The Third Volhard Lecture

Tension and the artery: the experimental elucidation of pseudo-uraemia and malignant nephrosclerosis

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One of the main obstacles to the understanding of Bright's disease is the fact that renal damage of many different kinds can cause secondary hypertension which, like some forms of primary hypertension, can impose its own pattern of vascular damage on the final picture. Disentangling cause and effect can come, in the first and last analysis, only from long observation of symptoms, signs and lesions and the first advance, after Bright's own work, came when Mahomed (1881), Huchard (1889) and in particular Clifford Allbutt (1895) identified 'hyperpiesia' (benign essential hypertension).

The next landmark was Volhard & Fahr's (1914) classification of Bright's disease, which isolated another entity, malignant nephrosclerosis, which led to early death from renal failure and hypertension. Volhard and Fahr were united in their description of the new syndrome, but differed widely in the interpretation of the picture. Fahr, the histologist, was impressed by the inflammatory reaction surrounding the arterial and glomerular lesions and maintained to the end that this pointed to primary inflammation of the kidney and its vessels caused by a wide range of damaging agents. Volhard, the clinician, on the other hand, was equally insistent that the hypertension was the cause of the renal lesions and that the 'convulsive uraemia' which complicated the disease was also hypertensive and should be called pseudo-uraemia. At a time when Allbutt's teaching had scarcely been assimilated, Volhard's revolutionary views, opposed as they were by Fahr, were difficult to grasp, but confirmation by experienced clinicians like Keith (Keith, Wagener & Kernohan, 1928), Fishberg (1925) and Ellis (1938) gradually brought acceptance and Fahr's dissenting views were inevitably but, as I hope to show, unfortunately discounted. For although much of my professional life in London and Sydney has been spent in verifying experimentally concepts developed by Franz Volhard, the prospect of a solo performance in his honour to a critical international audience in the Music Room of the Sydney Opera House concentrates the mind wonderfully and it has become increasingly clear to me in the last few months that the issue which bitterly divided Volhard and Fahr in 1914 has continued ever since to obstruct progress, yet can with a little patient analysis be very simply and, I hope, permanently resolved.

I entered this field in 1931 when at Ellis' suggestion, and with Clifford Wilson's help, I attempted to confirm a claim that vasopressin was present in ultrafiltrates of eclamptic plasma (Byrom & Wilson, 1934). We were unable to confirm the claim but we had formed a link between the clinical and experimental disciplines and learnt the value of the rat in experimental medicine. I went on to try to reproduce eclampsia in rats by injecting large doses of vasopressin subcutaneously (Byrom, 1937). When I opened the abdomen to observe its effects I noticed conspicuous pale areas on the surface of the kidney, slightly sunken at first, but swelling visibly as fluid leaked out of the ischaemic capillaries. At autopsy next day I found typical anaemic infarcts, clearly results of ischaemia. Repeated doses caused acute medical necrosis of renal arteries. I attributed this also to ischaemia and inferred that renal arteries were less vulnerable than renal tubules to ischaemia. I had produced renal cortical necrosis, not eclampsia, but I had accidentally learnt that a pressor agent could cause arterial necrosis.

Goldblatt's experiment

But the experimental study of hypertension stems
from Goldblatt's simple demonstration that constriction of a renal artery causes hypertension, which becomes permanent if the opposite kidney is removed, and has ever since been accepted as a convincing replica of the human disease (Goldblatt, Lynch, Hanzal & Summerville, 1934). If the hypertension is severe it pursues a malignant course, with acute cerebral crises and extensive arterial necrosis and proliferative endarteritis in many organs, but never in the kidney beyond the constricting clamp (Goldblatt, 1938; Wilson & Pickering, 1938).

