REORIENTATIONS IN HYPERTENSIVE DISORDERS*

BY

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The Retinal Changes

Helmholtz introduced the ophthalmoscope in 1851, and Sir Stewart Duke-Elder tells me that the first of all international medical congresses was called together by ophthalmologists in 1855 to discuss the significance of the dramatic retinal appearances revealed by this instrument. In the last generation excellent clinical descriptions and correlations of hypertensive retinopathy have been made by Foster Moore (1917), Leishman (1957), and Wagener (1961). For the most part, however, the literature remains clinically descriptive until we come to the more elaborate techniques of ophthalmic pathology developed by Professor Ashton, with whose co-operation Mr. David Hill and my colleague Dr. Colin Dollery have embarked on a further study.

Crushing, kinking, and displacement of veins under the arteries result from thickening of the arterial wall. Points of narrowing on the arteries have often been ascribed to spasm, and segments between the narrowed points have been called "blow outs" comparable to diffuse or fusiform aneurysm formation on these small vessels. Serial retinal photographs, however, demonstrate that relief of hypertension by hypotensive drugs or even cure of the disease by nephrectomy is not followed by any demonstrable change in the blown-out sausage-like segments of arteries, while the narrowed parts remain constant and unchanged. Spasm therefore seems to be very unusual in a localized form at least: changes in calibre must be due to actual anatomical narrowing which persists in a particular situation. Narrowing over considerable lengths of the retinal arteries is often quoted as evidence of spasm, especially when it is associated with the reduction of the ratio of arterial to venous diameter. When such arteries are measured by a micrometer eyepiece, however, it is found that the narrowing is mainly an optical illusion due to decreased visibility of the artery in a background of retinal oedema. This retinal oedema, which may also involve the disk, may be associated with some passive distension of the veins, which in turn become wider, thus altering the artery/vein diameter ratio. Treatment of hypertension is followed by subsidence of the oedema, restoration of the vein diameter to normal, and, of course, restoration of the artery/vein ratio to normal. The artery itself becomes more visible and appears wider, but no consistent widening or narrowing is demonstrable by measurement.

Most of the observed changes in the retinal arteries therefore seem to be anatomical. Empty retinal arteries can of course shrink to threads, as we are all aware, when the central retinal artery becomes occluded. It is perhaps worth emphasizing at this point that we have not yet extended these observations to the retinal vessels in acute nephritis and eclampsia, in which retinal arterial spasm is often mentioned.

The Exudative Lesions

Hard white exudates are not the residua of healed soft exudates but are quite different in character. They may appear simultaneously with or after the disappearance of soft exudates, but they tend to occur in previously unaffected parts of the retina quite unrelated to visible antecedent retinitis, and are often best seen between the macula and the papilla. They consist of fat-laden macrophages resulting from retinal damage.

Soft Exudates

It is well recognized that an occluded arteriole in the retina is often marked by a white line, and in the area which it supplies patches of mixed soft exudate and haemorrhage develop. The pathology of such patches of pallor and red-cell diapedesis is reminiscent of the pallor and surrounding haemorrhage familiar enough in infarctions elsewhere in the body. Although ischaemia therefore can have some part to play in the production of such appearances, the genesis of the cotton-wool exudates in severe hypertension is probably unrelated to any local obstruction of a definable vessel. On histological examination they consist of swollen fibres of the nerve-fibre layer of the retina ("cytoid" bodies), and on injection of the retinal vessels the patches are entirely avascular (Ashton, 1959). The pattern of avascularity within the lesion, however, bears no relation to the field supplied by any single retinal vessel, and often the "block" appears to affect a large number of small pre-capillary vessels running radially inwards to the ischaemic area. When the swollen nerve fibres are removed by tryptic digestion the underlying capillaries are clearly visible, intact but collapsed.

Followed by serial retinal photography, the developing soft exudates show almost kaleidoscopic changes. The exudate appears like a swelling cloud, pale in the centre and pinkish in the periphery, with an ill-defined edge growing larger and more densely white in a few days. When present in an angle between blood-vessels it pushes these vessels apart, and later, when it clears up, the vessels come closer together again. While blood-pressure reduction may lead to ultimate healing and clearing of these lesions they do not respond immediately to pressure-lowering, but may continue to appear, and even to develop, in new situations while vanishing elsewhere.

