Neurogenic hypertension revisited

C. J. DICKINSON

Department of Medicine, St Bartholomew's Hospital Medical College, London

Introduction

Sixteen years ago I reviewed (Dickinson, 1965) the evidence that essential hypertension was neurogenically initiated and suggested that its primary cause was a rise in the minimal resistance of the arteries supplying the brain stem. At that time very few investigators supported a neurogenic hypothesis and those that did believed that the neurogenic stimulus was psychological, rather than organic. Things have changed a bit. I shall try to show why.

The disproof of two popular theories

Primary increase in peripheral arterial resistance

Essential hypertension might result from a primary, generalized, non-neurogenic increase of peripheral systemic arterial resistance (e.g. Hoobler, 1961). This might be due to an increased salt content of arterial walls making them stiffer, or to an excess of a circulating constrictor substance, or to the lack of some normal arterial vasodilator material, perhaps secreted by the kidneys. I do not want to discuss details nor to go into the objections of Guyton (1980), with which I entirely agree, that without the active participation of the kidneys no such hypertension could be sustained. I simply wish to make the point that this theory demands that cardiac output in early essential hypertension should either be slightly reduced or normal. For, if the first change in essential hypertension is increased resistance to flow through the tissues, there must initially be a reduction in flow as arterial pressure rises. It is arguable that tissues might 'autoregulate' (i.e. control their intrinsic vascular resistance so as to maintain flow) so well that the eventual reduction in flow might be unmeasurable. But cardiac output in early essential hypertension has been found almost invariably to be slightly greater than normal (e.g. Widimský, Šejfarová & Šejfar, 1957; Eich, Peters & Lyons, 1958; Lund-Johansen, 1967; Frohlich, Tarazi & Dusant, 1971; Julius, 1976).

Such observations in many series of patients are incompatible with essential hypertension being initiated in the majority of patients solely by a generalized increase of systemic arterial resistance.

Primary renal salt and water retention

Essential hypertension might result from a primary retention of salt and water by the kidneys (Borst & Borst de Geus, 1963; Ledingham & Cohen, 1964; Coleman & Guyton, 1969). This theory envisages the following sequence of events.

Step 1: some genetic or acquired intrinsic renal change alters the functional relationship in the kidneys between perfusion pressure and sodium excretion. Step 2: given a moderate or high-sodium diet there is some sodium and water retention, thus increasing blood volume, mean circulatory filling pressure, venous return to the heart and cardiac output. Blood pressure rises until sodium and water balance is regained. Step 3: later there follows autoregulation of tissues generally, leading to a rise of peripheral resistance and return of blood volume and cardiac output towards normal.

This theory is plausible and may well explain some cases. Step 1 could be afferent glomerular arteriolar narrowing. There is good animal evidence for steps 2 and 3 (summarized by Guyton, 1980) though the events in step 3 are disputed, especially the time scale (Korner, 1979).

The theory demands that blood and plasma volume in early essential hypertension should be slightly increased or perhaps normal (since it is arguable that the increases might be too small or...
transient to detect). But blood and plasma volumes in early essential hypertension have almost invariably been found to be slightly less than normal in large series, often significantly so (Walser, Duffy & Griffith, 1956; Rochlin, Shohl & Blakemore, 1960; Tibblin, Bergentz, Bjure & Wilhelmsen, 1966; Brown, Brown & Krishan, 1971; Julius, Pascual, Reilly & London, 1971; Ibsen & Leth, 1973; Dustan, Tarazi, Bravo & Dart, 1973; Parving & Gygntberg, 1973; Safar, Weiss, London, Chau & Milliez, 1977; Weidmann, Hirsch, Beretta-Piccoli, Reubi & Ziegler, 1977; Messerli, DeCarvalho, Christie & Frohlich, 1979; Safar, London, Levenson, Simon & Chau, 1979; Simon, Franciosa & Cohn, 1979). I have found only one small series (Hansen, 1968) in which slightly increased volumes were reported. To quote a review by Tarazi (1976), 'an important characteristic of the majority of essential hypertensives is a reduction in plasma volume'.

Thus in their original form both theories are disproved by the evidence and it is surprising to me that both still have supporters. It is interesting that Guyton (1980) is concerned about evidence suggesting both that increased cardiac output can persist for long periods in young hypertensives and that blood volume is slightly less than normal, on average. He includes a special chapter (p. 483) listing fallacies in interpreting cardiac output and blood volume data. However, there is no reason a priori (e.g. a lower incidence of varicose veins) for supposing that the blood or plasma volume in essential hypertension should be on the low side of normal.