With this experiment Goldblatt provided at a stroke an explanation for the appearance of secondary hypertension in primary renal disease, a close copy of malignant hypertension, complete with Volhard's pseudo-uraemia, strong evidence—the protective effect of the clamp—that high arterial pressure itself was the direct cause of the arterial lesions and, as we shall see later, an elegant tool for analysing in depth some of the most difficult problems posed by Bright's disease. By any standards this was a rich harvest, but in a 'one-kidney' experiment it was not possible to study the effect of hypertension on an untouched kidney, or to challenge Goldblatt's reasonable opinion that renal failure, as well as hypertension, was essential to the production of pseudo-uraemia and malignant nephrosclerosis.

At this stage Clifford Wilson suggested applying Goldblatt's technique to the rat, using a simple staple made from neurosurgical silver tape ('Cushing's tape'), and a tail plethysmograph to measure blood pressure (Wilson & Byrom, 1938). The clip was an immediate success and remains today the best way of causing experimental renal hypertension. The choice of the rat was most fortunate because, like man, it develops permanent hypertension after constriction of only one renal artery, and so we were able to study the effect of hypertension on an untouched kidney in the absence of renal failure. In these 'two-kidney' experiments we observed acute vascular crises, some of which presented with convulsions and coma as in human hypertensive encephalopathy, others with weakness, cyanosis and rapid loss of weight (Wilson & Byrom, 1939, 1941), and after death we were able to demonstrate in the untouched kidney the full picture of malignant nephrosclerosis, matching lesion for lesion, and so to complete the experimental proof of Volhard's clinico-pathological concept of primary malignant hypertension.

Before our association ended in 1939 we were also able to demonstrate that hypertension sometimes persisted after removal of the clamped kidney, suggesting that the lesions in the untouched kidney, and especially endarteritis fibrosa, had initiated a vicious cycle. This seemed to me to imply the occurrence of secondary as well as primary malignant hypertension but Wilson felt, probably rightly, that it would be unwise to complicate the hypothesis at a time when Volhard's concept of malignant essential hypertension was still struggling for recognition. The implications of the vicious cycle were discussed by Wilson (Wilson & Byrom, 1941) and Ellis (1942).

On resuming research in 1946, now at St Vincent's Hospital, Sydney, my first aim was to re-examine the vicious circle in the light of the common belief that, given time, chronic hypertension tends to become self-perpetuating. If removing the clip in chronic one-kidney hypertension regularly abolished the hypertension self-perpetuation could be excluded, at least within the time-limits of the experiment. At this time clip removal had not been seriously attempted, probably for technical reasons, but I found that with a little practice Wilson's staple could be quickly and safely removed (Byrom, 1969, p. 103). I therefore began a long-term study of rats with solitary 'clipped' kidneys and hypertension which I allowed to persist at least 6 weeks before removing the clip (Byrom & Dodson, 1949). The hypertension was very severe and many rats died from cerebral or cardiac complications before clip removal could be attempted. These provided useful information about untreated encephalopathy. The heart became greatly hypertrophied and hypertensive lesions were found in many organs, often accompanied by focal oedema, and were sometimes the source of fatal arterial haemorrhage. None of these changes was ever found in the solitary kidney, which in these and in all subsequent 'one-kidney' experiments remained remarkably normal, both macro- and micro-scopically, leaving me with a very strong impression that renal hypertension is a very efficient homeostatic mechanism. Eventually the clip was removed, usually during an attack of encephalopathy, in thirty-four rats and in all except one rat with operative perinephritis the operation permanently abolished the hypertension in 2-4 h. Acute cerebral symptoms disappeared equally promptly and at post-mortem examination 2 weeks later only healed or healing lesions were found and the heart weight had fallen steeply. This experiment demonstrated clearly the reversible nature of Goldblatt hypertension, confirmed the concept of the
vicious circle and suggested that human hypertension should also be considered potentially reversible except where it derived from or had itself caused irreparable renal damage; and this can now be corrected by successful transplantation except, perhaps, in some systemic arterial diseases which might attack the new kidney.

