The Pathogenesis of Malignant Hypertension

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No doctor who has had to treat many patients with hypertension can have failed to be exercised by the tragic problem of malignant hypertension. There is now convincing evidence that this syndrome is a simple consequence of the high level of pressure reached in the small arteries and arterioles, and since this hypothesis has a very important therapeutic implication, the evidence on which it is based is assembled here.

In their classic work "Die Brightsche Nierenkrankheit" published in 1914, Volhard and Fahr pointed out that the course of primary or essential hypertension followed one of two paths. In most patients the course was long, and death, when it at length occurred, was due to cardiac failure, cerebral vascular disease or to a disease unrelated to hypertension. The kidneys obtained after death from such patients showed a simple bland sclerosis ("einfache blonde Sclerose"), the arteries showing hypertrophy of the elastica, and the arterioles a fatty hyaline change, but apart from the areas of sclerosis the nephrons were well preserved. In some patients, however, mostly younger and with a rather higher diastolic pressure, the onset of a different course was heralded by the appearance of albuminuric retinitis; soon afterwards renal failure appeared and progressed quickly to death in uremia, mostly within the year. In these the kidneys showed not only the changes in the larger and medium sized arteries already described, but intense endarteritis in the small arteries and arterioles, and changes in the renal substance resembling those of nephritis. This kidney they named the "konbinationform," and believed that it resulted from the superimposition of an exogenous infective nephritis on an endogenous primary vascular hypertension.

In 1919 Fahr described acute arterial lesions which were invariably present in the condition termed by him malignant nephrosclerosis. The lesions were of two types, the first an acute necrosis of the vessel wall with fragmentation of nuclei, deposition of fibrinoid material, and the occasional presence of red cells in the wall; the second, a cellular thickening of the intima without splitting or reduplication of the elastica intima. Fahr pointed out that these lesions were most severe in the kidneys, but that they occurred also, but less constantly, in other organs, notably gut, pancreas and adrenals, but not muscle or skin.

Subsequent work by others, notably Keith, Wagener and Kernohan, Fishberg, and Ellis has fully confirmed these early clinical and pathologic studies of Volhard and Fahr. But while the classic picture of malignant hypertension is clear enough, further experience has shown that its relation to other forms of hypertension is complex. The hypothesis here presented provides a simple explanation of these complex interrelationships.

Hypotheses of Pathogenesis

Volhard and Fahr, as has been mentioned, believed malignant hypertension to be the consequence of the superimposition of nephritis on...
essential hypertension. Fahr continued to believe that the decisive factor in the genesis of malignant hypertension was a toxin causing the acute arterial lesions and usually due to syphilis or polyarticular rheumatism. Volhard, however, changed his ideas after putting forward his hypothesis of pale and red hypertension in 1918. Volhard was struck with the similarity between the clinical features of malignant hypertension and chronic nephritis and with their contrast to those of benign hypertension. In the former, which he called pale hypertension, the arterial pressure, particularly the diastolic, was usually over 130 mm. Hg, the face was pale, the retinal arteries narrow, and the course rapidly fatal. In the latter, the diastolic pressure was usually lower, the retinal arteries were less narrow, the face was often red, and the course relatively stable. He considered that red hypertension was due to the effects of age on a certain genetic constitution, and attributed the hypertension to elastosis of the prearterioles, which became less distensible by the arterial pulse. Pale hypertension was due to active constriction of the small arteries and arterioles by a chemical substance, which he believed to arise from the kidneys as a result of ischemia. He supposed that when in red hypertension the prearterioles contracted sufficiently to the distending pressure to reduce renal blood flow below a certain level, the renal pressor substance was released, and the active vasoconstriction of pale hypertension was added; this change in the mechanism of hypertension was reflected clinically in the change from benign to malignant hypertension. He believed further that the distinctive clinical and pathologic features of malignant hypertension, albuminuric retinitis, acute necrosis, and intimal thickening of the arterioles, were likewise a result of local ischemia consequent on the intense vasoconstriction caused by the circulatory pressor substance. Thus he believed that the development of pale hypertension led to a vicious circle, renal ischemia leading to a release of a renal pressor substance, which led to further renal ischemia with a further intensification of the vasoconstriction.

Volhard's hypothesis is not unlike that put forward here. But his distinction between red and pale hypertension has never been substantiated, for the evidence of his pupils has not been confirmed. Thus Deicke and Hulse contented that the response to adrenaline was much greater in pale than in red hypertension was not confirmed by Pickering and Kissin. Bohn's claim that a pressor substance could be extracted with alcohol from the blood in pale hypertension but not in red hypertension was not substantiated by the careful experiments of de Wesselow and Griffiths, Aitken and Wilson and Page. Alleged differences in response to the cold pressor test, to overbreathing and to carbon dioxide were not confirmed by us, when care was taken to choose subjects of comparable age groups. In fact, the mechanism of hypertension in chronic nephritis and malignant hypertension is still as little known as it is in benign hypertension.

