EDITORIAL: CONTROVERSY IN CLINICAL SCIENCE

High arterial pressure versus humoral factors in the pathogenesis of the vascular lesions of malignant hypertension

The case for pressure alone

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A lingering controversy centres around the pathogenesis of arteriolar fibrinoid necrosis in malignant hypertension. One school of thought implicates the height of the arterial pressure as the dominant factor accounting for damage to the arteriolar wall. The other speculate on the existence of a circulating factor of renal origin, which, it is claimed, significantly contributes to arteriolar damage by increasing permeability of the vascular wall. Discussion about other types of hypertensive vascular disease have added to the confusion. Thus Brunner, Laragh, Baer, Newton, Goodwin, Lawrence, Bard & Bühler (1972) stated that renin is implicated in the causation of strokes and coronary artery disease. Although they have subsequently retracted their initial statements, this was not before publication of editorial advice against the use of diuretics in hypertension, so as to avoid raising plasma renin (British Medical Journal, 1972; Lancet, 1973; Goldby & Beilin, 1972a).

'Vascular permeability factor'

The idea of a vascular permeability factor of renal origin stems from the close relationship between renal disease and hypertension. Fahr (1919) described acute fibrinoid necrosis of arterioles in malignant hypertension, and favoured the view that renal disease resulted in arteriolar damage, possibly through the action of a toxin. This opinion was supported by Klemperer & Otani (1931) and Goldblatt (1938), the latter basing his conclusion on failure to find arteriolar necrosis in anephric hypertensive dogs. The propensity of anephric animals and man to develop malignant hypertension is, of course, now well established. There followed several reports of acute vascular lesions produced by injection of renal extracts in dogs (Winternitz, Mylon, Waters & Katzenstein, 1939; Leiter & Eichelberger, 1942). Masson, Corcoran, Page & Del Greco (1956) also observed serous and peritoneal effusions after injection of renal extracts in nephrectomized rats. Nairn, Masson & Corcoran (1956) postulated that the extracts increased permeability of both serous membranes and arterioles independent of their known pressor actions. However, Masson, McCormack, Dustan & Corcoran (1956) subsequently found that reducing the blood pressure with hydralazine prevented arteriolar necrosis in experimental hypertension, and conceded that a high arterial pressure was itself the main causal factor in the pathogenesis of the vascular lesions.

Interest in the concept of a vascular 'permeability factor' was renewed when Asscher & Anson (1963) reported that injection of renal extracts caused serous effusions, increased packed cell volume and vascular lesions. They did not measure arterial pressures. Cuthbert & Peart (1970) used changes in packed cell volume to assay 'permeability factor', but were unable to separate pressor and permeability properties of renal extracts; moreover, these effects were identical with those produced by angiotensin infusion.

A plausible interpretation of the above experiments is that the arteriolar necrosis was a direct consequence of the pressor action of angiotensin. The serous effusions, pulmonary oedema and increased packed cell volume could
be explained by cardiac and renal failure consequent on severe vasoconstriction and hypertension, with perhaps transudation of fluid through necrotic arterioles exposed to a high transmural pressure (Byrom, 1969; Goldby & Beilin, 1972b).

The dominant role of pressure: experimental evidence

Wilson & Pickering (1938) concluded that increased arterial pressure was the main factor in causing arteriolar necrosis when they noted an absence of lesions in clipped kidneys of all but one of their renal hypertensive rabbits, and found a correlation between the severity of vascular lesions and arterial pressure. Herbertson & Kellaway (1960), Byrom (1963) and more recently Giese (1964a) produced arteriolar necrosis in animals when they raised the blood pressure by infusion of methoxamine, noradrenaline and rapid intra-carotid injection of saline (Byrom & Dodson, 1948; Wolfgartern & Magerey, 1959). Byrom & Geise saw alternating constriction and dilatation of cerebral, retinal and gut arterioles in vivo. In Byrom's experiments injections of Evans Blue dye resulted in patchy leakage of the dye into the brain substance (Byrom, 1969). Giese (1964b) injected colloidal carbon into rats made acutely hypertensive by intravenous noradrenaline or angiotensin, and found that the carbon was deposited only in the walls of dilated segments of arterioles. We have extended the observations of Byrom and Giese with electron-microscopic studies of mesenteric arterioles of rats, using an abdominal window for direct visualization of areas of vascular damage (Goldby & Beilin, 1972c). Infusions of angiotensin, noradrenaline or renal extracts caused constriction followed by patchy dilatation of arterioles within minutes of mean arterial pressures exceeding 150 mmHg. If the high pressure was maintained, the dilated segments slowly extended proximally, but these arteriolar changes disappeared when normal pressure was restored. Injection of colloidal carbon, to which the vascular wall is normally impermeable, labelled dilated segments only, and the proportion of arterioles labelled correlated with the height of the arterial pressure, but not with a dose of angiotensin. When hydralazine was also infused, so preventing the rise in arterial pressure, no constriction or dilatation was seen, and there was no carbon labelling of arterioles. Electron microscopy showed damage only in dilated segments in the form of breaks in the endothelium, associated with amorphous deposits in the media. These deposits appeared to consist of plasma, containing carbon particles and fibrin-like material and they displaced and destroyed smooth muscle cells within their basement membranes.

