BENIGN AND MALIGNANT HYPERTENSION AND NEPHROSCLEROSIS *

A CLINICAL AND PATHOLOGICAL STUDY

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INTRODUCTION

In the classification of Bright's disease there still exists much confusion. The number of historical reviews on the subject makes it unnecessary to discuss in detail this aspect of the question. Our objective has been a clinical and pathological study of the renal manifestations of arterial hypertension in an endeavor to reach a clearer understanding of the conditions commonly labeled "benign and malignant hypertension or nephrosclerosis."

Owing to the reciprocal relationship of hypertension and kidney disease the later stages of both conditions often present great difficulty in differentiation to both pathologist and clinician. It is, therefore, essential to describe in detail the histological criteria we employed in excluding those renal conditions which produce "secondary hypertension." Disregard of these considerations by many authors is to a great extent responsible for the difficulty in reconciling the various classifications of Bright's disease.

Criteria Used for Differential Diagnosis

The outstanding conditions to be discussed are diffuse glomerulonephritis and ascending processes leading to contraction of the kidney.

(1) *Diffuse Glomerulonephritis:* In making the diagnosis of diffuse glomerulonephritis the most important feature is the diffuseness of the glomerular lesion. In the acute and subacute stages the clinical and histological pictures are sufficiently characteristic to make the diagnosis free from doubt. It is in the chronic stage — the so-

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called secondary contracted kidney — that difficulties arise. The past history of the patient is in many instances incomplete or reveals no evidence of a preceding attack of acute nephritis. Hypertension with variable albuminuria over a period of years is often the only manifestation. Histologically the glomerular lesion may not be an entirely diffuse one — the percentage of diseased glomeruli frequently not exceeding 60 to 70 per cent. Furthermore, secondary arterial and arteriolar changes may in the later stages complicate the picture to such an extent that it is impossible to decide whether the glomerular or vascular lesion predominates. We have excluded cases of this type for reasons which will be discussed later. The gross appearance of the kidney in diffuse glomerulonephritis, though in many cases characteristic, is subject to such wide variations that it is an unreliable criterion in differential diagnosis. In short, we based the differential diagnosis of glomerulonephritis on a predominantly diffuse glomerular lesion, especially in cases where the clinical data were inconclusive.

(2) *Ascending Contraction of the Kidney:* This often presents still greater difficulty in recognition. Here again the clinical history may afford little or no assistance. Histologically the main diagnostic feature is the interstitial infiltration which is usually, but not invariably, most marked in the medulla. The macroscopic appearance of the kidney may be more characteristic. Widening of the calyces, thickening, hyperemia and dullness of the mucosa may suggest the ascending nature of the process, while the breadth and flatness of the cortical scars indicate that the contraction originated in a large group of collecting tubules, thereby involving a wide zone of renal substance. It has to be emphasized that widening of the renal pelvis is not invariably present and in long-standing cases the gross appearance may be so indefinite that the diagnosis has to be made on histological grounds. Unfortunately, it is in this type of case that secondary vascular changes tend to be most severe and the picture may be so complicated as to make a definite decision impossible. Certain histological features are, however, characteristic. The distribution of the cellular infiltration has been mentioned. Its character is of importance — the presence of plasma cells, monocytes and leukocytes enabling us to discriminate between the inflammatory and purely ischemic scarring processes. Leukocytic cylinders are frequently encountered, particularly in the collecting tubules. Most

remarkable is the relative infrequency of inflammatory changes in the glomeruli. There may be thickening of the glomerular capsule, usually associated with some degree of atrophy, such atrophied glomeruli being characteristically crowded together in scarred areas from which the tubules have disappeared.

A picture closely resembling the above may be encountered in the condition Fahr [1] has termed "incomplete infarction" in which circulatory insufficiency causes atrophy of the tubules while the glomeruli for the most part remain intact. The finding of an old arterial thrombosis or very severe arteriosclerosis in the artery of supply points to the diagnosis, but in the absence of such indication the character of the interstitial infiltration must be taken as a guide. In the resorptive scar tissue of incomplete infarction inflammatory infiltration of the type described above is absent. The whole available evidence — clinical, macroscopic, and microscopic — must therefore be considered in making the exclusion diagnosis of old ascending processes.