The hypothesis which is here presented grew out of two chance observations. The first was the observation that the type of retinitis distinctive of malignant hypertension was nearly always associated with a raised cerebrospinal fluid pressure, which in turn seemed to be due to the intensity of the hypertension. The second was the finding that in the rabbit and rat, in which hypertension had been produced by renal artery constriction, the incidence of arteriolar lesions could be attributed to one factor only, the level of pressure reached in the arteries concerned. The hypothesis provides a simple explanation for the incidence of malignant hypertension in hypertensive disease. Further, it was predicted that if the hypothesis were correct, a reduction in arterial pressure should be accompanied by a transformation of the malignant to the benign type of hypertension; this, too, has been confirmed. These successive and cumulative pieces of evidence may now be considered.

The Pathogenesis of Albuminuric Retinitis

It should be clearly recognized that there are two forms of retinitis in hypertension, and that only one of these is characteristic of malignant hypertension. The distinction was first made by Foster Moore, when he showed that there was a type of retinitis, termed by him arterio-
sclerotic retinitis which differed from the albuminuric form in its appearance and its association with a much more favorable prognosis. Albuminuric retinitis, or hypertensive neuroretinopathy,\(^*\) is a bilateral condition characterized by papilledema, edema of the retina, large ill-defined exudates, hemorrhages and a macular star figure (fig. 1). Arteriosclerotic retinitis (arteriosclerotic retinopathy\(^\text{18}\) and "leichte atypische Retinitis"\(^\text{17}\)) is usually unilateral, edema of the disc and retina rarely occur; the exudates are small and sharply defined, and a star figure does not occur or consists of discrete dots rather than sheets or lines of exudate (fig. 2); the picture may of course be modified by retinal vein thrombosis. Foster Moore's figures for prognosis suggested, and subsequent experience has shown, that while albuminuric retinitis is the characteristic lesion of malignant hypertension, arteriosclerotic retinitis occurs in the benign form.

That albuminuric retinitis results from the action of a toxin retained or liberated by a diseased kidney has now been abandoned, because it can occur without albuminuria or renal insufficiency. Volhard (1931) suggested that the lesions were due to retinal ischemia, because they occurred only in hypertension, and then only in the type which he called pale hyper-

\(^*\) Albuminuric retinitis has been used throughout this paper because it was the term originally in use for the clinical picture to which it refers. Hypertensive neuroretinopathy is probably a better, if a more ugly, expression.

Fig. 1. Albuminuric retinitis; hypertensive neuroretininitis; grade IV retinitis; the retinitis of malignant hypertension. From a male, age 33, whose malignant hypertension was reversed to the benign form by excising a pyelonephritic kidney. Case quoted on page 609.

Fig. 2. Arteriosclerotic retinitis; arteriosclerotic retinopathy; "leichte atypische Retinitis"; the retinitis of benign hypertension. Reproduced from the original paper by Foster Moore, Quart. J. Med. 10: 29, 1916-17.

stressed the frequency of organic changes in the central artery of the retina in cases where generalized narrowing of the retinal arteries is found. The observations of Mylius\(^\text{21}\) and of Wagener,\(^\text{22}\) who observed localized constrictions of retinal arteries to come and go, particularly in toxemia of pregnancy, are also cited in favor of retinal artery spasm. For many years I made a practice of looking for such constrictions and never saw them, and such was the experience of most of my ophthalmologic colleagues; when a localized constriction was seen, it was visible in the same place at every subsequent examination. Recently, however, Juler,\(^\text{23}\) after very careful observation, has seen small constrictions that vary from day to day in toxemia of pregnancy. It is not my purpose to enter further into the con-
troversy of the extent and frequency of local spastic contraction of retinal arteries, except to record that most of the localized constrictions seen on ophthalmoscopic examination are organic not spastic, and to deplore the term "vasospastic retinitis," which embodies a conception based on speculation rather than evidence. While focal ischemic changes may be responsible for the exudates and hemorrhages seen in albuminuric retinitis, they may be supposed also to be the cause of the exudates and hemorrhages seen in the arteriosclerotic form. Thus Foster Moore showed that in both forms of retinitis the exudates consist of fibrin and of lipoid, both intra- and extracellular.

The distinction between the two forms, and thus between benign and malignant hypertension, is the presence of neuroretinal edema in the albuminuric form and its absence in the arteriosclerotic form, and for this distinction a very different cause is responsible. In 1934 I published a series of observations on the cerebrospinal fluid pressure in hypertension, observations which were made in the hope of explaining hypertensive encephalopathy and headache. It was found that for a given patient, the cerebrospinal fluid pressure measured on separate occasions was remarkably constant in the absence of cerebral vascular accidents, but that it varied from one patient to another. A close correlation was found between the height of the cerebrospinal fluid pressure and the type of retinal lesion found. Thus all of 12 patients with cerebrospinal fluid pressures above 250 mm. H2O had, or developed subsequently, albuminuric retinitis; of 21 patients with pressures below 250 mm. H2O, one had albuminuric retinitis, eight had arteriosclerotic retinitis and the remainder no retinal lesions other than arteriosclerosis; three patients provided an intermediate group in which the cerebrospinal fluid pressure was sometimes above, sometimes below the critical level. Shelburne, Blane and O'Hare found papilledema in 19 out of 20 patients with hypertension having cerebrospinal fluid pressures over 200 mm. H2O, but in only 2 of 30 patients with lower cerebrospinal fluid pressures. Although they made no other distinction between the retinal changes in the two groups, papilledema is usually accepted as the most constant distinguishing feature between albuminuric and arteriosclerotic retinitis.