My colleague Dr. G. F. Joplin has demonstrated unilateral changes of hypertensive neuroretinopathy in a patient with malignant hypertension, the other retina escaping damage, as the internal carotid artery was occluded on that side. Necropsy later confirmed the diagnosis. High pressure in the retinal vessels therefore must be an important and decisive factor in the genesis of retinopathy. As the pressure in the retinal arteries falls away towards the periphery of the retina this may play some part in determining the central location of retinitis. Swelling of the retinal fibres is surely the consequence rather than the cause of local capillary ischaemia, and soft exudate may in fact be likened to a weal inducing pressure collapse of the capillaries in its centre. The accompanying haemorrhages may in fact be due to diapedesis of red corpuscles from similar capillary leakage, and the occasional presence of micro-aneurysms round soft exudates may be another manifestation of capillary injury to the minute vessels. Ashton has demonstrated that disappearance of the soft

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patches is accompanied by re-establishment of a normal capillary pattern within the area—a further indication that local anatomical (for example, thrombotic) vascular obstruction is an unlikely causal mechanism.

The idea of exudation from the capillaries of the retina may also be in keeping with the more general oedema of the whole retina or of the nerve head as a more widespread manifestation of the same disorder. The injected nerve head from patients with papilloedema and malignant hypertension shows a greatly dilated and tortuous capillary network.

In their extreme form these exudative lesions in the retina show a remarkable correlation with, and are accurately diagnostic of, a rapidly fatal course, with the development of the most severe exudative and endothelial proliferative vascular lesions in the kidney in malignant essential hypertension (Kincaid-Smith *et al.*, 1958). Such severe vascular lesions in the same patient certainly invite comparison, and the old name "albuminuric retinitis" is by no means inappropriate. The endothelium of small blood vessels is certainly liable to injury in malignant hypertension. It reacts by proliferation in the interlobular renal arterioles; fibrin leakage may be responsible for fibrinoid material in arteriolonecrosis; red cells and fluid may exude in the retina, causing soft exudative lesions, while papilloedema appears when these lesions are most extensive and severe; retinal microaneurysms indicate damage to minute vessels; albumin and fibrin leak into and through the renal glomeruli, and proliferative glomerulitis is common.

Malignant Hypertension

The close correlation of papilloedema and severe retinitis with the pathological and clinical course of malignant hypertension leads on to a consideration of some recent observations on this complication. There is no reason why the characteristic pathological vascular exudative changes should be confined to the kidney and the retina. The latter, after all, is a visible extension of the brain. Elevated cerebrospinal-fluid pressure, though common in severe neuroretinopathy, is an inconstant feature. Other arguments have been presented elsewhere why high cerebrospinal-fluid pressure cannot be accepted as the cause of papilloedema (Kincaid-Smith *et al.*, 1958). It may be better to regard elevated cerebrospinal-fluid pressure as an occasional parallel manifestation of a similar exudative angitis in the brain. The cerebrospinal fluid often has an increased protein content, and occasionally cerebral oedema with certain other features of vascular pathological change (Scheinker, 1948) and minute brain haemorrhages (Rosenberg, 1940; Hudson and Hyland, 1958) are demonstrable at necropsy. Small haemorrhages in the facial nerve were demonstrated by Moxon, of Guy's Hospital, in 1869 and held to account for the lower-neurone facial palsy which is a well-recognized complication of severe hypertension. Moxon, indeed, compared these lesions to the fundal haemorrhages with which he was then familiar.

I should make it clear at this point that the majority of attacks of local transient cerebral ischaemia (encephalopathy) which tend to recur in the same pattern in the same affected individual result most commonly from organic narrowing of some part of the vascular supply of the cranial contents. These attacks may also be a consequence of an actual occlusion

of the cerebral vessels with temporary inadequacy of collateral supply, as Pickering (1948) has emphasized. It is now a matter of widespread and somewhat chastening experience that overenthusiastic blood-pressure reduction may bring about a repetition of these ischaemic episodes, which unfortunately may not always be transient.