We have briefly referred above to examples of extreme contraction of the kidney in which vascular and glomerular lesions are inextricably mixed. To these may be added advanced cases of ascending contraction. All such instances represent the final stages of a disease whose early origin it is impossible to recognize with certainty. They constituted only a very small group in our series and we felt it justifiable to exclude them on the above grounds.

Benign Hypertension, Benign Nephrosclerosis and Malignant Nephrosclerosis (Fahr [1])

We have discussed above the method of exclusion of cases of glomerulonephritis and ascending contraction. The remaining cases appear under a somewhat confusing variety of terms. Histologically the kidneys show all degrees of arterial and arteriolar changes of different types overshadowing any glomerular and tubular lesions which may be present. Clinically renal involvement may or may not be evident. According to Fahr these cases would fall into three groups — essential hypertension, benign nephrosclerosis and malignant nephrosclerosis. Since a critical analysis of this classification has been our special objective, it is desirable to outline the general conceptions involved. As "essential hypertension" Fahr designates cases in which renal vascular changes are absent. When the kidneys show arterial and arteriolar sclerosis the term benign nephrosclerosis

is used and the hypertension is considered to be secondary to the renal vascular changes. The differentiation of essential and benign renal hypertension is therefore made on the basis of a quantitative estimation of the diffuseness of arterial involvement (Fahr [2]). Histologically there is no clear line of demarcation between benign nephrosclerosis and Ziegler's "Arteriosclerotische Schrumpfniere," that is, circulatory atrophy without hypertension, but a presumption in favor of the former may be made on the basis of a diffuse arteriolar sclerosis.

As a subgroup of benign nephrosclerosis Fahr has described a series of cases showing histologically focal glomerulitis. On the basis of these lesions and the presence of elevated non-protein nitrogen in the blood in such cases, Fahr regards this as a decompensated form of benign nephrosclerosis. Other observers (Volhard,[3] Lichtwitz [4]) consider that a true renal decompensation cannot be recognized clinically and maintain that cardiac failure is chiefly responsible for the nitrogen retention (see page 66).

The malignant nephrosclerosis of Fahr is characterized by specific arterial lesions in the kidneys, namely, productive endarteritis and necrotizing arteriolitis. The latter change is considered of greater diagnostic value since the former may occasionally be absent. Focal glomerular lesions are present similar to those found in decompensated benign nephrosclerosis but are usually more severe in character and extent. The tubules commonly show degenerative changes. The hypertension is regarded as secondary to the arterial and arteriolar lesions which in turn are believed to result from the action of an exogenous toxin. Characteristically the lesions are fairly diffuse in the kidney and may be present in other organs, especially those of the splanchnic area. The vascular necrosis with reactive, exudative and proliferative changes resembles in its most marked form the condition known as periarteritis nodosa, though the latter usually affects larger vessels and has a wider organ distribution.

As Volhard points out, it has become an urgent clinical necessity to establish criteria for the differential diagnosis of benign and malignant hypertension. Fahr has given us certain criteria for making the differentiation histologically. The reasons why Volhard and Fahr's conception of malignant nephrosclerosis as a definite disease entity has not received universal acceptance are twofold. First, there exist many borderline or transitional cases which give rise to great diffi-

culties in classification; second, the "specific" arterial changes are frequently encountered in other conditions, such as diffuse glomerulonephritis, where their rôle as primary lesions can obviously not be maintained. To these criticisms we have directed our attention — in particular examining the controversial "borderline" cases from a clinical and histological standpoint. We have come to the conclusion that these cases are of vital importance, not only as a criticism of the classifications presented by Volhard and by Fahr but more especially in giving a clearer conception of the nature and course of the malignant type of hypertension.

General Histological Changes

A. Arteries

For rough comparative purposes we made a distinction between large, medium-sized and small arteries and studied the lesions in each. In conformity with the majority of observers we considered as small vessels (arterioles) all sizes up to the interlobular arteries. We differ in this respect from Bell and Clawson,[5] who would confine the term arteriole to the vasa afferentia. Arterial changes were studied not only in the kidney but in other organs, especially the pancreas and adrenals.