The association between cerebrospinal fluid pressure and albuminuric retinitis in hypertension is about as close as that between cerebrospinal fluid pressure and papilledema in cerebral tumor. In Ayer's series of 61 patients with cerebral tumor, 42 had cerebrospinal fluid pressures above 250 mm. H2O and of these 39 had papilledema and three had not; 19 patients had lower cerebrospinal fluid pressures and of these six had papilledema and 13 had not. Thus it would seem that the neuroretinal edema which is characteristic of albuminuric retinitis is due, as in cerebral tumor, to raised intracranial pressure. This explanation was first suggested by Cushing and Bordley in 1908 on the grounds that a raised cerebrospinal fluid pressure was found in many cases of albuminuric retinitis, and that in two cases the retinitis cleared after cerebral decompression. This would, however, seem to be an exceptional result, for in Grant's cases in which decompression was performed for suspected cerebral tumor, both retinitis and raised cerebrospinal fluid pressure persisted after operation.

An investigation into the factors that might be responsible for the raised intracranial pressure in albuminuric retinitis detected only two, namely, the degree of anemia, and the degree of hypertension. The relationship between cerebrospinal fluid pressure and diastolic arterial pressure is shown in figure 3 and is statistically significant. Brain's observations on cerebral tumor showed no relationship between the degree of raised intracranial pressure and the arterial pressure, and it would seem, therefore, that in some way the raised cerebrospinal fluid pressure is a consequence of a sufficiently severe hypertension. Volhard (personal communication) suggested that this relationship was due to ischemic cerebral damage, but the protein concentrations in the cerebrospinal fluid were very little different in the two series. It would seem more likely that the level of arterial pressure is in part transmitted to the choroid plexus, owing to the poor contractility of the cerebral arteries. Curiously enough, when raised cerebrospinal fluid pressure is a
consequence of raised venous pressure, as it may be in cardiac failure or superior caval obstruction, papilledema does not usually occur, perhaps because in this instance intraocular and intracranial pressure may be equally affected by the same cause.  

In its full form the hypothesis of the pathogenesis of the retinal lesions is thus as follows. Focal lesions such as hemorrhages and exudates are probably due to focal vascular obstruction, either arterial, due to organic or spastic occlusion and more commonly the former, or venous; for, as Moore showed, retinal venous occlusion is not uncommon in hypertension and is characterized by exudates and hemorrhage in the affected territory. These focal lesions are common to the albuminuric and the arteriosclerotic form. But the distinguishing feature of albuminuric retinitis is the presence of widespread neuroretinal edema and this is a consequence of the level of intracranial pressure and indirectly of the severity of the hypertension.

This explanation of arteriosclerotic and albuminuric retinitis is in conformity with the fact that while most cases belong clearly to one or other type, it is not uncommon to see intermediate forms or to see one develop out of the other. For instance, small, hard-edged exudates may be the sole lesion until bilateral papilledema marks the transition to the malignant phase. Again, when the arterial pressure is reduced, and the malignant converted to the benign phase, papilledema goes first, and the exudates shrink and become more sharply defined.

**The Pathogenesis of Acute Arteriolar Necroses**

The experimental production of acute arteriolar necroses in hypertension was first described by Goldblatt in 1938. He observed these lesions in dogs in which the renal arteries had been tightly constricted, leading to gross hypertension and renal insufficiency. The lesions resembled those found in malignant hypertension in man, both in their appearance and in their distribution amongst the tissues of the body, except for their absence in the kidneys, the arteries to which had been clamped. Goldblatt considered that two factors participated in producing these lesions, a gross rise in intravascular pressure, and renal insufficiency. Shortly afterwards, and independently, similar lesions were described in the rabbit. As in malignant hypertension in man the lesions were of two kinds, namely, acute fibrinoid necrosis of the media and intima or both, with or without a cellular reaction, and cellular intimal thickening which, we suggested, represented an organization of an earlier fibrinoid necrosis. These lesions were most frequent and severe in the intestine; they were present in occasional vessels in the stomach, suprarenal, liver, myocardium and eye. No lesions were found in skin or striated muscle; nor were lesions found in the kidney of which the renal artery had been constricted, except in one rabbit, in which both renal arteries had been constricted, and in which a few lesions were found close to the areas of infarction in the smaller kidney. These acute arterial lesions were only found in rabbits in which the arterial pressure had risen above a certain point, and we therefore attributed them to the gross rise in intra-arterial pressure, attributing the sparing of the kidney to the protection afforded by the constricting clamp on the renal artery. It was not possible to put...
this hypothesis to the test of a crucial experiment in the rabbit, because in this animal as in the dog, the grosser degrees of hypertension necessary to produce the lesion can only be produced by constricting both renal arteries, or by constricting one after the other kidney has been removed. The crucial experiment was, however, carried out in the rat by Wilson and Byrom. These authors showed that in the rat gross persistent hypertension can be produced by constricting one renal artery while the other kidney is intact. In such animals acute arterial lesions identical with those of malignant hypertension were found in the intestine, pancreas, suprarenal and heart and in the kidney, the artery to which was not clamped. The lesions were absent from the kidney whose artery was clamped, at least in the early stages, although later this kidney also showed similar but less extensive lesions. They showed, in beautiful illustrations, that the lesions in the unclamped kidney of the rat were identical in all stages with those found in the human kidney in malignant hypertension. Since the blood urea was normal in many of their animals they concluded that hypertension alone was the causative factor. Unlike Wilson and Pickering in the rabbit, they did not find a relation between the intensity of hypertension and the presence or absence of lesions, but whereas in the rabbit the arterial pressure was measured without anesthesia, in the rat the pressure was measured under anesthesia, which itself may influence the arterial pressure.