The vascular lesions of malignant hypertension are commonly ascribed to the effects of a greatly elevated intravascular pressure, and certainly they can be induced by the vascular damage of mechanically applied pressure (Byrom and Dodson, 1948; Masson *et al.*, 1951). Wilson and Byrom's (1939) beautiful experiment, showing protection of renal vessels beyond a Goldblatt clip while the other kidney was affected by severe lesions resulting from its exposure to the high pressure, seemed to put the matter beyond argument that some critically high level of arterial pressure was a decisive factor in the production of this form of vascular pathology. Our own observations on reversal and healing of these lesions by therapeutic pressure reduction also support the importance of the mechanical pressure factor. We should never forget, however, that while reactions of individual tissues to injury follow a standard histological pattern this does not permit precise identification of the damaging agent. That some other or additional injurious factor may be at work in the severe arterial lesions of malignant hypertension is suggested by the following observations:

1. The pressure range in malignant hypertension is not always higher than that seen in severe "benign" hypertension. Some patients, especially with nephritis, may develop malignant hypertension with arterial systolic pressures under 200 mm. Hg.
2. In Goldblatt experiments in rabbits Fleming (1953) showed that the severe arterial lesions of malignant hypertension occurred only in those animals dying with uraemia due to secondary renal damage. Those which escaped this mode of death but with equally high pressures did not show the lesions.
3. The lesions of microscopic polyarteritis in the pre-glomerular arteries of the kidney are barely distinguishable from the lesions of malignant hypertension.
4. Males are more liable to this disorder than females in spite of greater frequency of long-lasting and higher arterial pressures among the latter.
5. Malignant hypertension is very rare after the age of 65 in spite of the frequent incidence of very high pressures at this time of life.

At this stage I should like to interpolate two illuminating recent clinical experiences:

Case 1

A male art teacher had passed two insurance examinations when aged 36 and 38, being accepted as a first-class life. In 1951, at the age of 40, he presented with vague shoulder pains and was in an anxious state because his father had recently died of coronary disease. On examination his B.P. was 210/150 with grade III retinitis. There was mild albuminuria: pyelography showed normal renal shadows. He was treated intermittently with ganglion-blocking agents, including hexamethonium and pentolinium injections and later mecamlamine. However, his artistic temperament made him suspicious of doctors, and from time to time he abandoned treatment, resorting to nature healers, herbalists, or diets recommended by his friends.

In April, 1959, his B.P. was 280/190, albuminuria was 1.5 g./litre, and blood urea was 49 mg./100 ml. He developed hypertensive encephalopathic seizures, with

dysphasia, right facial weakness, and right hemiparesis. Bretylium tosylate was given to reduce his pressure, but within two months the hypertension was again completely out of control. Encephalopathic attacks recurred. In August, 1959, his serum potassium was ranging from 2.6 to 3.6 mEq/100 ml. Treatment was continued with pempidine, but drastic pressure control was not attempted on account of his recurrent cerebral ischaemic episodes. In September, 1960, grade IV neuroretinopathy became apparent, and later that month he suddenly became deeply comatose, with dilated pupils and fresh fundal haemorrhages. He died on September 24, aged 49, the terminal event being pontine haemorrhage.

At necropsy the kidneys were slightly but equally shrunken without recognizable differences on the surface. He had severe stenosis of the right renal artery due to organization of old mural thrombosis, but the left renal artery had a good lumen. Microscopical examination of the kidneys showed to an equal degree in both the characteristic changes of malignant hypertension—that is, proliferative endarteritis and widespread fibrinoid arteriolonecrosis.

Comment.—Occlusive changes in the right renal artery had probably been responsible for the entire development of severe hypertensive disease, beginning in this patient at the age of 40. A fully developed malignant phase was clinically recognizable only in the last few weeks of life. The arterial changes of florid malignant hypertension were equally distributed in both kidneys in spite of a very pronounced narrowing of one renal artery. It is also notable that there was no inequality of size of the two kidneys either radiologically or at necropsy.

It is widely held that narrowing of a renal artery as in the Goldblatt experiment will protect the kidney on

that side from the damage of the excessively high pressure which results. It is noteworthy, however, that Wilson and Byrom (1941) did comment that removal of the unclipped kidney might be followed by the development of malignant hypertensive lesions on the clipped side: they assumed that this finding resulted from further elevation of the blood-pressure after the second operation. It is apparent that the protective influence of renal artery narrowing is incomplete.

Case 2

A married woman aged 45 developed a pelvic mass in January, 1958. At that time her B.P. was 180/110. In February, 1958, an extensive removal of uterus, tubes, and ovaries was carried out for a papillary cyst adenocarcinoma invading the adjoining pelvic organs. During February and March, 1958, she was treated by extensive radiation to the abdomen, receiving 3,125 r. In February, 1960, her B.P. was 195/110; a further secondary mass had developed in the pelvis and further radiation was given with a mean tumour dose of 4,500 r. In June she complained of severe headaches and mistiness of vision, and hypertensive retinopathy due to malignant hypertension was diagnosed at Moorfields Hospital.