(*1*) *Large and Medium Sized Arteries:* Passing over the common form of arteriosclerosis we would call attention to one special form of it, the so-called productive endarteritis, especially to emphasize the difficulties that may arise in differentiating it from pure arteriosclerosis or "elastosis" of Volhard. Between the two, all transitional stages are encountered. In clear-cut cases of productive endarteritis degenerative changes are absent from the media, which tends rather to undergo muscular hypertrophy. The subintima is nucleated and has the appearance of "onion layers." In this pure form there is no difficulty in distinguishing the lesion from fully developed degenerative arteriosclerosis. Secondary degenerative changes may, however, occur in endarteritis, for example, mucoid and hyaline material may appear in the intima, in which case the latter has a less nucleated appearance. There is no clear line of demarcation between this picture and that of a purely degenerative arteriosclerotic change. Since both types of lesion may occur in different stages in the same kidney it may be almost impossible to make a definite decision.

In taking productive endarteritis as a criterion for the provisional diagnosis of malignant nephrosclerosis we accept, therefore, only those cases in which it occurs diffusely or at least in which it is the predominating arterial lesion. Focal endarteritis, especially of the transitional type described above, is a fairly common finding in scarred kidneys and is of no diagnostic value.

(2) *Small Arteries:* It is unnecessary to comment on the common arteriosclerotic changes — hyalinization and fatty degeneration. One point should be emphasized — the frequency of severe arteriosclerosis in the suprarenal glands is given surprisingly little notice in the literature, yet we found that this organ was affected with about the same degree of severity as the pancreas. In the case of the suprarenal the arteriosclerosis is predominant in the arteries of the periadrenal fatty tissue from which the gland receives the blood supply.

We have, furthermore, occasionally encountered a peculiar type of staining reaction with eosin-methylene blue which appears to be of some significance. The arteriolar wall takes on a fairly diffuse bluish appearance contrasting strongly with the bright red hyalinized arterioles. In a severer form the vessel wall may give a homogeneous dark blue stain (Fig. 1), or the dark staining material may appear as cloudy bluish masses, or again as sharply defined flakes (Fig. 2). The latter appearance is particularly common in the periadrenal fatty tissue. The exact significance of this change is uncertain. It is most frequently seen where arteriosclerosis is severe and is often associated with true arteriolonecrosis. We did not feel that it could be regarded as an acute necrosis in Fahr's sense since disintegration of the vessel wall, invasion by red blood cells and exudative and proliferative changes were absent. We termed it "fibrinoid degeneration," concluding that in rate of development and severity it probably occupies an intermediate place between arteriolar necrosis and hyalinization.

The term "necrotizing arteriolitis" (Fahr) is used to bring this type of lesion into contrast with hyalinization of the arterioles, and is employed on account of the frequent association of the arteriolar necrosis with an inflammatory reaction, which is never found in hyalinization.

In small, medium and large arteries respectively, we attempted to make a rough quantitative estimate of the severity of the arteriosclerotic process for comparative purposes. Taking into account the

differences of distribution, as well as the degree of change in the individual vessels, four degrees of severity were arbitrarily recognized for each vessel group and expressed numerically (1–4). The sum of these figures for all three vessel groups is taken as representative of the degree of arteriosclerosis in the kidney under examination.

B. Glomeruli

(*1*) *Purely Degenerative Changes:* The processes of atrophy and hyalinization of the glomeruli in kidneys showing arterial or arteriolar sclerosis do not require detailed consideration. Their modes of development have recently been reported in a paper by one of us.[6] An occasional finding of some interest is a diffuse and very striking thickening of the intercapillary connective tissue. A detailed study of this condition will be presented in a separate communication.