Logical investigators must, I believe, conclude that neither hypothesis can be sustained in its original form as an explanation for the majority of cases of essential hypertension. More complex mechanisms need to be invoked. For example, generalized arterial vasoconstriction or fluid retention by the kidneys might be accompanied by generalized venous constriction, thus reducing the capacitance of the circulation and hence allowing a higher than normal venous return and cardiac output to be associated with a reduced blood volume. There are many other theoretically possible variants, but they all lack the simplicity of the original concepts and demand that more than one initiating mechanism is involved.

There is an important further objection to both these theories, even in a more complex or modified form. All theories which deny a primary role to the central nervous system necessarily embrace the corollary that the nervous system, through the peripheral arterial baroreceptor reflex, should react in the first instance to a peripherally induced pressure rise by slowing the heart. As the sensitivity curve of the baroreceptors becomes reset (McCubbin, Green & Page, 1956) the heart rate would return towards normal. Thus the heart rate in early essential hypertension should be slightly decreased or normal.

But the heart rate in early essential hypertension has almost invariably been found to be slightly increased and, in large series, significantly so (Lund-Johansen, 1967; Frohlich et al., 1971; Julius, 1976; Esler, Zweifler, Randall, Julius & de Quattro, 1977; Chau, Safar, Weiss, London, Simon & Milliez, 1978; Johnston, 1980).

By invoking more complex mechanisms the slightly increased heart rate can be 'explained', e.g. by increased reactivity of the sinus node to a normal or reduced amount of nerve impulse traffic, but the original simplicity of the volume-overload theory is lost.

Some will object to the use of the type of clinical evidence I have cited (i.e. slightly increased cardiac output and heart rate, and slightly decreased blood and plasma volume) on the basis simply that the changes are slight, even though statistically impressive. To this I would reply that regulation of blood pressure is immensely complicated and is known to involve a host of different mechanisms. Nearly all the mechanisms we know about eventually reset their sensitivity so as to stabilize hypertension on their own account, whatever its cause. This diminishes the intensity of the initiating stimulus needed. I can cite an exact analogy.

Using conscious rabbits with indwelling catheters, I arranged a control system in which blood pressure was continuously measured and kept at a constant high level by automatic controlled intravenous infusion of synthetic angiotensin II. When blood pressure went down, the infusion rate was increased and vice versa. Plate 21 of my book (Dickinson, 1965; p. 130) shows that an elevation of 35 mmHg in mean arterial pressure could eventually be sustained by an infusion rate of angiotensin initially without measurable pressor effect. This led to the discovery that low infusion rates of angiotensin, initially having no measurable pressor effect, could eventually bring about and sustain hypertension (Dickinson & Lawrence, 1963). This observation has since been widely confirmed (e.g., McCubbin, DeMoura, Page & Olmsted, 1965; Cowley & McCaa, 1976; Bean, Brown, Casals-Stenzel, Fraser, Lever, Millar, Morton, Petch, Riegger, Robertson & Tree, 1979).

When we seek the initiating cause of essential hypertension, therefore, it is unreasonable to
expect, or to seek, large changes in blood volume, cardiac output and heart rate or, for that matter, in circulating catecholamines (as I shall discuss below). Because of the variability of all these things from minute to minute we must be prepared to look for and take account of small changes and tendencies only apparent when examining large numbers of patients and control subjects under comparable conditions.

Positive attractions of a primary neurogenic hypothesis

Compatibility with clinical measurements in essential hypertension

If essential hypertension is due to a primary increase in efferent sympathetic nervous activity, to both heart and periphery, it is logical that early on there should be slightly increased cardiac output and heart rate, such as are in practice found. It is not logically obvious that there should be a slightly decreased blood volume, but much clinical and experimental evidence suggests that both acutely and over long periods of time blood volume tends to change in the opposite direction to any change in efferent sympathetic nerve activity. In man chronic noradrenaline hypersecretion from a phaeochromocytoma is often associated with hypovolaemia (Tarazi, Dustan, Frohlich, Gifford & Hoffman, 1970; Deoreo, Stewart, Tarazi & Gifford, 1974), suggesting that neurogenic vasoconstriction, which is mediated by noradrenaline, should have the same effect in animals. Conversely, a generalized reduction of efferent vasoconstrictor sympathetic activity by adrenergic neuron blockade (Page & Dustan, 1959; Dollery, Emslie-Smith & Milne, 1960; Smith, 1963) tends to cause fluid retention and increased blood volume, to the extent that congestive heart failure is sometimes precipitated.