Wilson and Byrom went further. They showed that after acute arterial lesions had developed in the untouched kidney, excision of the clamped kidney was not followed by a return of arterial pressure to normal. They showed that the extent to which hypertension persisted after removal of the kidney whose renal artery had been clamped was related to the intensity of the lesions in the other kidney. They were therefore led to the conception of a vicious circle in Bright’s disease, as Volhard had suggested on clinical grounds, in which hypertension produces arteriolar lesions in the kidney, which in turn produce an intensification of hypertension. The role of the kidney in the mechanism of chronic hypertension is still so obscure that the conception of a vicious circle is still based on rather slender evidence and is no part of the thesis presented here.

Goldblatt’s objection to the experiments of Byrom and Wilson, namely, that the acute arterial lesions were due to spontaneous pyelonephritis, has been effectively answered by Byrom and Dodson, who produced further evidence that a rise of intravascular pressure can itself produce the lesions. Injecting 2 cc. of warm saline through a wide bore needle into the aorta 10 or 15 times in anesthetized rats, they found acute arteriolar necroses in the kidney, when the animals were killed three days later. When one kidney was protected during the injections by traction on a ligature looped around its renal artery, lesions were absent in that kidney though present in the other which had been subjected to the full pressure rise. The degree to which intra-aortic pressure was raised was at least 80 to 90 mm. Hg. These experiments lend support to the idea, put forward by Schurmann and MacMahon that acute necrosis is due to a breach of the endothelial lining which, if mild, would allow the escape of plasma into the wall, and if severe would permit the passage of red and white cells also.

While these experiments would seem to provide a convincing explanation of the acute arterial lesions of malignant hypertension, the question is so important that other possibilities must be considered. Volhard thought the lesions were due to vascular spasm producing local ischemia. Arteriolar necrosis has been found in the edge of infarcts by Russel and by Byrom in the kidney in which intense vasoconstriction has been induced by intravenous injection of vasopressin. It is not easy to dismiss with finality the idea that local ischemia may cause these lesions in man, where Goldring, Chasis, Ranges and Smith have shown the renal blood flow is diminished per unit of functioning renal substance; for while it may be stated that the degree of reduction of blood flow is insufficient, it is a possible, if rather tenuous, argument that the over-all picture obscures local decreases that are much more extreme. The evidence already detailed
makes such an explanation of acute arterial lesions in hypertension quite unnecessary. Moreover, ischemia probably plays no part in the genesis of these lesions in experimental hypertension, since the kidney with clamped artery, far from being most affected, is actually spared. *

A very different explanation has been put forward by Winternitz and his colleagues. 32 They found that, in the dog, bilateral nephrectomy killed the animal without hypertension or vascular lesions. Bilateral ligature of the renal arteries or of the ureters produced hypertension and necrosis of muscle "including heart muscle, smooth muscle of blood vessel walls, hollow visceras and diaphragmatic muscle." Thinking that a renal substance might be responsible for these tissue lesions, they showed that injection of stored saline extracts of necrotic and fresh dog's kidney produced a profound fall followed by a prolonged rise of pressure in nephrectomized dogs, the same lesions being found at post-mortem examination as after ureteric or renal artery ligation. Working with hog renin, they were unable to separate the pressor fraction from that producing the tissue injury. Experiments differing in detail but with a similar import were published by Leiter and Eichelberger. 43 They injected hog renin into dogs which developed a foreign protein reaction. In 15 dogs with experimental renal lesions death occurred within a few days of the injection, and in 12 of these the arterioles showed hyaline degeneration and fibrinoid necrosis with leukocyte emigration and hemorrhage; in four of these dogs there was not sufficient renal damage nor severe enough hypertension to account for the lesions. So far as our present problem is concerned these experiments are open to two very serious criticisms. In the first place, hog renin is known to be antigenic in the dog, 44 and Rich and Gregory 45 have shown that the injection of foreign protein produces widespread arterial lesions, in which fibrinoid necrosis is a prominent constituent, though the whole picture is akin to that of periarteritis nodosa. In the second place, none of these extracts were prepared under aseptic precautions, nor were they sterilized before use. It is a well-known trap in the case of the dog, that the tissues contain Clostridium welchii even when excised aseptically. 46 47 Experiments from this laboratory have shown that intravenous infusions of rabbit renin into rabbits produce death with widespread hemorrhage unless extreme care is taken to sterilize the extracts and to work under strict aseptic conditions. With strict asepsis, infusions of rabbit renin into rabbits produces hypertension that is maintained for the duration of the infusion (up to 18 days), the intensity of the hypertension varying with the logarithm of the dose of renin infused. 48 In such animals acute arteriolar necroses were not found, except mildly in two animals in which the level of arterial pressure had been previously raised by subtotal nephrectomy. 49 Surveying these animals together with those earlier reported in which hypertension had been produced by renal artery constriction it was clear that the factor producing arterial necrosis was the level of arterial pressure actually attained.

