Pathogenesis of Malignant Hypertension

I N THE usual definition, the benign phase of essential hypertension is characterized by elevated diastolic pressure associated with diffuse vascular disease (arterial and arteriolar sclerosis) of unknown origin but without significant impairment of renal excretory function.

Malignant hypertension has been defined in a variety of ways and there is no complete agreement about its pathognomonic features. The most common definition is that it usually represents an accelerated phase of benign essential hypertension, which was previously existent for a variable period, and that it is characterized by cerebral and ocular signs and symptoms as constant diagnostic features, with death occurring in a short time, usually from terminal renal failure. The recent definition of malignant hypertension, proposed by the Medical Advisory Board of the Council for High Blood Pressure of the American Heart Association, is perhaps a happy compromise, for it reads: "A clinical phase, rarely occurring de novo, more often appearing after a primary or secondary hypertension, characterized by diastolic hypertension and by accelerated and progressive renal damage, usually (but not necessarily) accompanied by papilledema, often by retinal hemorrhages and 'exudate,' and giving rise to early death from uremia unless the course is terminated along the way by complicating brain or heart damage." There can be no great quarrel with this definition, even by those who stress the primary pathogenetic importance of the kidney, because there is no reference to the origin of the hypertension.

There is even greater diversity of opinion about the pathogenesis of malignant hypertension than there is about the definition. Some consider it to be a form of essential hypertension, not of renal origin, but marked by renal excretory impairment occurring as a late or terminal manifestation; others (including the writer) believe that the malignant phase, like the benign, is primarily, and even more obviously, of renal origin. There are reasons, clinical, pathologic, and experimental, for this wide difference of view. One source of confusion has been the failure of many investigators to recognize that the pathologic changes of the kidneys in the malignant phase are neither uniform nor unique. Another source of difficulty has been lack of agreement about the nature and pathogenesis of the necrotizing arteriolar lesion that is found in the kidneys and other organs, and that is regarded by most investigators as a pathognomonic feature of malignant hypertension.

Experimental investigations carried out on the rat have contributed to this confusion. In this animal, so-called "necrotizing arteriolitis" has been produced by a variety of means—from injections of desoxycorticosterone acetate and methyl-androstenediol to repeated elevation of the blood pressure produced by intravenous injections of pitressin or by sudden injections of Ringer's solution directly into the systemic arterial stream. The fact is, however, that the rat is unusually susceptible to periarteritis nodosa, which usually involves arterial branches larger than the arterioles, and most investigators, unfortunately, have misinterpreted periarteritis nodosa as equivalent to, or identical with, arteriolar necrosis. To what extent the incidence and severity of spontaneous lesions may have been increased by these experimental procedures is not germane.
to this subject—the important fact is that the lesions represent periarteritis nodosa and not arteriolar sclerosis or necrosis, the characteristic lesions of essential hypertension.

In the dog, in which both the benign and malignant phases of human essential hypertension were first reproduced, periarteritis nodosa rarely occurs under natural conditions and does not complicate the microscopic picture in the hypertensive animal. In the dog, also, the necrotizing arteriolar lesions are the exact counterpart of the lesions found in malignant hypertension in man, and, as in man, accompany impaired renal function. Arteriolar necrosis has also been observed in bilaterally nephrectomized, "treated" dogs, with hypertension and azotemia (but not in untreated animals). The dog, and not the rat, should therefore be the animal of choice for investigations of the future dealing with the elucidation of the pathogenesis of arteriolar necrosis.

A common, but erroneous, belief is that arteriolar necrosis (with fibrinoid degeneration and with or without some perivascular inflammation), which is pathognomonic of malignant hypertension, represents an accelerated form of arteriolar sclerosis. There is no morphologic or pathogenetic basis for the confusion of this lesion with arteriolar sclerosis. There is no better reason for regarding arteriolar necrosis as accelerated arteriolar sclerosis than there is for considering the fibrinoid necrosis of periarteritis nodosa as an accelerated form of arterial sclerosis, even though it may be difficult, at times, to differentiate the healed (or terminal) stage of panvasculitis from arterial sclerosis.