Compatibility with plasma catecholamine measurements in essential hypertension

I have already pointed out that a very small stimulus (e.g., an initially subpressor infusion of angiotensin) may be enough to raise blood pressure substantially over periods of days or weeks. We might anticipate, however, that if the primary cause of essential hypertension is an increased impulse traffic in efferent sympathetic nerves there would be a slightly greater than normal overspill of transmitter and thus plasma catecholamines should be increased. However, as I pointed out previously (Dickinson, 1965) there is very little overspill of transmitter except at very high rates of impulse traffic. Therefore, using my previous argument about the importance of studying very large numbers of patients, we should be looking for a small (e.g., 5%) difference in plasma noradrenaline in young essential hypertensive patients when compared with control subjects carefully matched not only for age and sex, but also for the conditions of study. (Hospital patients generally have higher plasma noradrenaline values than matched 'control' laboratory workers who are familiar with the hospital environment; Jones, Hamilton & Reid, 1979.)

My impression is that a majority of workers have found slight increases in plasma noradrenaline in essential hypertension, but it would not be difficult by selective citation from the huge literature to support the opposite conclusion. Much larger studies are needed. I previously argued on theoretical grounds (Dickinson, 1965) that resetting of basal pressure, especially during deep sleep, might be of greater importance than a generalized round-the-clock increase of sympathetic nervous activity, and it might be best to look for a difference in plasma noradrenaline between essential hypertensives and normotensives during sleep rather than during waking hours.

Close resemblance between essential hypertension and the Okamoto spontaneously hypertensive rat and the evidence of neurogenic initiation of hypertension in the Okamoto rat

Several strains of rat have been selectively inbred to develop hypertension, but the most important has been that developed by Okamoto. Virtually all investigators concur that this animal is the closest model of essential hypertension in man. In particular, in contradistinction to all other animal models, cerebral haemorrhage is common, even in the absence of malignant hypertension. All the drugs which are effective in treating human hypertension can be used to treat Okamoto hypertension (e.g., Freis, Ragan, Pillsbury & Mathews, 1972).

I have mentioned three characteristics of human essential hypertension seen when large series of patients are examined, i.e.: (1) slightly low blood volume; (2) slightly increased cardiac output; (3) slightly increased heart rate. All these changes, in similarly slight but, in most series, significant degree, have been reported in the Okamoto spontaneously hypertensive rat (SH rat): e.g., blood volume (Okamoto, Yamori, Ooshima, Park, Haebara & Matsumoto, 1972;
Rippe, Lundin & Folkow, 1978; Gross & Dietz, 1979; Samari & Coleman, 1979); cardiac output (Pfeffer, Frohlich, Pfeffer & Weiss, 1974; Gross & Dietz, 1979); heart rate (Iriuchijima, 1973a; Trippodo, Walsh & Frohlich, 1979).

Most investigators at present believe that the hypertension of the Okamoto SH rat is neurogenically initiated, though subsequently maintained by other means (Okamoto, Nosaka, Yamori & Matsumoto, 1967; Iriuchijima, 1973b; Bell & Kushinsky, 1978; Judy, Watanabe, Henry, Besch & Aprison, 1978; Saavedra, Grobecker, Besch, & Axlerod, 1978; Clark, Jones, Phelan & Devine, 1979; Schramm & Barton, 1979).

Treatment of newborn SH rats with 6-hydroxydopamine or anti-nerve growth factor (thus preventing proper development of the sympathetic nervous system: Folkow, Hallbäck, Lundgren & Weiss, 1972; Dietz, Haebara, Schömig, Rascher, Berecek, Mann, Lüth & Gross, 1979) and administration of large doses of guanethidine or combinations of the other agents (Johnson & Macia, 1979) largely prevents the subsequent development of hypertension.

Implications of a primary neurogenic hypothesis

Some implications are mundane. For example, I do not dispute Guyton's contention that no long-term blood pressure rise can be maintained unless there is resetting of the renal sodium and water excretion curve in such a way that the high arterial perfusion pressure does not cause a massive salt and water diuresis. The central nervous system has all sorts of ways of resetting renal function, e.g. by increased sympathetically induced arterial vasoconstriction, by increased vasopressin secretion and (indirectly) by increased aldosterone secretion. However, observations on isolated perfused rabbit kidneys (Thompson & Dickinson, 1975) showed that renal artery clip hypertension brought about long-standing changes in the opposite (untouched) kidney such that the excretion threshold for salt and water was shifted to a higher level. It is likely that a neurogenically mediated rise of blood pressure, and/or a neurogenically mediated change in renal excretory function, results in a sustained change in renal function which would restrain renal salt and water excretion without the need for a continual high level of nervous influence on the kidneys. Narrowing of afferent arterioles is well known to occur in the untouched kidney in longstanding two-kidney, one-clip renovascular hypertension and could provide a structural basis for renal sodium excretion curve resetting. In this connection it is important to note that chronic neurogenic hypertension from extensive arterial baroreceptor denervation (Ito & Scher, 1979) or from bilateral solitary tract lesions (Nathan & Reis, 1977) can be sustained for long periods, even with the animals at rest. Thus we can be reasonably sure that a chronic neurogenic stimulus for hypertension can force the kidneys to co-operate in maintaining an elevated blood pressure.