**The Natural History of Malignant Hypertension**

A test of the validity of a hypothesis is its usefulness in interpreting established data. The hypothesis now under consideration provides a simple explanation for many of the features of the natural history of malignant hypertension that have previously been obscure.

The syndrome of malignant hypertension has three chief components: albuminuric retinitis, rapidly progressing renal failure, and the presence after death of arteriolar necrosis. While albuminuric retinitis is the rule it is not indispensable. Thus Goldring and Chasis 50 state that in their 68 patients in whom the diagnosis of malignant hypertension was established at necropsy, papilledema was absent in 16, or 23 per cent. In two out of five patients in whom acute necroses were found in a surgically excised pyelonephritic kidney, exudates similar
to those of albuminuric retinitis were present in the fundus but no papilledema; conversely in one patient with typical albuminuric retinitis no acute necroses were found in the excised kidney or in either excised adrenal.\textsuperscript{42} Derow and Altschule\textsuperscript{55} failed to find arteriolar necroses in the kidneys of some of their patients with malignant hypertension and in others found only few, but necroses were found in the arterioles of other organs. Keith and Wagener\textsuperscript{53} and Ellis\textsuperscript{5} have described cases in which albuminuric retinitis was present during life and arteriolar necroses after death and in which renal function and renal anatomy were essentially normal at death from cardiac or cerebral cause. The variability in these findings becomes at once comprehensible on the present hypothesis, for albuminuric retinitis and arteriolar necroses are separately caused by the sustained rise of arterial pressure above a certain level; and it would not be in conformity with other biologic phenomena if these two responses had precisely the same threshold to a given stimulus in all individuals. Moreover, if we are right in believing that productive endarteritis may sometimes be due to the organization and healing of arteriolar necroses, gross arteriolar disease can be present in the absence of necroses themselves. Since rapid renal failure is the effect of acute arteriolar lesions developing and progressing in the kidneys, since these lesions are not confined to the kidney and since there may be other consequences of gross hypertension such as cardiac failure, death may occur before renal function has significantly declined.

Even if we employ the strictest criteria and demand for its diagnosis all three phenomena, albuminuric retinitis, progressive renal failure and the presence after death of arteriolar necroses, we find that the malignant hypertension group is not homogeneous. Thus all three phenomena are found in certain cases of glomerulonephritis either in the acute, the subacute or the chronic stages. It was this above all that led to the delayed recognition of malignant hypertension and still makes its diagnosis difficult. Thus it is often difficult to be sure whether a patient is suffering from the malignant termination of essential hypertension or that of nephritis. When a patient appears with no history of acute nephritis, with albuminuric retinitis and normal urea clearance or capacity to concentrate urea, the malignant phase of essential hypertension can be diagnosed with confidence. When he presents a past history of acute nephritis, albuminuric retinitis and renal failure, the terminal phase of nephritis is probable. But when, as is common, the patient has no unequivocal history of acute nephritis and is first seen with albuminuric retinitis, gross hypertension and renal failure, it is impossible during life, and often difficult after death, to distinguish between nephritis and the malignant phase of essential hypertension. In the older British writings malignant hypertension was referred to as “chronic interstitial nephritis,” and in Russell’s\textsuperscript{39} classification of Bright’s disease as “nephritis repens, type IV.” Volhard and Fahr’s\textsuperscript{8} recognition of the entity of malignant hypertension was a masterly example of clinical insight, but even they were so impressed by the similarity of the histologic features that they at first regarded the condition as nephritis grafted on to essential hypertension, naming it the “Kombinationsform.” It was only later with further experience and reflection that they severally recognized its distinctive features. Rapid renal failure in glomerulonephritis can, of course, occur as a result of the nephritic process itself. But hypertension is the rule in nephritis and, if sufficiently severe and acute, it can cause albuminuric retinitis and arteriolar necroses, the presence of which were demonstrated in nephritis by Klemperer and Otani,\textsuperscript{44} Fishberg,\textsuperscript{4} Derow and Altschule.\textsuperscript{51} These acute arteriolar lesions located in the kidney add to the rate and extent of renal destruction, as Wilson and Byrom\textsuperscript{35, 36} pointed out and illustrated so beautifully.