Another common belief is that arteriolar necrosis is so diffuse and so severe in the kidneys that it is actually the cause of the renal failure. The development of widespread arteriolar necrosis throughout the body has even been referred to by one investigator as a "conflagration." There is no basis for such a statement. As a result of a study of many kidneys and other organs from patients in the malignant phase of essential hypertension who had pronounced renal insufficiency, many of whom had died in uremia, I have found that in some the number of intrarenal necrotic arterioles was small. As a result of this study and of investigations dealing with experimental renal hypertension produced by constriction of the main renal arteries, I have come to regard the arteriolar necrosis as merely a rapidly developing, sporadic, variable, secondary, and usually terminal, manifestation of the malignant (accelerated) phase of essential hypertension.

Exactly what it is that brings about the fibrinoid necrosis of previously normal or sclerotic arterioles is not yet known. The old view that it is the result of intense vasospasm is certainly not tenable, because spasm as intense and much more prolonged occurs in the benign phase without resulting in arteriolar necrosis. Perhaps the best evidence for the view that the arteriolar necrosis of the malignant phase, though pathognomonic, is not of primary pathogenetic significance, insofar as both the hypertension and the renal insufficiency are concerned, is that it has been observed to develop in 2 or 3 days in many organs of dogs with previously normal blood vessels, but with experimental hypertension and renal insufficiency produced by excessive constriction of both main renal arteries. In these animals the hypertension and the impairment of the excretory function begin early and the development of the wide-spread necrotizing arteriolar lesions usually occurs in the terminal stage, when the animal is in convulsive uremia. It should be obvious, therefore, that in this type of experimental hypertension, which mimies in every way the malignant phase of essential hypertension, the necrotizing arteriolar lesions play no part in the pathogenesis of either the hypertension or the renal insufficiency, and are merely a consequence of both. The probability is great, therefore, that the same holds true for the malignant phase of hypertension in man.

In my opinion, excretory failure is not caused by the arteriolar necrosis but by obliterative arterial and arteriolar sclerosis of unusually great degree or by one of several complicating renal pathologic conditions the occurrence of which brings about the impairment of renal function and the development of the necrotizing arteriolar lesions. The most common of these renal complications, the importance of which has not been sufficiently
stressed, because it is an insidious disease and frequently overlooked clinically, is chronic interstitial nephritis (pyelonephritis) which, when sufficiently severe, brings about the excretory failure of kidneys previously the seat of only arterial and arteriolar sclerosis and determines the development of the malignant phase. The other complicating renal diseases which may have the same effect are glomerulonephritis and various types of glomerulonephritis, which, when superimposed upon renal arterial and arteriolar sclerosis, of even moderate degree, may precipitate the change from the benign to the malignant phase. Interstitial nephritis (pyelonephritis), however, does this far more frequently; and some of the histologic features of the kidneys, such as the focal glomerulitis and the proliferative endarterial fibrosis and elastosis of vessels larger than arterioles, frequently regarded as specific for malignant nephrosclerosis, are really characteristics of the chronic pyelonephritis that helps to bring about the accelerated hypertension. Less commonly, the malignant phase occurs as a result of the development of arteriolar sclerosis or periarteritis nodosa in an individual with a previously existent chronic bilateral pyelonephritis and its accompanying glomerular and vascular disease.

The importance of the part played by interstitial nephritis as one of the possible causes of malignant hypertension cannot be stressed too greatly because it promises possible treatment, and even prevention, of the most common pathologic condition responsible for bringing about the change from the benign to the malignant phase of essential hypertension.

Harry Goldblatt

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As the student, fresh from the schools, and proud of his supposed superiority in the refinements of diagnosis, advances into the stern realities of practice, he will be taught greater modesty and a more wholesome caution: he will find, especially in chronic disease, that important changes may exist without corresponding physical signs,—that as disease advances, its original special evidences may disappear,—that the signs of a recent and trivial affection at one portion of the heart may altogether obscure or prevent those of a disease longer in standing and much more important,—that functional alteration may not only cause the signs of organic lesion to vary infinitely, but even to wholly disappear,—that the signs on which he has formed his opinion to-day may be wanting tomorrow,—and lastly, that to settle the simple question between the existence of functional and that of organic disease will occasionally baffle the powers of even the most enlightened and experienced physician.—William Stokes. The Diseases of the Heart and the Aorta. Dublin, 1854.
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HARRY GOLDBLATT

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