The general conclusion that high blood pressure is the damaging agent in Goldblatt hypertension and in malignant essential hypertension is borne out by many other facts. Arterial lesions are found in bronchial arteries, but not in pulmonary arteries except in pulmonary hypertension (Turnbull, 1915). Arterial necrosis of the type seen in early Goldblatt hypertension can be provoked by exposure of arteries to high pressure by physical manoeuvres such as distending the arterial tree, releasing a Goldblatt clip (Byrom, 1969, p. 60), resecting an aortic constriction (Benson & Sealy, 1956), or by injecting pressor agents such as vasopressin, oxytocin (Byrom & Pratt, 1959), methoxamine (Herbertson & Kellaway, 1960), serotonin (Byrom, 1969, p. 58) and especially angiotensin (Byrom, 1958–59, 1964).

Having established that high pressure causes the symptoms, signs and lesions of Volhard's malignant hypertension, the next step is to discover how it does so. This is not easy because the essential structural lesion appears suddenly as a minute breach in the intima of a terminal artery marked by a patchy disruption or necrosis of medial muscle fibres, containing erythrocytes or plasma, in short a leak which provokes a vigorous inflammatory reaction designed to contain and repair the breach and so forms the chronic 'fibrinoid' necrosis and, later, the proliferative cellular intimal thickening, narrowed lumen, stretched fragmented elastica and stretched, scarred media and adventitia of endarteritis fibrosa. The early stages of the process can be studied in the acute cerebral crises of chronic hypertension or in very early, very severe 'two-kidney' hypertension (Byrom, 1969, p. 61). Even so, the exact time of onset of the lesion is uncertain and it is necessary to turn first to acute experiments, where the blood pressure is raised suddenly by pressor agents or manoeuvres already mentioned, checking any positive findings in the Goldblatt rat where possible.

I first attempted to study the problem by forcibly distending the arterial tree in the anaesthetized rat with Ringer's solution (Byrom & Dodson, 1948). This crude manoeuvre caused acute medial necrosis of renal arteries and, sometimes an aortic dissecting aneurysm (Wolfgarten & Magarey, 1959)—an occasional complication of malignant hypertension (MacMahon, 1966). The necrosis of the renal arteries could not have been caused by spasm because the more vulnerable renal tubules irrigated by these end-arteries remained undamaged. I therefore concluded that I had caused the necrosis by simply overstretching the arterial wall. The experiment was unphysiological but it is sometimes forgotten that disease is by definition unphysiological and that experimental medicine starts where physiology ends. It now seems probable that the conclusion was correct, but much more work, some of it misleading, was to follow before it became acceptable.

I next turned back to the acute encephalopathy which had made the clip-removal experiment so difficult. The picture of acute epileptiform convulsions and/or rapidly deepening coma in these 'one-kidney' experiments, appearing without warning after weeks or months of uncomplicated hypertension and responding dramatically to removal of the clip, was much more like the human syndrome than the more complex crises seen in 'two-kidney' experiments (Wilson & Byrom, 1939, 1941; Byrom, 1969, pp. 61, 86, 92). In the 'one-kidney' animals used in the main study of encephalopathy (Byrom, 1954) the hypertension varied greatly in tempo and degree, and moderate or severe hypertension often persisted indefinitely with no outward signs of disease. Intracranial tension and internal carotid blood flow, measured with a miniature Ludwig stromuhr, were normal and the water content of whole brain and its various fractions were also unchanged post mortem, with rare exceptions where long-standing extra-high blood pressure was accompanied by undetected cerebral oedema (Byrom, 1969, p. 45), a finding suggestive of the chronic cerebral oedema of human malignant hypertension. In the main series (Byrom, 1954) evidence of cerebral oedema was hardly ever detected until symptoms of encephalopathy appeared and these were always accompanied by a steep rise in intracranial tension and a parallel fall in carotid flow as the water content of the brain rose. Vital staining with Trypan Blue, combined with accurate gravimetric micro-assays of water, showed that the cerebral oedema springs from a number of discrete points in the grey matter of the cerebral cortex, from which it spreads rapidly, unless the hypertension is abolished. The leaking points occasionally tally with obvious hypertensive lesions or a small
haemorrhage but more often will pass as histologically normal (Byrom, 1954). However, serial sections and special stains, particularly the periodic acid–Schiff technique, almost always show early structural damage in or around terminal arteries (Byrom, 1969). The significance of the lowered blood flow in early encephalopathy was obscured by the cerebral oedema, which can mimic arterial spasm or mask increased blood flow. I was therefore left with indirect observation of the cerebral arteries as the only way of examining the century-old controversy of whether encephalopathy is a symptom of cerebral ischaemia from arterial spasm (Küssmaul & Tenner, 1859; Pal, 1905), or overperfusion through diluted arteries (Traube, 1871). With the indispensable help of Professor D. A. Cameron I developed a technique for casting and fitting individually moulded acrylic windows in the dorsal surface of the skull (Byrom & Cameron, 1955) and obtained serial photographs before and during cerebral crises and after removing the clip in a large series of rats. All control photographs showed normal cerebral arteries, but during crises the brain was paler and branches of the cerebral arteries regularly showed intense focal constriction alternating with dilatation. I assumed, erroneously, that these changes appeared as suddenly at the onset of a crisis as they disappeared on removing the clip. At that time the pallor, constriction, focal oedema and occasional arterial necrosis, taken together with my original finding of these same changes in the kidney after vasopressin (Byrom, 1937), seemed to lend strong support to the view that the essential change was spasm provoked by the high blood pressure. But I was never happy about attributing arterial necrosis to spasm and in a footnote (Byrom, 1954) I suggested overstretching as an alternative explanation.