Nephritis is, however, not the only disease that may confuse the picture. In 1929 Ask-Upmark\textsuperscript{55} described six cases of malignant hypertension in adolescents in which was found a peculiar renal lesion characterized by unilateral hypoplasia, and an enlarged and deformed renal pelvis having one or more recesses ending blindly near the surface of the kidney. It is probable from the description of these cases that the kidney was the seat of pyelonephritis,
the relation of which to hypertension and to its malignant phase was first clearly presented by Longcope in 1937.66 Since then very many cases of pyelonephritis complicated by malignant hypertension have been described. In fact, in Weiss and Parker’s experience at the Boston City Hospital pyelonephritis accounted for some 15 to 20 per cent of patients with malignant hypertension.

In 1934 MacMahon, Close and Hass described two cases of Cushing’s syndrome in which the post-mortem findings were those of malignant hypertension. In 1935 MacMahon and Pratt reviewing malignant nephrosclerosis, concluded that it was not merely a progression of benign sclerosis, but a distinct and separate disease that might exist alone or complicate benign sclerosis. They considered that the etiology of benign and malignant hypertension had much in common since they might both occur in lead poisoning, pituitary basophilism, and toxemias of pregnancy. In the same year, Derow and Altschule described a series of cases, and, after reviewing previous writings, concluded that malignant hypertension is “a syndrome which may occur (a) with no evidence of previously existing hypertension, (b) as the end stage of essential hypertension, with, or without uremia and (c) as the end stage of a miscellaneous group of conditions characterized by hypertension secondary to acute, subacute or chronic glomerular nephritis, pyelonephritis, adrenal tumor, pituitary basophilism, periarteritis nodosa, hyperemesis gravidarum, chronic lead poisoning, et cetera.” Derow and Altschule repeated their suggestion in 1941, and gave a comprehensive review of the relevant material. They stated that “The mechanism by which the benign course of primary or secondary hypertension is suddenly and dramatically transformed into the rapid, progressive, downhill course of the syndrome of malignant hypertension is not understood. Attempts to incriminate infectious toxins, mental stress or other factors have been inconclusive.”

In 1942, influenced by the considerations earlier presented in this paper, and ignorant of Derow and Altschule’s views, I wrote: “Thus we see on the one hand that the causal lesion is not always the same in malignant hypertension, and on the other that a given kind of lesion may be accompanied by a hypertension that follows either the benign or the malignant course. These features are readily explained on the view that the benign and malignant courses of hypertension are merely expressive of the severity of the hypertensive process, irrespective of the lesion which alternately determines it.”

We still know very little of the mechanism that produces hypertension, though there are grounds for believing that it may differ in different diseases. In pheochromocytoma, paroxysmal hypertension is almost certainly due to discharge of adrenaline and noradrenaline into the blood stream; in this disease I have seen albuminuric retinitis, as have others, but know of no recorded instance of arteriolar necroses. In some cases of unilateral pyelonephritis, hypertension is renal in origin and is cured by excising the kidney; albuminuric retinitis, arteriolar necroses and rapid renal failure are well known in such cases, but the precise mechanism by which the kidney raises blood pressure is still obscure. In nephritis the occurrence of malignant hypertension has been discussed. I have seen albuminuric retinitis, rapid renal failure and the occurrence of arteriolar necroses in polycystic kidney with gross hypertension. Other renal abnormalities are discussed by Derow and Altschule, but in none of these is it known with certainty whether the hypertension arises from a renal cause. The cause of hypertension in toxemia of pregnancy, Cushing’s syndrome and in essential hypertension is also still obscure. Since the mechanism causing hypertension is still unknown in these diseases, it is not surprising that the factors which lead to the accentuation of hypertension and thus, ex hypothesi, to the transition from the benign to the malignant form, are also quite unknown. The question has been reviewed elsewhere. Finally, in coarctation of the aorta, hypertension is abolished by excision of the constriction, though by what process is not known. Coarctation of the aorta is the only form of hypertension yet recognized in which I have never seen albuminuric retinitis, progressive renal failure or arteriolar necroses, nor am I acquainted with a description of them.
In all these forms of hypertension, then, except coarctation of the aorta, the course of hypertension may be benign throughout, or at first benign and then malignant, and the contention here is that the nature of the course is determined by the level of the arterial pressure. This hypothesis can not be fully investigated, chiefly because of the large and unknown variations in arterial pressure during the 24 hours, and the possibility, from Byrom and Dodson's work, that arteriolar necroses are caused by very high pressure operating for quite short periods. But what is known of the arterial pressure seems to be in conformity with the hypothesis. Thus all who have studied malignant hypertension from the time of Volhard have been impressed with the high level of diastolic arterial pressure (usually over 140 mm. Hg). In Woods and Peet's series of patients who had sympathectomy for hypertension, the average pressures were 191/115, 217/131, 225/134 and 227/148, respectively, in groups 1, 2, 3 and 4 before operation, group 4 being malignant hypertension. Similarly, in Bechgaard and Hammerstrom's series the incidence of high systolic and diastolic pressures was greatest in the malignant group. But while it is true in general that the arterial pressure is higher in malignant than in benign hypertension, there are individual exceptions. On the one hand, the diastolic arterial pressure may be persistently above 140 mm. Hg for many years without albuminuric retinitis or renal impairment developing. On the other, albuminuric retinitis and arteriolar necroses may develop in patients who have persistently had lower pressures, especially in those whose hypertension is of recent origin. There are several possible explanations for these anomalies. The most probable is that these anomalies may represent no more than the usual variations in susceptibility of a heterogeneous population to a stimulus of given intensity. Other possible, but quite unproved, causes are that the arterioles may be protected by organic arterial changes developing proximally in long continued hypertension, or conversely, that the arterioles may be unduly exposed to the arterial pressure by vasodilatation induced by anemia, which often accompanies the more acute hypertension. These are the kind of anomalies met with in all biologic work and their occurrence does not diminish the importance of the statement that the arterial pressure is in general higher in malignant than in benign hypertension.