Other implications, however, are far from mundane. Proponents of neurogenic hypotheses have generally assumed that subconscious emotional conflicts lie at the root of essential hypertension in man. It is difficult to attribute the hypertension of SH rats to subconscious emotional conflicts. If the Okamoto rat and the essential hypertensive human share a common neurogenic initiating factor this must have a tangible organic nature. Perhaps a majority view would now favour some disturbance of central neurotransmitter function, possibly in the brain stem (e.g. Judy et al., 1978). This could be excessive activity in excitatory noradrenergic pathways (Saavedra et al., 1978) or diminished activity in inhibitory pathways, perhaps involving 7-aminobutyric acid.

There has been some very exciting new work in the last few years, mainly from Reis and his collaborators, e.g. Kumada, Dampney & Reis (1979). Reis began by trying to uncover the mechanisms underlying the 'Cushing' reflex, i.e. the rise of blood pressure produced by cerebral compression. This led to the identification of small discrete bilateral regions of the brain stem, just beneath the floor of the fourth ventricle in cats and rabbits.

The integrity of the brain is necessary for most kinds of hypertension to be sustained. For example, 6-hydroxydopamine treatment can prevent the development of deoxycorticosterone acetate (DOCA)-salt hypertension in Dahl rats (Takeshita, Mark & Brody, 1979) and efferent sympathetic activity is increased in DOCA-salt hypertension (De Champlain & Van Ameringen, 1972).

Lesions of brain stem centres prevent the development of neurogenic hypertension acutely, the cerebral ischaemic pressor response (the 'Cushing' reflex; Dampney, Kumada & Reis, 1979) and the hypertension induced by axial brain stem distortion. Bilateral lesions also cause an irreversible fall of 30–40 mmHg blood pressure (Kumada et al., 1979). Slightly higher brain stem lesions can prevent the development of experimental renal hypertension (Brody, Buggy, Fink & Johnson, 1976). If essential hypertension is due to some primary neurogenic and organic
(as opposed to psychological) malfunction, it seems most likely that the disorder is located in these highly specific and localized centres in the brain stem.

I would like to speculate that the Okamoto rat's inbreeding might have gradually altered the vascular anatomy of the rat hindbrain in such a way that minimal vascular resistance was increased, thus necessitating a neurogenically mediated rise in blood pressure similar to that which I have envisaged for essential hypertension. There is some evidence already that in the forebrain vascular lesions particularly occur in territories supplied by (badly named) 're-curent' arteries, i.e. arteries whose take-off from the parent trunk is at an acute angle, which might increase flow resistance (Yamori, Horie, Handa, Sato & Fukase, 1976; Yamori, Horie, Akiguchi, Nara, Ohtaka & Fukase, 1977). It is noteworthy that bilateral carotid artery occlusion in SH rats produces a greater incidence of brain damage and greater proportional reduction in cerebral blood flow than in normotensive controls (Shima, Yokoyama, Ishihara, Kuwabara, Iguchi, Miyazaki, Hibino, Ishikawa & Vozume, 1977; Yamori, Horie & Handa, 1977). I am at present investigating the vascular supply of the brain of the Okamoto rat, because if a similar consistent vascular anomaly were found it would open the possibility of a common aetiology along the lines which I have envisaged for essential hypertension in man (Dickinson, 1965).

Conclusions

Most investigators have remained suspicious of theories of hypertension involving the brain stem blood supply and I will not reiterate my own. A consensus, which appears to me to be supported by a substantial body of evidence, and contradicted by none, is as follows. (1) Essential hypertension could, in certain cases, be plausibly attributed to volume-overload and could have a renal origin. (2) In the majority of cases, however, it is primarily initiated by the central nervous system, specifically the brain stem. (3) The disorder is probably not, in most cases, psychologic in origin, but represents some change in function of localized, discrete and bilaterally represented parts of the bulbar reticular formation.

Rational treatment of any disease begins with recognition of its likely cause. We might not yet agree the cause, but it seems possible to envisage at least the possibility of a cure for essential hypertension directed at the specific brain stem centres I have mentioned, e.g. by controlled infusion of drugs into the vertebral arteries or by stereotactic surgery. This is doubtless premature speculation, but I have the strong feeling that essential hypertension is very close to yielding up its long-sought secrets and thus becoming at last potentially curable.

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