When I returned to England in 1957 I re-examined the calibre changes, using the retina. An attempt, with Professor P. M. Daniel, to adapt a retinal camera, in which we were forced to devise Perspex shells to protect the cornea, led to the accidental rediscovery of a three-century-old observation that the retina becomes visible if the eye is immersed in water (Mery, 1684). It thus became possible, by using a flat coverslip over a drop of mydriatic, to take still or moving photographs of the retinal arteries of the untouched eye of the anaesthetized rat at will, and in rats with 'one-kidney' hypertension I was soon able to see the gross irregularity of calibre I had found in the cerebral arteries during crises, and this was often accompanied by oedema, retinal detachment and, rarely, massive haemorrhage (Byrom, 1963). But daily retinoscopy showed one vital difference, namely, that the calibre changes appeared gradually over days or weeks before cerebral symptoms. I therefore revived the cranial window technique and, with the retina as a guide, found that in the brain, too, calibre changes developed gradually before crises. I was also able to examine the changes in greater detail. In both organs any change in calibre, from wide, even aneurysmal, dilatation to tight constriction can occur in any length of any artery of any size, but as a rule the largest vessels tended to be dilated and tortuous, the smallest constricted and straight, while intermediate vessels showed a completely irregular pattern of gross segmental constriction and dilatation, constriction predominating. Both constriction and dilatation vary directly in degree with the blood pressure and can be made to come and go promptly and smoothly if the pressure is made to rise and fall, for example by varying the level of ether anaesthesia which in Goldblatt hypertension has a marked but rapidly reversible depressor effect. The pattern is not changed by these manoeuvres and I have never seen or recorded a constriction give way before a rising pressure in chronic hypertension—the vessel always constricts still further where this is possible. Acute constriction caused by angiotensin, however, has been observed to give way before advancing dilatation (Byrom, 1964; Goldby & Beilin, 1972). Apart from aneurysms and some long-standing constrictions calibre changes disappear overnight if the hypertension is abolished. This study made it clear that the tight constriction observed in cerebral arteries during crisis is not a sudden cramp-like spasm, but a finely controlled contraction against rising tension, and it was equally clear that in the precritical phase it was not causing ischaemia in an organ which is exquisitely sensitive to lack of oxygen. The significance of this, the earliest detectable abnormality in acute hypertensive vascular disease, was still not clear and I turned again to acute experiments. As soon as angiotensin became available I examined its effects on the kidney and its vessels (Byrom, 1958–59, 1964(1)). In normal rats very large single intravenous injections caused acute necrosis of renal arteries of all sizes, the necrosed