(*2*) *Inflammatory Changes:* (Figs. 3–6) Inflammatory lesions of the glomeruli in cases of hypertension associated with renal vascular disease are subject to wide differences in interpretation. In Fahr's malignant nephrosclerosis, glomerulitis, though essentially focal in distribution, may be so severe and extensive that some observers regard it as a primary glomerulonephritis.[21] Cases of benign hypertension showing glomerular changes of this type are much less frequent and the lesions relatively scanty, so much so in fact that occasionally a careful search reveals only two or three affected glomeruli in each section. Their existence, however, is of sufficient importance to merit a detailed description, especially since Fahr emphasizes the proliferative character of the lesion which in our cases has been minimal. The earliest change to be observed is a swelling of the epithelial cells of the glomerular loops. The cells may present a honeycomb appearance which is occasionally attributable to the deposition of fat droplets. The capillary basement membrane may undergo slight degenerative changes, giving it an irregular appearance, and collapse of the capillary makes the affected loop stand out from the remaining patent capillaries of the glomerulus. In other glomeruli the cytoplasm of the enlarged epithelial cells takes on a bluish stain and the nuclei undergo fragmentation. Early fibrinous adhesions to the parietal layer of Bowman's capsule may be present. In later stages there is definite broadening of the capillary wall, which takes on a turbid, finely granular, purplish red appearance with blurring of its

outline. The nuclei become irregular and pyknotic and at the center of the glomerular loop disappear entirely. At the periphery, especially at the site of adhesions, nuclear proliferation may be seen, but increase in polymorphonuclear leukocytes is very rare. Occasionally areas of capillary collapse give the impression of an increase in nuclei, but the phenomenon is more probably a crowding effect. In still later stages the affected loops take on a homogeneous appearance resembling hyalinization which may be focal or may involve the whole glomerulus. This picture is very characteristic and the eosin-methylene blue stain reveals a pinkish, homogeneous hyaline area containing sharply demarcated, flake-like masses which have a vivid red or bluish hue. The fat stain reveals much neutral fat and lipoids in these areas of "hyalin necrosis," and doubly refractile substances are frequently present.

These glomerular lesions are principally of an "alterative" nature but according to the severity of the process may be followed by exudative or proliferative changes in varying degree. Even in the presence of the latter, however, the primary necrotizing process is always evident. On this account we applied the term "alterative glomerulitis" and contrast the lesion with that of acute diffuse glomerulonephritis in which the primary alterative changes can be demonstrated only with difficulty.

Other forms of glomerulitis, such as are produced by embolic processes, acute suppurative changes, periglomerular infiltrations and agonal fibrin thrombi, are occasionally encountered but their presence is so obviously incidental that no further mention is considered necessary.

C. Tubules

The common regressive changes, albuminuric degeneration, hyaline droplet degeneration, necrosis and fat deposition do not demand detailed consideration. Their occurrence is common to all types of arteriosclerotic kidneys, although hyaline droplet degeneration is more frequently seen in the malignant type than in the benign type of nephrosclerosis. The features to which we pay special attention are tubular dilatation and hyperplasia. It is a rather obvious assumption that tubular dilatation is associated with decrease of kidney function, but we have been unable to find any comparative study of the relationship from the clinical and histological aspects.

Jores [7] distinguishes different forms of tubular hyperplasia. Among these are (1) dilatation of the lumen with enlargement of epithelial cells, (2) lateral sprouting and (3) prolongation of tubules — recognizable by the increase in number of tubular cross-sections relative to the number of glomeruli. We confined our observations to types (1) and (2) and recognized four degrees of dilatation—slight, moderate, considerable and severe. The first degree may perhaps be described as questionable; the last, so commonly found in chronic glomerulonephritis, is rarely to be seen in arteriosclerotic contracted kidneys. We realize that this method is only roughly quantitative and open to subjective errors. Nevertheless, it is in our opinion the only reliable morphological guide to functional impairment. The degree of kidney shrinkage in the individual case may be misleading, although the average kidney weight in severe arteriosclerosis is subnormal. Histologically resorptive scar tissue and hyalinized glomeruli may give a false impression of the extent of reduction of kidney parenchyma. The severity of the arteriosclerosis may be an equally unreliable guide to impairment of function, since it has been shown by perfusion experiments (Kimmelstiel [8]) that no exact parallelism exists between the degree of arteriosclerosis and diminution of blood flow through the kidney. Tubular dilatation with hyperplasia, on the other hand, is a direct response to reduction of kidney parenchyma below the functional reserve, and for this reason has received our special attention. According to the rate and distribution of the scarring process tubular dilatation may be focal or more or less diffuse, and this variation has to be considered in estimating its degree of development. It is furthermore a common observation, and one for which we have no adequate explanation, that in early cases tubular dilatation is confined to the periphery of the cortex immediately below the kidney capsule.