Similar lesions, identical with the fibrinoid necrosis of malignant hypertension in man, were seen in rats which had been hypertensive for several weeks after renal artery constriction (Goldby & Beilin, 1974), or after deoxycorticosterone administration (Goldby, 1976) (with the latter renin secretion is suppressed). In the chronically hypertensive animals there were also extensive intimal deposits of plasma, again labelled with carbon particles and cellular debris, and in places carbon deposition was seen in and around the adventitia.

Mechanism of hypertensive vascular disease

Our interpretation of these changes was that when the arterial pressure was raised sufficiently, by whatever means, local areas of the arteriolar wall were unable to withstand the stress and became dilated. As a consequence, the underlying endothelium was stretched and damaged, and plasma then passed into the vessel wall under high pressure, compressing and destroying smooth muscle cells. When the pressure elevation was sustained, plasma accumulated in the intima, narrowing and sometimes occluding the lumen of small vessels. Fibrin was deposited in the vessel wall as a result of contact between plasma fibrinogen and cell constituents. Fibrin was also forced out of the vessel into surrounding tissues, causing oedema and serous effusions.

Although the extent of the dilatation is determined by the height and duration of raised arterial pressure, initially focal arteriolar dilatation alone is reversible, without underlying vascular damage. However, after periods ranging from minutes in Giese's experiments, to an hour or more in ours, carbon labelling of the vessel wall indicated that endothelial damage had allowed plasma to penetrate into the vessel wall.

The consequences of these vascular lesions are well known; they include tissue ischaemia and
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oedema due to vascular occlusion, the so-called breakdown of cerebral autoregulation due to vascular dilatation at increasing pressure (Johansson, Strangaard & Lassen, 1974), petechial haemorrhages and fragmentation of erythrocytes as they pass through narrowed vessels containing fibrin strands (Brain, Dacie & Hourihane, 1962).

Conclusion

All the changes reported can be ascribed to the pressor actions of substances used to produce vascular damage. Many of the workers claiming the existence of permeability factors have failed to measure arterial pressure, or have been unaware that relatively short surges of severe hypertension can produce arteriolar necrosis.

These conclusions in no way dispute the capacity of humoral substances such as renin, angiotensin or noradrenaline to produce and accelerate a rise in arterial pressure, and by this means to cause the vascular lesions of malignant hypertension. Nor do they deny the importance of a vicious circle by which hypertensive vascular damage to the microcirculation of the kidneys leads to rapidly accelerating hypertension and renal failure.

There appears to us to be no substantial evidence to support the existence of a circulating vascular permeability factor which makes any significant contribution to arteriolar necrosis in malignant hypertension. From the evidence cited above it seems reasonable to suppose that when an arteriole is exposed to a sufficiently high filling pressure, vascular smooth muscle contractility will be overcome, and focal dilatation and structural damage will result, and that this is the first and essential change in the development of the pathological lesion of fibrinoid necrosis in hypertensive patients.

The case for humoral factors as well as pressure

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Pressure, if it is great enough, will eventually disrupt any structure. Obviously, this is also true of blood pressure. It is therefore not surprising that an experimentally induced great increase in pressure disrupts the integrity of the blood vessel wall (Byrom, 1969; Helmchem, 1971; Johansson, 1974; Wolfarten & Magarey, 1959).

Role of increased blood pressure

In man, monkey and the rat hypertension will generally become malignant when blood pressure increases into a ‘critically high range’ (Byrom, 1954; Garner, Ashton, Tripathi, Kohnen, Bulpitt & Dollery, 1975; Heptinstall, 1953; Möhring, 1975; Möhring, Möhring, Petri & Hack, 1977; Okamoto, Yamori & Nagaoka, 1974; Pickering, 1968). Arteriolar necrosis then develops rapidly except in those vascular beds which lie beyond a constricted artery and thus are protected from the consequences of high blood pressure (Wilson & Byrom, 1941). This ‘critically high’ blood pressure is comparable with the pressures at which ‘breakthrough of autoregulation’ occurs in acute experiments (Lassen & Agnoli, 1972), which in turn results when the resistance vessels are no longer able to constrict in response to the rise of blood pressure, but rather give way and dilate. Then, according to La Place’s law, the pressure load on the vascular wall will increase markedly; with increasing blood pressure the vessel radius will continue to increase until ‘blow out’ occurs because of the mechanical effect of the pressure. This notion is referred to as the ‘pressure hypothesis’.