(1) The clause on lines 12 and 13, page 10 of this reference should read “by provoking spasm or by extruding blood or plasma into the media”. 
zones being saturated with PAS-positive colloid-containing erythrocytes, but no necrosis of renal tubules. The necrosis was therefore not caused by ischaemia. The steep rise in pressure caused immediate overstretching of some arteries but no obvious evidence of leakage. I also observed that angiotensin injected into rats with chronic 'two-kidney' hypertension, especially after removing the clip (Byrom, 1969, p. 69), caused almost total necrosis in the involuted arteries of this kidney, but none in the hypertrophied arteries of the opposite kidney. This finding was also consistent with overstretching, which would be aggravated by involution and mitigated by muscular hypertrophy of the arteries concerned. Meanwhile an independent study of angiotensin by Giese (1964) was making much better progress. After demonstrating that plasma was present in necrosed zones of arteries, Giese examined the effect of angiotensin on the arteries of the peritoneal surface of the intestine, which showed gross calibre changes in Goldblatt hypertension (Byrom, 1954), and found that identical changes appeared as the pressure rose and that plasma marked with colloidal carbon leaked into the wall of the artery at the peak of the pressor response and always in zones of dilatation. These crucial observations, which have been confirmed and extended (Olsen, 1964; Goldby & Beilin, 1972; Johansson, 1974), though still indirect, brought the problem to the point where it became possible to form a simple concept of how high blood pressure causes pseudo-uraemia and malignant nephrosclerosis. The vital clue is the irregularity of arterial calibre which heralds an attack of encephalopathy. The change clearly stems directly from the rising pressure which is threatening the reserves of compensatory hypertrophy of the resistance arteries and if it is assumed that these reserves are limited and that muscle fibres are not quite evenly distributed along the course of the vessels a simple explanation of the calibre changes can be derived from first principles. The problems of a small artery derive from the fact that, as a muscular tube containing a high pressure, it becomes progressively weaker when it dilates and stronger when it constricts, because the tension imposed on its fibres by the filling tension of a normal blood pressure varies directly not only with that pressure, but also with the first power of the diameter of the vessel, according to the law of Laplace. But although the artery has the remarkable ability to contract or relax against a rising or falling blood pressure it is not free to protect itself fully because the flow of blood which it is controlling varies with the fourth power of the calibre, and only small changes in calibre are acceptable. Thus filling tension is the burden of the muscular artery from the first heart beat to the last and it is logical to look first at the high filling tension of a normal blood pressure as the damaging agent in unexplained arterial disease, from atheroma to migraine. And when the blood pressure itself rises the burden all too easily becomes an intolerable dilemma. For if the rising pressure outstrips reserves a uniformly strong vessel must either constrict uniformly to save itself at the expense of the tissues, or dilate uniformly to open the flood-gates. If the muscle is uneven, however, a sufficiently steep rise will cause weaker zones or branches to dilate and become weaker at a time when stronger zones are still able to contract and in so doing become stronger and better able to maintain autoregulation of flow. The result would be a progressive irregularity of calibre, fixed in pattern by its anatomical background, labile in nature and accompanied by no necessary change in flow, at least in its early stages, and therefore no symptoms. This is the situation in the precritical phase of severe hypertension. But the balance is not stable and a further increase in blood pressure or in the demand for blood may breach the weaker zones and cause the essential lesions of encephalopathy and malignant nephrosclerosis. In concluding this analysis of the mechanism of acute hypertensive arterial disease I must emphasize that the choice between overstretching and excessive constriction has not been lightly made. The spectacle of narrow zones in hypertensive cerebral arteries contracting to the full against maximal rises of pressure and maintaining this constriction indefinitely is unforgettable; and in man competent clinicians from Gowers to Volhard have been impressed by arterial constriction in hypertension. It would be unwise to overlook its possible significance in transient cerebral disorders.