In hospital practice it is not common to see the transition from the benign to the malignant type of hypertension, since most cases of malignant hypertension are seen for the first time with albuminuric retinitis. But I have followed five cases over several years before the development of malignant hypertension and through the malignant phase to its termination. Three of these cases were of essential hypertension and two of pyelonephritis. In all five the arterial pressure was considerably lower when first seen than it was at the onset and throughout the course of the malignant phase.

One further feature of the natural history of the disease requires notice. Since, ex hypothesi, the benign and malignant courses are mere consequences of the degree of hypertension, it would be expected that the difference between them is not absolute, and that in certain patients where the pressure is close to the threshold level, characteristic features of malignant hypertension may come and go. This is most easily seen in the fundus oculi, where it is not uncommon to see exudates, that are too large and too ill-defined for those typical of the arteriosclerotic form, to come and go before the accession of bilateral papilledema completes the picture of albuminuric retinitis. That the retinal picture of malignant hypertension may on occasion spontaneously revert to that of the benign type has been pointed out by Keith and Wagener.

The Treatment of Malignant Hypertension

A further test of the validity of a hypothesis is its ability to predict new data.

The hypothesis here presented enabled the prediction to be made that if the arterial pressure could be reduced sufficiently, the malignant course of hypertension would be reverted to the benign type. For many years there has been little doubt that this in fact is so. When arterial pressure is reduced by sympathectomy, by anterior spinal root section, by pyrogens, or
by salt free diet, albuminuric retinitis disappears, and the experience of Smithwick and Hammerstrom and Beechgaard suggest that life is prolonged, though it is to be noted that none of their series fulfills the conditions as to controls rightly demanded by Hill. However, no cases of reversion had been published with histologic proof of malignant hypertension until we recently described three. The cases were of pyelonephritis, unilateral in one, bilateral in two; all had the full picture of albuminuric retinitis with bilateral papilledema, large ill-defined exudates and star figure; and in all arteriolar necroses were found in kidney and suprarenal at operation. In a male aged 33 hypertension was reduced from an average 230/160 to 150/110 over a period of six years by removal of the affected kidney and the adrenal, splanchnic nerves and lumbar ganglia on the same side. Retinitis cleared quickly and renal function is normal six years later. In a girl aged 13, removal of the more affected kidney produced a slight fall, and excision of the whole of one and three-fourths of the other adrenal produced a further fall of arterial pressure not fully maintained. Six years later she has still some hypertension, gross organic changes in the retinal arteries and normal renal function. In the third case, a girl aged 11, bilateral splanchnic section and excision of seven-eighths of the adrenals produced a fall in pressure from 250/175 to 150/110 which has been maintained since. Five years later she has mild hypertension, normal fundi and normal renal function. Survival for six years with no retinitis or urea retention at the end seems to us clear evidence that the malignant course had been altered to the benign by measures which had only this in common, that they produced a significant and prolonged reduction in arterial pressure.

Thus it may be stated with some confidence that in any patient with hypertension due to any cause and at any age, the appearance of albuminuric retinitis makes it imperative that measures should be taken at once to reduce arterial pressure and keep it down, if the patient’s life is to be spared. If not, the arteriolar necroses consequent on severe hypertension will kill him.