High blood pressure produces adaptive changes in the vascular wall, which alter the wall-to-lumen ratio (Folkow, 1971), so that for
a given blood pressure the pressure load on the vascular wall of the resistance vessels should be less. It is thus conceivable that the 'break-through point' of autoregulation could be substantially raised in hypertensive subjects (Strandgaard, Olsen, Skinhøj & Lassen, 1973). This hypothesis is supported by observations in rats with chronic renal hypertension where a further increase in blood pressure, induced by the injection of angiotensin II, did not cause vascular damage in the contralateral, so-called unprotected kidney, but surprisingly induced vascular lesions in the clamped, so-called protected kidney (Byrom, 1964). These findings are in contrast to what would be expected from similar experiments in normal rats (Giese, 1973; Goldby & Beilin, 1972; Kincaid-Smith, Hobbs, Friedman & Mathews, 1972). Thus: 'the all-important question is, whether the experience obtained from hyperacute animal experiments can be readily applied to the understanding and interpretation of microcirculatory events in hypertensive man' (Giese, 1976). In addition the 'pressure hypothesis' is opposed to the 'renin hypothesis', which contends that the renin-angiotensin system is involved in the pathogenesis of hypertensive vascular disease (Brown, Fraser, Lever & Robertson, 1971; Gavras, Brunner & Laragh, 1974; Laragh, Baer, Brunner, Bühler, Sealey & Vaughan, 1972; Möhring, 1975). During a world-wide debate on this topic, which took place most recently at the Fourth Meeting of the International Society of Hypertension (Clinical Science and Molecular Medicine, 51, Suppl. 3) the time-honoured case of malignant hypertension produced by deoxycorticosterone injections earned renewed interest, since this condition is associated with subnormal renin concentrations. While protagonists of the renin hypothesis had to elaborate alternative concepts (Gavras, Brown, Brown, Lever, Linton, MacAdam, McNicol, Robertson & Wardrop, 1971; Gavras et al., 1972; Möhring, Möhring, Petri & Haack, 1976a), the advocates of the 'pressure hypothesis' pointed out that in the one situation, where vascular damage occurs, renin is elevated, whereas in another situation it is suppressed but nonetheless vascular damage still develops, yet the blood pressure is of similar height in both. We are therefore left with the conclusion that the common denominator, 'pressure alone is responsible for arteriolar damage in severe hypertension and the renin angiotensin system is not implicated' (Goldby, 1976; Dietz, Haebara, Lüth, Mast, Nemes, Schönig & Szokol, 1976).

Theoretical critique of the 'pressure hypothesis'

However, it will be seen that such a conclusion is a conclusio per exclusionem, and the logical consequences of such reasoning have been nicely pointed out by Wright (1965). The pressure hypothesis can therefore only be validated by experiments which ensure: (1) that when the vasoconstrictor hormone renin is activated it does not play a role in the pathogenesis of vascular damage; (2) when renin activity is suppressed vasoconstrictor substances other than renin are not involved in the genesis of vascular damage. This possibility has not so far been investigated by the advocates of the 'pressure hypothesis'. What they have repeatedly shown is that vascular damage may also occur when renin activity is hardly measurable. From this it may safely be concluded that renin is not necessary for vascular damage to develop (Giese, 1973).

When one is dealing with a multifactorial system, as the circulation, an analysis including only one or two factors could easily be misleading in establishing a cause-effect relationship. There is no doubt that high blood pressure is a conditio sine qua non and so necessary for the development of vascular damage in hypertensive subjects (Byrom, 1969), but the relevant question remains as to how far hypertensive vascular disease results solely from the mechanical effect of blood pressure.

Experimental critique of the 'pressure hypothesis'