Cerebral and general blood flow in hypertensive crises

The present concept attributes encephalopathy and arterial necrosis to leakage through arteries which are nevertheless able to maintain autoregulation of flow. But this does not exclude the possibility that compensatory contraction of stronger zones may be inadequate or excessive and no analysis of encephalopathy would be complete without reference to

Tension and the artery

7s
cerebral flow. Conclusive proof of altered flow would require serial measurements before, during and after spontaneous attacks of a rare, grave, unpredictable medical emergency which is complicated by progressive cerebral oedema. Only consistently high readings in early encephalopathy would be significant. In these circumstances only indirect evidence is available and this comes from several sources. First, carefully regulated intravenous infusions of angiotensin have been shown to cause a sudden increase in cerebral blood flow at high pressures in man and animals (Lassen & Agnoli, 1972; Skinhoj & Strandgaard, 1973) and this is evidence in favour of overperfusion. It has also been shown that if severe acute hypertension is induced in 'two-kidney' experiments by clipping one renal artery rather tightly the steep rise in pressure a few days later is accompanied by a steep fall in body weight, weakness (Wilson & Byrom, 1939, 1941), polyuria, a marked rise in the packed cell volume and, in the untouched kidney, acute arterial necrosis (Byrom, 1969, p. 62), together with an important glomerular lesion which seems to have been overlooked, namely capillary glomerular aneurysms, some of which become completely occluded overnight by structureless colloidal material. This swift transformation from aneurysm to what histologists would call a focal 'necrosis' is apparently brought about by accumulation of the colloidal residue of ultrafiltration which the damaged endothelium can no longer remove (Byrom, 1964, 1969, p. 62). Very similar changes occur in 'one-kidney' hypertension, where removal of the clip causes an immediate increase in ureteric activity (Byrom, 1969, p. 60), polyuria, a rise in the packed cell volume accompanying transient peaks in the falling blood pressure curve (Ledingham & Cohen, 1962), renal arterial necrosis and capillary glomerular aneurysms (Byrom, 1969, p. 60). Finally, in nephrectomized rats renin or angiotensin cause hypertension, arterial necrosis, haemoconcentration and gross serous effusions (Asscher & Anson, 1963). Taken together these facts indicate that when the blood pressure rises too steeply in a normal arterial tree a sudden general increase in blood flow and intracapillary pressure occurs which leads directly to a simple mechanical glomerular diuresis, however 'unphysiological' this may seem to be, or, in nephrectomized animals, an equally mechanical anasarca. But I am not convinced that breakthrough of cerebral autoregulation occurs in spontaneous encephalopathy. I have seen no reference to haemoconcentration or loss of weight in human encephalopathy. In the spontaneous crises of one-kidney hypertension, where the kidney is protected by the clamp, loss of weight does not occur although oedema, usually related to arterial lesions, is common, but I have not followed the packed cell volume closely (Byrom, 1954). Conversely the symptoms observed in the various examples of breakthrough just mentioned do not suggest encephalopathy. It seems that more work is needed before the breakthrough hypothesis of encephalopathy can be accepted. The spontaneous crises in experimental 'one-kidney' and 'two-kidney' hypertension would repay re-examination with today's techniques, with retinoscopy used to monitor calibre changes. I suspect that any change in flow is likely to be localized to leaking zones, but the subject is too important to be abandoned.