Clinical Investigations

(*a*) *Hypertension:* Elevation of blood pressure was the basis of selection of our cases. As to the duration of the hypertension our information is naturally incomplete in many instances. Moreover, on the final admission to the hospital a number of the cases showed slight or absent elevation on account of heart failure or coronary thrombosis. There was, however, in such cases a well authenticated

previous history of hypertension, or an increased heart weight with left ventricular hypertrophy but without valvular lesion was found at autopsy.

(*b*) *Renal Function Tests:* Chief emphasis has been placed on urine concentration tests and the level of the non-protein nitrogen of the blood. Volhard's dilution-concentration tests are available in many instances but in their absence repeated routine specific gravity tests have been accepted. Any inaccuracy arising from this source is in a positive direction, that is, values for concentrating power, obtained from repeated specific gravity tests on routine specimens, tend to be higher than those given by the concentration dilution test. Abnormal urinary constituents — albumin, erythrocytes, leukocytes and casts — have been noted. Other tests of renal function, creatinine clearance, urea clearance and the phenolsulphonephthalein tests have been studied, but as these are not available in the majority of cases, they are used only as supporting evidence and have not been employed for comparative purposes.

(*c*) *General Features:* Particular attention was paid to the age of the patient, past history of renal disease, scarlet fever or toxemia of pregnancy. Details of ophthalmoscopic examination of the retina were obtained whenever possible. We studied with special care the terminal manifestations of the disease. In cases of hypertension with renal involvement "uremia" is often reported as a cause of death. Regarding uremia as a complex syndrome with renal, cerebral and cardiac elements we feel that the term as such is misleading and, if used, requires strict definition. This is especially important in "malignant" hypertension, and we shall elaborate the point when discussing these cases.

Analysis of Clinical and Histological Data

Our material was drawn from consecutive clinical and autopsy records for 1932, 1933 and 1934.* All cases showing evidence of hypertension were investigated. From these, diffuse glomerulonephritis, ascending contraction and other obviously renal conditions were eliminated by the methods discussed above. The remaining series, in all 250 cases, were provisionally regarded as vascular or

* From the Mallory Institute and Second and Fourth Medical Services of the Boston City Hospital.

"essential" hypertension. There was in these cases no evidence of antecedent renal disease. A provisional separation of this series into benign and malignant groups was made on the basis of Fahr's criteria, *i.e.* productive endarteritis and necrotizing arteriolitis in the kidney. Borderline cases showing these arterial changes in atypical form or distribution were placed in a separate class, the significance of which is discussed under the malignant group. For reasons which will become obvious later, we have used the clinical expressions benign and malignant hypertension, rather than the morphological term "nephrosclerosis."

A. Benign Hypertension

A careful analysis of the degree of renal involvement in these cases was first made from the clinical and histological aspects in an attempt to substantiate or disprove Fahr's conception of a true renal decompensation in benign hypertension. On the basis of this analysis the cases fall into four groups. The findings are summarized in Table I.

(*1*) *Benign Hypertension with No Renal Involvement:* This is the largest group, constituting some 60 per cent of the whole. Clinically, the concentrating power of the kidneys is within normal limits, and there is no elevation of non-protein nitrogen of the blood. Histologically the kidneys of this group show no tubular dilatation and no glomerulitis. Arteriosclerosis is present in all degrees with an average comparative figure of $4\frac{1}{2}$.

(*2*) *Benign Hypertension with "Extrarenal" Nitrogen Retention:* (15 per cent of cases.) Elevation of non-protein nitrogen is in these cases attributable to diminished blood flow through the kidney arising from cardiac failure or some other extrarenal cause. Concentrating power is unimpaired, however, and histologically there is no tubular dilatation and no glomerulitis. The degree of arteriosclerosis is essentially the same as in Group 1.

(*3*) *Benign Hypertension with Renal Impairment:* (10 per cent of cases.) These cases show the early stages of renal involvement. The non-protein nitrogen of the blood is within normal limits but concentration-dilution tests show slight to moderate impairment of function, the maximum specific gravity being 1021. Histologically we find slight to moderate tubular dilatation but no glomerulitis. Ar-

teriosclerosis is more severe than in Groups 1 and 2 with a comparative figure of 6½.

