequently by increased peripheral resistance after a few days. The autoregulatory hypothesis of Guyton and his colleagues was accepted widely for several years as it appeared to be consistent with the apparent increase of cardiac output in the early phase of essential hypertension, although, as we have seen, this is now rather uncertain. However, the hypothesis has been subjected to other criticisms over the past few years. For instance, when dialysis patients were loaded with saline in one study (Kim et al., 1976) the accompanying hypertension was associated usually with an increase in peripheral resistance without an initial phase of high cardiac output. In addition, by changing sodium balance in dogs with experimental hypertension, it was possible to increase cardiac output without changing arterial pressure and to produce hypertension without increasing cardiac output (Stephens et al., 1979).

It may be that the original experiments of Guyton and co-workers were misleading. Autoregulation is an instantaneous process and adjustments of cardiac output and peripheral resistance may take place almost simultaneously and be impossible to detect as arterial pressure increases with volume overload. This makes the hypothesis extremely difficult to test but, using conventional methods, it appears that the hypertension produced by sodium overload may be dissociated from changes in cardiac output and that increased cardiac output is not a sine qua non. Additionally, it is worth emphasizing that, although autoregulation is a well documented physiological phenomenon in isolated vessels, it is frequently overridden in vivo; increased peripheral resistance is certainly not an inevitable consequence of an increase in cardiac output.

How far can the mechanisms responsible for volume overload hypertension in nephrectomized patients be responsible for essential hypertension? There is no evidence that exchangeable sodium is increased in essential hypertension (Swales 1975b). In one recent study exchangeable sodium was significantly subnormal in hypertensive subjects under the age of 35yr (Beretta-Piccoclli et al., 1982). Plasma volume and interstitial volume are reduced in proportion to the degree of hypertension (Tarazi, Frohlich and Dustan, 1968; Bing and Smith, 1981; Bauer and Brooks, 1982). Guyton and colleagues (1974) observed that, despite these findings, there is apparently an anomaly in the renal excretion of sodium. Thus even small increases of renal perfusion pressure produce an immediate natriuresis and diuresis. This system of modulating arterial pressure by sodium depletion does not operate over the restricted range of other arterial pressure control systems such as the baroreflex arc, and could therefore assume over-riding dominance. Since renal perfusion pressure is increased in essential hypertension without such a profound natriuresis, the pressure-natriuresis response curve must be shifted to the right (fig. 2). The important question, however, is whether or not this apparent anomaly is a

![Fig. 2. Altered perfusion natriuresis relationship in essential hypertension. The anticipated increase in sodium and water output produced by increased systemic pressure is not seen.](https://academic.oup.com/bja/article-abstract/56/7/677/44225 by guest on 26 December 2018)
cause or a consequence of hypertension. A perfusion pressure natriuresis inevitably produces plasma volume contraction which in turn causes renal tubular retention of sodium. Ultimately a new steady state is produced with slightly contracted plasma and extracellular fluid volumes and this indeed appears to be the situation in essential hypertension (Swales, 1977; Omvik, Tarazi and Bravo, 1980). The same process may be mimicked by experimental renovascular hypertension induced by applying a constricting clip to one renal artery. Provided that the opposite kidney is left in place as arterial pressure increases, sodium balance becomes negative until a new steady state is reached without further loss of sodium (Swales et al., 1972).

There is some evidence that there is a genetically induced alteration in renal function in patients with hypertension. Grim and colleagues (1979) observed that urinary sodium excretion after saline infusion was less in first degree relatives of hypertensive patients compared with normal subjects. However, a later report indicated that plasma renin was slightly higher, suggesting that genetically predisposed individuals did not have significant sodium retention before infusion (Luft, Weinberger and Grim, 1982). Indeed, these observations are more consistent with a mild sodium deficit in this group. Another study using a shorter saline infusion period showed the converse effect, with an immediate natriuretic response in relatives of hypertensive patients (Wiggins, Basar and Slater, 1978).

Whilst plasma volume is not increased in essential hypertension it does tend to be distributed slightly differently, with an increased proportion of blood in the cardiopulmonary circuit (Ulrych et al., 1969). Importance has been attached to this observation in that it might explain an initial increase in cardiac output despite a contracted overall plasma volume; however, this interpretation is open to considerable doubt (Birkenhager and Schalekamp, 1976) and it seems rather more likely that redistribution of plasma volume is a consequence and not a cause of essential hypertension, or at least the pattern of autonomic activity which underlies it.