**Summary and Some Conclusions**

The response of the body to raised arterial pressure includes cardiac hypertrophy and medial hypertrophy of the arteries. There is also some evidence that affections of the largest and moderate sized arteries, atheroma and elastosis, are more widespread and severe when the arterial pressure is raised for long periods. Provided the arterial pressure does not pass a certain critical level, these are the major consequences of hypertension, and on the whole they present a rather stable picture, except for the thrombotic occlusion of atheromatous coronary or cerebral arteries, and the accession of cardiac failure, which is not necessarily ischemic in origin. This relatively stable picture in which the patient’s condition remains unchanged often for many years is termed the benign phase of hypertension, and is most commonly seen in those types of hypertension in which the causal lesion is itself stable, particularly in essential hypertension and coarctation of the aorta, to a less extent in chronic pyelonephritis, polycystic kidney and Cushing’s syndrome; it may also occur in chronic nephritis in which, however, the clinical course is often dominated by the nephritis lesion itself.

Should, however, the pressure rise above a certain critical value, which varies from one patient to another about an average of 140 mm. Hg diastolic, then albuminuric retinitis is seen, and acute necroses occur in the arterioles of many organs, particularly of kidney, intestine, abdominal viscera, heart and brain. These acute necroses expand the wall at the expense of the lumen and seriously interfere with the blood flow to territories they supply. This is particularly important in the kidney and results in the appearance of albumin and red cells in the urine and progressive decline of renal function terminating in uremia. The weakening of the arterial wall consequent on its necrosis is prob-

*Volhard* and Wilson and Byrom have drawn attention to this type of case of which I have seen many examples. The patient has had acute nephritis, followed by persistent albuminuria, and has a moderate hypertension with albumen and usually a small excess of red cells and casts in the urine and normal or slightly impaired renal function; the condition remains unchanged for years.
ably the chief cause of cerebral hemorrhage that may also terminate the malignant phase. The great load imposed on the heart by the high pressure of malignant hypertension may also be held responsible for left ventricular failure, the third mode of death in this condition. The course of hypertension may change from benign to malignant in any disease in which the pressure rises above the critical level. Because essential hypertension is by far the commonest type, this provides the bulk of malignant hypertension, followed by chronic pyelonephritis, acute, subacute and chronic nephritis, polycystic kidneys, periarteritis nodosa, Cushing’s syndrome, pregnancy toxemia, and possibly pheochromocyctoma, in roughly that order. In coarctation it would seem that hypertension is never gross enough to produce the malignant phase. Once albuminuric retinitis has appeared or the malignant phase has been diagnosed, a persistent and considerable reduction of the arterial pressure becomes the single and urgent aim of therapeutics.

There has been in the past much argument as to when the term malignant hypertension should be used. In the light of the considerations discussed here much of this argument would seem specious and irrelevant. The malignant phase has a reasonably precise implication for both prognosis and therapeutics and can complicate nearly any type of hypertension. It would therefore seem proper to speak as Fishberg does of the malignant phase of hypertension, but also to relate it to the underlying disease whether this be essential hypertension, pyelonephritis, pregnancy toxemia, nephritis, polycystic kidney or the like. In this way, the name given by the doctor in his diagnosis is not only reasonably full and accurate, but prepares the way for the correct management of the case.

**Summary**

Whether hypertension follows the benign or the malignant course depends chiefly on the severity of the hypertension. Malignant hypertension may develop in hypertension due to any cause, provided it is sufficiently severe. The evidence for this hypothesis is as follows:

1. The characteristic finding in malignant hypertension during life is albuminuric retinitis (hypertensive neuroretinopathy) which differs from the retinitis of benign hypertension (arteriosclerotic retinitis) in the presence of neuroretinal edema. This neuroretinal edema is due to raised intracranial pressure, which in turn seems to be a consequence of the high level of diastolic arterial pressure.

2. The characteristic finding in malignant hypertension after death is acute arteriolar necrosis, the occurrence of which in the kidneys is chiefly responsible for the rapid renal failure which is so often the cause of death. Evidence from animal experiments suggest that the chief factor determining these arteriolar necroses is the high level of arterial pressure.

3. Albuminuric retinitis, rapid renal failure and acute arteriolar necroses may occur in essential hypertension, acute and chronic nephritis, pyelonephritis, polycystic kidney, Cushing’s syndrome and toxemia of pregnancy; these conditions may terminate therefore in the malignant phase. Alternatively, the hypertension may be stable, and, provided the underlying disease is stationary, the patient’s condition may remain unchanged for many years; the hypertension may thus have the characteristics of the benign type.

4. In patients whose hypertension changes from the benign to the malignant phase, it is usual to find that the arterial pressure is higher in the malignant than in the benign phase.

5. It has been proved that hypertension can be reversed from the malignant to the benign phase by measures which reduce the arterial pressure.

It would therefore seem correct to speak of the malignant phase of hypertension and to relate this to the underlying malady whether this be essential hypertension, pyelonephritis or the like. The diagnosis of the malignant phase of hypertension carries a single and urgent therapeutic implication, namely, the prompt and persistent lowering of arterial pressure.

**REFERENCES**


52 Pickering, G. W., and Heptinstall, R. H.: Nephrectomy and other treatment for hypertension in pyelonephritis. 1952 (to be published).


54 Klempener, P., and Otani, S.: Malignant nephrosclerosis. (Fahr) Arch. Path. 11: 60, 1931.


The Pathogenesis of Malignant Hypertension

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