Additional factors in acute hypertensive arterial disease

Finally, it remains to consider whether high pressure alone is sufficient to cause encephalopathy and malignant nephrosclerosis. Although the evidence seems to be conclusive as far as it concerns Goldblatt's renal hypertension and Volhard's primary malignant hypertension, many writers have insisted that other quite separate factors play an essential or even dominant role. In a multifactorial universe anything is possible and every hypothesis a legitimate target for criticism. But the law of parsimony insists that hypotheses must not be needlessly multiplied and it is here that Occam's razor comes to hand in the unlikely shape of Goldblatt's clamp, and we are once more reminded of the importance of this simple experiment. For if constricting a renal artery reproduces the full picture of malignant hypertensive nephrosclerosis and encephalopathy, then any factor essential to the picture but separate from the hypertension, must be shown to follow clipping of the renal artery and to be independent of the hypertension which has been accepted as essential. Second factors which have been suggested have included uraemia (Goldblatt, 1938), a renal permeability factor, a rise in plasma \( P_{CO_2} \) and intravascular thrombosis and/or endarteritis fibrosa. Clipping a renal artery does not cause uraemia in the presence of a second untouched kidney. The renal permeability factor (Asscher & Anson, 1963) has been exhaustively studied and has been shown to be inseparable from renin, from angiotensin and from...
the pressor effect of angiotensin (Cuthbert & Peart, 1970) and can therefore be excluded. Increased plasma carbon dioxide tension has been shown to lower the level of blood pressure at which breakthrough of cerebral autoregulation occurs, by causing vasodilatation, and it has been suggested that in acute encephalopathy it is as important to avoid hypercapnia as it is to control blood pressure' (Skinhoj & Strandgaard, 1973). This finding is in harmony with the present concept and may explain why cooling hypertensive rats at 4°C for several hours a day seemed to precipitate cerebral crises (Byrom, 1954), but I know of no evidence that constricting a renal artery alters the plasma PCO₂ and I would prefer to regard carbonic acidosis as a possibly important but not essential contributory factor. Its importance could be assessed by observing how often, if at all, different concentrations of carbon dioxide precipitated spontaneous attacks of encephalopathy in rats with severe chronic 'one-kidney' hypertension, and how often, if at all, spontaneous convulsions in such animals are abolished by oxygen or by alkalies.

Intravascular thrombosis, endarteritis fibrosa and malignant hypertension

In recent years the possibility that intravascular thrombosis and/or endarteritis fibrosa may be concerned in translating benign into malignant hypertension has been suggested (Linton, Gavras, Gleadle, Hutchison, Lawson, Lever, Macadam, McNicol & Robertson, 1969). The suggestion seems to have arisen from the discovery of a specific type of anaemia, micro-angiopathic haemolytic anaemia, in malignant hypertension and in a number of unrelated diseases in which endarteritis and/or intravascular thrombosis occur, and in which the blood pressure is always, or initially, normal (Brain, Dacie & Hourihane, 1962). The diseases include scleroderma, post-partum acute renal failure and haemolytic uraemia, and the anaemia is attributed to damage to erythrocytes from contact with thrombus. Somewhat similar changes are seen in rejected renal homografts (Kincaid-Smith, 1967). As it stands the suggestion seems completely incompatible with the concept developed in this Lecture, for the evidence that the endarteritis fibrosa and associated lesions found in Goldblatt hypertension are caused by the high pressure is in my opinion conclusive and implies that the same is true of Volhard's primary malignant hypertension; and there is no evidence that clipping a renal artery causes these lesions in any other way. But the fact remains that the lesions of malignant hypertension occur not only in the diseases mentioned but also in a wide range of obscure vascular disorders covered by the term plasmatic vasculosus (Lendrum, 1963), in which the blood pressure is either normal or only secondarily raised. The study of these normotensive arterial lesions is vital to the present Lecture because it is directly related to the concept of primary malignant nephrosclerosis so tenaciously held by Fahr and so well illustrated this morning by Professor Bohle (Bohle et al., 1976). In 1929 Schüermann & MacMahon were assigned the task of analysing Fahr's material in his laboratory at Hamburg. Four years later, in an important paper (Schüermann & MacMahon, 1933) they offered an explanation of the vascular and glomerular lesions of malignant nephrosclerosis, whether hypertensive (Volhard) or renal (Fahr) in origin, by postulating an alteration in the selective permeability of the endothelial barrier induced in the former case by high pressure and in the latter by physical, chemical or biological agents, including burns, irradiation, bacterial toxins, antigens, antibodies and allergens acting directly on the endothelial barrier to allow any or all of the components of blood to seep into the arterial wall and excite an inflammatory reaction, and to allow coagulating factors to leak into the blood to cause thrombosis. In reviewing this work MacMahon (1966) expressed the opinion that most cases of malignant nephrosclerosis were hypertensive in origin, but some were examples of primary malignant nephrosclerosis with secondary hypertension, as Fahr had insisted. The Schüermann–MacMahon concept of 'dysoria' was an important attempt at synthesis, but altered permeability, unless very exactly defined, is an unhelpful word and I believe we are now in a position to attempt a simpler generalization. For if a pathologically high blood pressure can cause the lesions of malignant nephrosclerosis by overstretching normal (or even hypertrophied) arteries, a normal blood pressure, which is still high, may reasonably be expected to cause identical lesions in an artery weakened by disease or adverse circumstances such as storage for transplantation (Byrom, 1969, p. 72) or, perhaps, rejection reactions. This prediction is supported by irradiation experiments. Exposure of hypertensive arteries to X-rays precipitates arterial necrosis in various organs (Asscher, Wilson & Anson, 1961) including the brain (Byrom,
1969, p. 70), where dilatation, tortuosity and increased pulsation were recorded in experiments with bilateral cranial windows, followed by fatal ipsilateral cerebral haemorrhage associated with aneurysmal dilatation of necrosed arteries. This indicates that irradiation lowers the pressure at which overstretching occurs, but the effective pressure is still higher than normal. The gap is bridged, however, by the fact that irradiation, in larger doses, of the cerebral arteries in normotensive patients, or in normal rabbits (Russell, Wilson & Tansley, 1949), causes lesions indistinguishable from those of malignant nephrosclerosis. What applies to cerebral arteries must apply to others, and the 'hypertensive' lesions in the irradiated normal kidney (Wilson, Ledingham & Cohen, 1958) are cause, not effect, of the accompanying hypertension\(^{(1)}\); and this is the picture of Fahr's primary malignant nephrosclerosis—he included irradiation in his list of causes. I submit therefore that fibrinoid arterial necrosis and endarteritis fibrosa should be regarded (though not, for obvious reasons, named) as angiotensive rather than hypertensive, since the overstretching which causes them may be derived on the one hand from Volhard's malignant hypertension, whether renal or essential, or, on the other, from the weakening of the arterial wall envisaged by Fahr and subsequent workers.