Sodium intake in essential hypertension

Different evidence has been produced from anthropological studies of sodium intake. Thus, some primitive cultures exhibit a low arterial pressure which does not increase with advancing age. Further, immigration to a more Western style of living is associated in some of these with increase of arterial pressure values (Cruz-Coke, Etcheverry and Nagel, 1964). Such studies have to be interpreted with considerable caution (Swales, 1980; Laragh and Pecker, 1983). The data are extremely uncertain. Attempts to demonstrate a relationship between sodium intake and arterial pressure in a single population have usually failed, although the measurement of sodium intake is difficult and insensitive to small differences between individuals (Watt and Foy, 1982). Nevertheless, the relationship between salt intake and arterial pressure is clearly not a close one, and it has to be borne in mind that differences in salt intake act as a marker for other factors. Usually, salt intake increases with acceptance of a Western lifestyle. Many other factors change, mostly subsumed under the general title of “stress” (Seedat, 1983).

The role of other dietary factors such as lipid and protein intake, malnutrition and chronic infection is very difficult to assess in this type of study. There is, for instance, good evidence that vegetarian diets, and diets modifying the ratio of polyunsaturated to saturated fats decrease arterial pressure independently of electrolyte intake (Puska et al., 1983; Rouse et al., 1983). Whilst salt restriction, particularly if sufficiently severe, reduces arterial pressure, this does not necessarily indicate a pathogenetic role for salt intake; it may simply reflect the fact that patients with essential hypertension are unable to maintain normotension in the face of extracellular fluid volume contraction as well as normal subjects. This may reflect impaired responsiveness of the renin-angiotensin system (see below).

In summary, there is no convincing evidence that overall retention of sodium or redistribution of sodium within the body plays any role in essential hypertension; there is also no evidence that excessive ingestion of sodium can be incriminated in essential hypertension.

Cell membrane abnormalities in essential hypertension

There are abnormalities in the transport of sodium and potassium across the erythrocyte and leucocyte cell membrane. Early studies showed increased red cell sodium content (Losse, Wehmeyer and Wessels, 1960). More recently it has become clear that hypertensive patients are heterogeneous in this respect: intracellular sodium concentration is increased in a minority of patients who have values above the normal range (Clegg, Morgan and Davidson, 1982). These abnormalities are shared by first degree blood relatives of hypertensive patients in
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addition, and so a genetic factor is likely.

To understand how such a change can be produced it is necessary to undertake dynamic studies of electrolyte fluxes. Opposing the passive movement of sodium and potassium down their respective concentration gradients there is an active energy-consuming sodium pump which is dependent on the activity of an enzyme, $\text{Na}^+\text{K}^+\text{ATPase}$, composed of a phospholipid protein complex lying within the cell membrane (fig. 3). The sodium pump moves potassium inwards and sodium outwards and is responsible for maintaining the potential difference across cell membranes. Since it is specifically inhibited by ouabain, it is referred to as the ouabain-sensitive sodium pump. Whilst conflicting results have been obtained with the erythrocyte (Swales, 1982), reduced sodium pump activity in the white cell has been demonstrated by several groups (Edmondson et al., 1975; Heagerty et al., 1982).

The situation is complicated, however, by the fact that abnormalities in other transport processes may occur. The physiological role of such processes is uncertain. For instance, a carrier protein within the erythrocyte cell membrane exchanges one external sodium ion for one internal sodium ion (sodium–sodium countertransport). This process (usually measured as lithium–sodium countertransport) is increased in some hypertensive patients (Canessa et al., 1980). Another process transports sodium and potassium together across the cell membrane; this is inhibited by frusemide (frusemide-sensitive sodium–potassium co-transport). Early reports suggested that this was diminished in essential hypertension (Garay et al., 1980). Indeed, there was so little overlap between values obtained from patients with essential hypertension and patients with renovascular hypertension that it was advocated as a laboratory test for essential hypertension. Later studies, however, revealed a more confusing situation and in other populations only minor differences were observed (Davidson, Opie and Keding, 1982), whilst in an American hypertensive population sodium–potassium co-transport was increased (Canessa et al., 1981). Changes in sodium–sodium countertransport could not of course influence intracellular cations, and it is doubtful if sodium–potassium co-transport could produce a net effect as it is a bi-directional process; unidirectional fluxes inwards and outwards are probably equal (Brand and Whitam, 1984).

Assuming that such changes are somehow related to the cause of hypertension and not a consequence of hypertension, there are two types of explanation. According to the first explanation, one or more of the abnormal processes is present in vascular smooth muscle and participates directly in the mechanism which causes vasoconstriction. According to the second hypothesis there is a global abnormality of cell membrane function in patients with essential hypertension which gives rise to increased vasoconstriction and to the abnormalities in ion fluxes.