The fact that some hypertensive patients and animals may tolerate extremely high blood pressures without the occurrence of vascular damage has led classically to the proposal that other factors in addition to the high blood pressure are necessary to induce vascular damage. Recent observations during the development of malignant hypertension in rats with unilateral renal artery stenosis and an untouched contralateral kidney strongly support this view. During the course of this malignant hypertension, hypertensive vascular crises were followed by periods of remission until death (Möhring, 1975). During these
remissions blood pressure usually remained as high as previously, but the signs of malignant hypertension could completely disappear, and the histological appearances showed the so-called healing processes (Goldby & Beilin, 1974). At the onset of the malignant phase sodium and water loss ensued and renin values were elevated. As soon as this was prevented or compensated by drinking isotonic saline signs of malignant hypertension were prevented or eliminated, although blood pressures were as high as before (Mohring, Petri, Szokol, Haack & Möhring, 1976b). These findings, which can hardly be explained in terms of the 'pressure hypothesis' alone, can be interpreted as follows: when blood pressure increases into a critically high range, and depending on the rate at which pressure rises (Mohring, 1975), sodium and water loss ensue causing hypovolaemia. Subsequent activation of the renin–angiotensin system maintains the high blood pressure and a vicious circle develops (Brown et al., 1971; Gavras et al., 1974; Möhring, 1975). Owing to progressive vasoconstriction and haemoconcentration, in the presence of high blood pressure, the microcirculation and vascular permeability are altered sufficiently to induce the chain of events which produces vascular damage. If vasopressor agents are administered repeatedly, ischaemia-type lesions seem to occur first, whereas vascular damage develops later (Byrom, 1954, 1969; Mathias, Engler, Herrmann & Becker, 1974; Melissinos, Papadimitriou, Bartoskas, Katapotis & Hadjiminias, 1973; Z. Nemes, H. Mann, R. Dietz, J. B. Lüth, M. Szokol & F. Gross, unpublished work). In Goldblatt hypertension the clamped kidney (which is thus protected from the mechanical effects of pressure rise) often shows histological alterations not unlike those found in other organs, with the exception of fibrinoid insudation and necrosis (Byrom, 1969; Z. Nemes et al., unpublished work). Moreover, the above concept would explain why vascular damage can already occur at blood pressures below the 'critical range', under certain conditions (Chusilp, Hua & Kincaid-Smith, 1976). Such damage could also be due to another pathological process, as in toxaeemia of pregnancy or acute glomerulonephritis (Byrom, 1969). Finally, 'primary malignant nephrosclerosis', i.e. the development of malignant nephrosclerosis in normotensive subjects (Bohle, Helmchen, Meyer, Bock, Brüning, Edel, Heimsoth & Scheler, 1973), could result from pathological weakening of the vascular wall to the point at which it cannot tolerate a normal pressure load.

Vascular damage seems to follow volume depletion and this vasopressin-induced vasoconstriction (Möhring et al., 1977). Moreover it seems probable that during the onset of malignant deoxycorticosterone hypertension noradrenaline concentrations may also increase significantly (Reid, Zivin & Kopin, 1975). Then the vasoconstrictor effect of vasopressin may be enhanced and vice versa (Möhring et al., 1977). These data provide the first evidence that in those forms of malignant hypertension where renin appears to play no role, other vasopressor systems could come into play, thus maintaining high blood pressures and creating a vicious circle. At the same time, 'extreme and unrelieved vasoconstriction at the level of the precapillary arterioles' (Garner et al., 1975) would represent the first step leading to vascular damage (Byrom, 1954, 1969).

Several observations are compatible with the notion that severe vasoconstriction is probably a necessary predecessor to the development of vascular damage. If vasopressor agents are administered repeatedly, ischaemia-type lesions seem to occur first, whereas vascular damage develops later (Byrom, 1954, 1969; Mathias, Engler, Herrmann & Becker, 1974; Melissinos, Papadimitriou, Bartoskas, Katapotis & Hadjiminias, 1973; Z. Nemes, H. Mann, R. Dietz, J. B. Lüth, M. Szokol & F. Gross, unpublished work). In Goldblatt hypertension the clamped kidney (which is thus protected from the mechanical effects of pressure rise) often shows histological alterations not unlike those found in other organs, with the exception of fibrinoid insudation and necrosis (Byrom, 1969; Z. Nemes et al., unpublished work). Moreover, the above concept would explain why vascular damage can already occur at blood pressures below the 'critical range', under certain conditions (Chusilp, Hua & Kincaid-Smith, 1976). Such damage could also be due to another pathological process, as in toxaeemia of pregnancy or acute glomerulonephritis (Byrom, 1969). Finally, 'primary malignant nephrosclerosis', i.e. the development of malignant nephrosclerosis in normotensive subjects (Bohle, Helmchen, Meyer, Bock, Brüning, Edel, Heimsoth & Scheler, 1973), could result from pathological weakening of the vascular wall to the point at which it cannot tolerate a normal pressure load.
Conclusion
Neither the blood pressure nor a particular humoral factor, nor any other factor which might alter the microcirculation and vascular permeability, should be taken as the sole agent that causes hypertensive vascular disease. They should be considered as concurrent factors, of which the blood pressure is the **primum movens** as well as the final effector. The quantitative contribution of each of these factors, and particularly of vasoconstrictor hormones, might obviously vary in the pathogenesis of vascular damage depending on the natural course of high blood pressure, the interference of other pathological processes, or upon the experimental procedure by which vascular damage has been produced.

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