(4) *Benign Hypertension with Renal Decompensation:* This group constitutes 11 per cent of the cases. The main histological features are focal alterative glomerulitis of the types already described, considerable tubular dilatation and severe arteriosclerosis. Clinically the concentrating power of the kidneys is impaired, specific gravities of urine in the Volhard test falling between 1012 and 1017. The

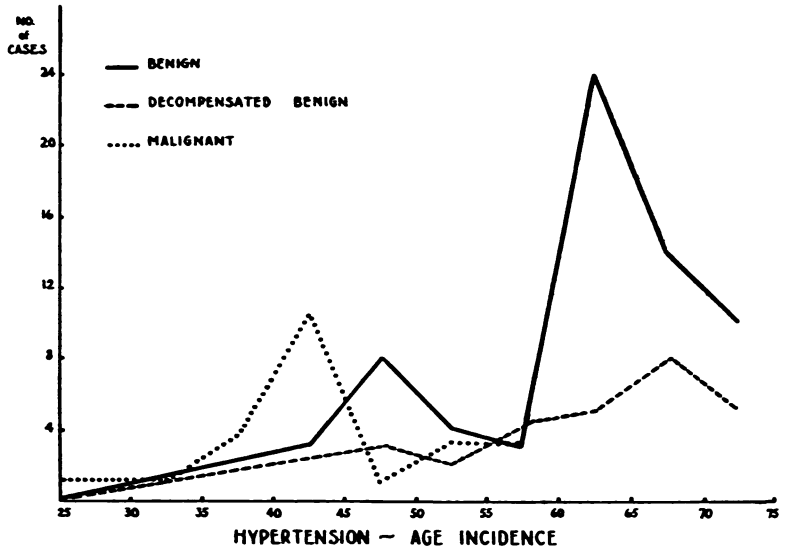
TABLE I

Renal Involvement in Benign Hypertension and Kidney Changes

Groups	Percentage	Average specific gravity of urine	Limits of N. P. N.	Average arteriosclerosis	Tubular dilatation	Glomerulitis
1. No renal involvement	60	Within normal limits	Within normal limits	4½	Negative	Negative
2. Extrarenal nitrogen retention	15	Within normal limits	50–135	4	Negative	Negative
3. Renal impairment	10	1012–1021	33–60	6½	Slight to moderate	Negative
4. Renal decompensation	11	1012–1017	57–200	8	Moderate to considerable	Present

non-protein nitrogen of the blood is elevated in all cases except two, the limits being 57–200 with an average value of 73 mg. per 100 cc. It is necessary to review the evidence which convinced us that this is a true renal decompensation occurring in the course of benign hypertension. In the first place the clinical picture up to the stage of renal failure is that of other cases of benign hypertension (Group 1). Uremia plays a subordinate part in the terminal picture, the common causes of death being cardiac failure, coronary thrombosis, cerebral accidents or bronchopneumonia. In a few cases, however, true uremic coma was undoubtedly present. The most characteristic clinical feature is the age group into which these cases fall. When the age incidence is compared with that of Group 1 it is seen that the peak falls several years later (Text-Fig. 1). Histologically the relation of these cases to the previous groups of benign hypertension is even

more clearly brought out. As we pass from Group 1 through the stage of renal impairment to that of insufficiency there is a striking increase in the severity of arteriosclerosis. As seen in the summarizing table (Table I), Groups 1 and 2 show the same average degree of arteriosclerosis (4–4½), Group 3 an intermediate figure (6½) and Group 4 a still severer degree (8). This gradation in kidney involvement receives strong support from the existence of Group 3, in which tubular dilatation and impaired concentrating power are alone pres-