An intriguing hypothesis was proposed by Blaustein (1977), who argued that there is a linked countertransport system in vascular smooth muscle which exchanges calcium for sodium ions. This is inhibited by the increased concentration of intracellular sodium so that the efflux of calcium from the cell is reduced, and there is an increase in intracellular calcium and enhanced smooth muscle contractility (fig. 4). There is little doubt that calcium is an essential messenger in the chain of processes which causes smooth muscle to contract (Bolton, 1979). The existence of a sodium–calcium exchange sys-

![Fig. 3. Passive diffusion of sodium into the cell is opposed by the ouabain-sensitive sodium pump.](https://academic.oup.com/bja/article-abstract/56/7/677/442725/figs/fig03)

![Fig. 4. The Blaustein hypothesis. A sodium–calcium countertransport mechanism (2) is inhibited by increased intracellular sodium and so intracellular calcium accumulates and causes increased reactivity.](https://academic.oup.com/bja/article-abstract/56/7/677/442725/figs/fig04)
tern in vascular smooth muscle is, however, still debatable (Mulvaney et al., 1982).

There are no satisfactory data on intracellular sodium in vascular smooth muscle in essential hypertension and the increase in intracellular sodium in blood cells is (even where reported) relatively small; values overlap with those obtained from normotensive individuals. Consequently, the essential data necessary to test the Blaustein hypothesis, that is intracellular sodium and calcium concentrations in vascular smooth muscle, are not available; in addition the Blaustein hypothesis does not explain the other abnormalities in ion fluxes. It does, however, offer an attractive mechanism to explain the undoubted increase in arterial pressure when, for instance, dialysis patients are loaded with sodium.

De Wardener and MacGregor (1982) have developed the further Blaustein hypothesis. They have suggested that the extrusion of sodium is impaired by a circulating inhibitor of the sodium pump, and that this increases the intracellular calcium by the mechanism postulated by Blaustein. They argue that in essential hypertension there is a genetic inability to excrete sodium; the resultant minor degrees of sodium retention cause secretion of natriuretic hormone which inhibits sodium transport in the renal tubule, thereby causing natriuresis. However, this hormone also has the less desirable action of inhibiting sodium transport in other tissues. Thus the sodium pump is depressed and smooth muscle intracellular sodium increased. Cytochemical evidence has been advanced for the existence of such an inhibitor in essential hypertension. Furthermore, it has been shown that this inhibitory activity is also increased in normal patients receiving a high-salt diet (de Wardener and MacGregor, 1982). This hypothesis also depends critically upon very debatable evidence for sodium retention as a primary event in essential hypertension (see above). In its latter formulation the hypothesis has been modified to suggest that central diversion of the vascular compartment could stimulate secretion of natriuretic hormone even though, overall, there was no increase, or indeed perhaps a slight decrease, in plasma volume.

An alternative hypothesis is that there is a generalized intrinsic abnormality in the cell membrane in essential hypertension. Thus sodium—potassium ATPase, sodium—potassium co-transport and probably lithium—sodium countertransport are dependent upon the nature of the lipid content of the cell membrane bilayer (Swales, 1983). Cell membrane viscosity reflecting phospholipid content is an important determinant of ion fluxes across the cell membrane (Cooper, 1977). Increased cell membrane viscosity has been demonstrated in the erythrocytes of patients with essential hypertension (Orlov and Postnov, 1982) and in spontaneously hypertensive rats. It seems possible, therefore, that this defect underlies the multiple defects which have been described in essential hypertension. If so, the presence of similar abnormalities in normotensive relatives (Meyer et al., 1981; Heagerty et al., 1982; Woods et al., 1982) would be explained. Likewise, this would provide an explanation for the fact that reduced red cell sodium pump activity may be demonstrated in conditions not necessarily associated with hypertension, such as renal failure (Cole, Balfe and Welt, 1968), and obesity (de Luise, Blackburn and Flier, 1980). Further, there is strong evidence that there are important ethnic differences in sodium pump activity (Beutler, Kuhl and Sacks, 1983).