In other words the highly specific histological picture of malignant nephrosclerosis is shared by two diametrically opposite processes, each demanding an entirely different approach. In this Lecture I have approached the problem from the standpoint of Volhard's primary malignant hypertension and used the almost perfect 'two-kidney' Goldblatt model to demonstrate that high blood pressure—and high blood pressure alone—whether renal or 'extrarenal' in origin, is sufficient to cause the secondary malignant nephrosclerosis which Volhard postulated and which is now universally accepted.

But having made that point, I now have gone round to the other side of the problem, to find everything back to front, logic included. For there is the same malignant nephrosclerosis, now labelled primary, not following but followed by, the same malignant hypertension, now labelled secondary; its origins largely unexplored but embracing many different kinds of arterial disease which happen to involve the kidney. This, then, was the lesion which permanently divorced Volhard and Fahr and until you and I learn always to specify exactly what we are thinking, talking or writing about we shall, as likely as not, be at cross purposes. For Volhard's primary malignant hypertension and Fahr's primary malignant nephrosclerosis each have many possible causes, known or unknown, while Volhard's secondary malignant nephrosclerosis and Fahr's secondary malignant hypertension each have one and only one—hypertension and renal ischaemia respectively—and it is counter-productive to postulate more.

Only when we perceive that we are all dealing with nothing more obscure than an overstretched artery can we comprehend that the views of Franz Volhard and Theodor Fahr are not contradictory but complementary, appreciate the full significance of their joint contribution to the understanding of Bright's disease, and proceed rationally to build on that contribution.

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\(^{(1)}\) Irradiation of the solitary kidney in chronic one-kidney clip hypertension and in unilaterally nephrectomized normal control rats should permit comparison of normotensive and hypertensive malignant nephrosclerosis lesions.