On examination her B.P. was 265/145 with gross bilateral papilloedema, haemorrhages, and exudates in the retinae. Albuminuria was heavy (2.4 g. in 24 hours); blood urea 85 mg.; Hb 6.1 g./100 ml. Radiological examination of the renal areas showed both kidneys to be slightly reduced in size, about 10.5 cm. in length. Blood-pressure was reasonably well controlled and heart failure subsided particularly after guanethidine and hydrochlorothiazide. The retinitis improved and blood urea remained about 60 mg./100 ml. She was discharged home at the end of July, but early in October she died in a nursing-home.

At necropsy widespread abdominal secondaries from the malignant ovarian tumour were found. The lower poles of both kidneys which had lain in the irradiation field were shrunken. Injection of the renal vessels showed narrowing and tortuosity of the arteries in the lower segments of both kidneys (Fig. 3). The arteries in the upper parts of both kidneys were of normal calibre or showed no more than the changes of benign hypertension (Fig. 4 B). In the lower poles there was considerable intimal cellular proliferation (Fig. 4 A) and extensive arteriolonecrotic lesions. The shrinkage of the kidneys in the lower poles was due to tubular atrophy.

Comment.—This case illustrates the influence of the damaging role of x rays, which has recently been studied experimentally by Wilson *et al.* (1958) and by Asscher *et al.* (1961). There is no doubt that radiation injury to the vessels was the factor precipitating and localizing severe malignant hypertensive changes in the lower poles of the kidneys. *In spite of the gross elevation of pressure, however, the vessels in the upper poles were virtually unaffected.* The importance of vascular damage by agencies other than mere elevation of arterial pressure in producing the most severe manifestations of malignant hypertensive vascular disease is clearly illustrated. The renal vessels, undamaged by radiation but exposed to an extremely high pressure, were unaffected.

FIG. 3.—Case 2. Injected kidneys. Contrast the narrowing and tortuosity of the arteries in the shrunken lower poles with the straight tapering vessels in the upper poles.

FIG. 4.—Case 2. (A) From lower radiated pole, showing proliferative endarteritis of malignant hypertension. (B) Corresponding upper pole artery, showing normal vessel wall. (Both vessels contain injection material. $\times 260$.)

laboratory methods of production of hypertension may have no obvious clinical counterpart and may be largely irrelevant to the human problem. On the other hand, the problems of pulmonary hypertension may illuminate similar problems in the systemic circulation. There are hosts of clinical problems in need of detailed study and solution. Why does an apparently mild myocardial infarction often abolish or reduce hypertension? Speed of cardiac ejection may contribute substantially to the development of impedance in a pulsating flow system. In pregnancy hypertension, what is the relationship of bacilluria and "pyelitis" of pregnancy? And how much of the pathology of toxæmia is related to the glomerular lesions demonstrated on renal biopsy by Pollak and Nettles (1960)? Sometimes surgical removal of a defined cause of hypertension cures promptly, sometimes it merely alleviates (coarctation), and sometimes the cure takes many months (Cushing's syndrome). Occasionally even malignant hypertension can vanish spontaneously: has a partially occluded renal artery become recanalized?

If the St. Mary's survey (Hamilton *et al.*, 1954) is correct, about 13% of the adult population have systolic blood-pressures over 160 mm. Hg. The problems before us are substantial, but they will repay direct and detailed attack in proportion to the resources we can devote to them. New ideas and methods of approach are with us in good measure, and both facilities and resources should be increased to match our opportunity.

I appreciate the unstinted help of past and present colleagues, especially Drs. Colin Dollery and Michael Harrington and Professors Norman Ashton and Malcolm Milne. The references are mainly recent useful key articles or based on personal experience. It would be impossible to quote all the voluminous literature from which many of the concepts are derived: to the many unmentioned contributors I also make my acknowledgments.

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The Ministry of Works has offered a substantial grant towards an appeal fund which is being launched for the restoration of St. John's Hospital, Coventry. The hospital was founded in the mid-twelfth century under the patronage of the Benedictine priory there, and the present building was probably erected in the second quarter of the fourteenth century.