If there is a generalized cell membrane defect in essential hypertension for which these abnormalities act as a marker, there still remains the problem of whether or not there is a direct link between the membrane abnormality and hypertension. There is no certain answer to this question, but there are some possibilities. For instance it may be that the cell membrane is slightly depolarized (fig. 5) causing an increased sensitivity to vasoconstrictor agents (Jones, 1974; Hermsmeyer, 1976). Alternatively or perhaps associated with such a change, it is possible that there is an additional abnormality in calcium...
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handling. Unfortunately, technology in this area is only in its infancy. However, the binding of calcium by the inner aspect of the cell membrane is reduced both in patients with essential hypertension and in rats with genetic hypertension (Orlov and Postnov, 1982). Calcium pumping may also be abnormal. For instance, ATP-dependent transport of calcium is decreased in smooth muscle plasma membranes prepared from the mesenteric artery of spontaneously hypertensive rats and some other forms of experimental hypertension (Kwan and Daniel, 1981). It is possible, therefore, that at some stage in the development of essential hypertension a cell membrane abnormality gives rise to increased cytosolic calcium (Swales, 1983). There is indirect evidence for this, since there is an apparent hyper-responsive sensitivity of forearm resistance vessels to the vasodilator action of the calcium antagonist verapamil (Robinson, Dobbs and Bayley, 1982). It is likely that major developments will occur in this important area over the next few years.

Other arterial pressure control systems

There is little evidence that the renin-angiotensin system plays any significant role in essential hypertension (Swales, 1979). In a small minority of patients, plasma renin concentrations are slightly increased. This is associated, in some patients, with malignant hypertension and it seems likely that hyper-reninaemia is a secondary change either as a result of vascular damage at the juxtaglomerular level, or perhaps as a result of fluid volume depletion which may occur in severe hypertension. In other cases, high renin concentrations may be associated with increased sympathetic nerve activity (Esler et al., 1978). In a rather higher proportion of patients, plasma renin concentrations are low and respond subnormally to such stimuli as salt restriction and diuretic therapy. These patients are usually slightly older than patients with normal or high renin essential hypertension, and this abnormality may represent an acquired defect of renin storage or release (Esler et al., 1978).

It has been suggested that, in essential hypertension, there is a balance between the renin-angiotensin system tending to promote vasoconstriction and volume expansion which would normally suppress plasma renin. According to this view, low renin hypertension represents the "volume end of the spectrum" whilst high renin hypertension represents the vasoconstrictor end (Laragh, 1976). A recent study has demonstrated a factor in the plasma of patients with "low renin hypertension" which inhibits the ouabain-sensitive sodium pump and has concluded that such activity is produced in response to volume expansion (Haddy, 1983). There is, however, no evidence that plasma renin is suppressed by volume expansion in low renin hypertension (Dunn and Tanner, 1974: Padfield et al., 1975) and it seems much more likely that changes in plasma renin in essential hypertension are secondary to other factors, such as increased renal perfusion pressure or structural changes in the juxtaglomerular apparatus (Swales 1975a).

It is possible that other humoral systems are implicated in the pathogenesis of essential hypertension. One of the most interesting possibilities is that there is a humoral vasodepressor system originating in the renal medulla. The interstitial cells of the renal medulla contain secretory granules. In tissue culture these cells may be shown to produce both prostaglandins and non-prostanoid lipids (Muirhead, 1980). Vasodepressor material can be detected in the renal effluent blood when renal artery stenosis is relieved experimentally and subcutaneous transplants of renal medullary tissue decrease arterial pressure in certain experimental models of hypertension. Chemical destruction of the renal medulla produces sustained hypertension in rats and this is associated with neither renin secretion nor sodium retention (Bing et al., 1983).

Unfortunately it is not possible at present to assay such lipids in human plasma and the role of the postulated reno-medullary vasodepressor system in essential hypertension cannot therefore be assessed.

SUMMARY

We are still uncertain of the way in which environment and heredity interact to produce increased arterial pressure in patients with essential hypertension. Few indisputable abnormalities can be demonstrated. Of these there is universal agreement that structural vessel hypertrophy is present and this acts probably as a maintenance and perhaps amplifying system resulting from an initial increase in arterial pressure. It cannot of course explain an increase in arterial pressure ab initio. Most of the well defined systems of arterial pressure control do not show any marked abnormality, although there is some evidence for a modest degree of sympathetic nervous system overactivity. Although some of the changes in cation fluxes across erythrocyte and leucocyte membranes are still debatable, there is general agreement that cation handling by erythrocytes
and leucocytes is abnormal in many patients with essential hypertension and that some of these abnormalities are shared by the normotensive relatives of hypertensive patients. The most promising approach is that there is an abnormality of the cell membrane vascular smooth muscle which is partly genetically determined and perhaps also involves the autonomic nervous system. This produces an increased pressor response to environmental stimuli which becomes perpetuated and perhaps amplified by structural hypertrophy of the resistance vessels.

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