TEXT-FIG. 1

ent. When the average kidney weights are similarly compared, the decompensated group shows a greater shrinkage than the cases with no clinical or histological evidence of renal involvement (256 and 326 gm. respectively). We are led to the conclusion, therefore, that if the patient lives long enough the arteriosclerotic process leads eventually to diminution in kidney parenchyma below the limits of its functional reserve. The high percentage of cases with renal decompensation in our series is probably attributable to the relatively late age incidence of our benign hypertensive groups as a whole as is seen from Text-Figure 1. The evidence presented above shows clearly that we are dealing with true renal decompensation as Fahr maintains, and not merely with a nitrogen retention due to terminal

heart failure. The existence of Group 2 with no histological evidence of renal impairment but with extrarenal nitrogen retention emphasizes this point. Lastly, these cases cannot be regarded as malignant hypertension. They fall into a much later age group, they lack the fulminating element of malignant hypertension, hypertensive retinopathy is never observed, and histologically the "specific" arterial lesions of the latter are absent. To Fahr's distinction between essential hypertension and benign nephrosclerosis the above analysis lends no support but rather emphasizes the unity of the whole group of benign hypertension as a primary generalized vascular disease.

B. Malignant Hypertension

We have now to consider those cases which were separated from the main group on account of "specific" arterial lesions — necrotizing arteriolitis or endarteritis. The classical picture of malignant hypertension presented by Volhard and Fahr is that of unusually high blood pressure occurring in relatively young subjects and having a rapid termination in uremia. Hypertensive retinopathy (edema of the disc and retina, with retinal exudates)* is a constant feature. Histologically necrotizing arteriolitis is found in the kidney and in other organs, usually associated with productive endarteritis. Focal glomerulitis is invariably present. Twelve of our cases fall into the above group. We have, however, made a careful study of the borderline cases previously referred to in which there are discrepancies from the classical picture described above. These cases have led us to the conclusion that the malignant nephrosclerosis of Volhard and Fahr does not give a true picture of the disease "malignant hypertension" but represents only the renal end-stage. Cases exist in which malignant hypertension is present but death occurs before this renal end-stage is reached.

As in benign hypertension, the malignant group can be arranged on clinical and histological grounds in increasing order of renal involvement. Such an arrangement has been made in Tables II and III. Owing to the fulminating nature of the disease, cases with *no renal involvement* are very rare. In the first group of cases, however, (Table II) renal failure plays little or no part in the final picture. Clinically the diagnosis of malignant hypertension is supported by the relatively young age incidence, the unusually high blood pres-

* The term hypertensive retinopathy is used in this sense throughout the paper.

sure, the presence of hypertensive retinopathy, and the fulminating termination. In certain cases the actual cause of death was obscure, being termed clinically "hypertensive encephalopathy" (*vide infra*) and at autopsy no organic lesion could be demonstrated except in one case which showed multiple small hemorrhages in the cerebral cortex.

Referring again to Table II, there was little or no elevation of non-protein nitrogen of the blood in these cases. Renal impairment, as indicated by diminished concentrating power of the urine, was slight or absent.

The small extent of clinical involvement of the kidney is paralleled in the histological picture. Tubular dilatation is either absent or slight compared with Group II. Glomerulitis is absent in Case 1, and only one instance was found in several sections in Case 4. The remaining members of the group show scanty focal glomerulitis compared with the more extensive changes in Group II. The same holds true for necrotizing arteriolitis. This lesion is absent in Cases 4 and 8. In Case 2 it is confined to the pancreas and adrenal and in the remainder its distribution is so scanty that only occasional examples are seen in going through several sections. Productive endarteritis is found as a diffuse lesion in only two cases and is absent or focally distributed in the remainder.

Finally, Cases 9 to 19 (Table III) show the *fully developed picture with uremia*. Histologically the findings are characteristic and it is to be noted that in this group necrotizing arteriolitis, endarteritis and focal glomerulitis are as a rule far more severe in extent than in the previous cases.

The separation of the above cases into groups is somewhat artificial. They show a gradual increase in kidney involvement. The arrangement is made solely to bring out the relation of malignant hypertension as such to the end-stage which has been termed malignant nephrosclerosis. According to Fahr's criteria cases of the first group showing no necrotizing arteriolitis cannot be regarded as malignant nephrosclerosis, but we feel that their clinical course warrants the diagnosis of malignant hypertension — a malignant hypertension which proves fatal from extrarenal causes before the kidneys are seriously involved.

As we pass from Group I to Group II, the extensiveness of the lesions in the kidney increases and the individual elements, which at

TABLE II

Malignant Hypertension. Group I

Case No.	Autopsy No.	Age	Blood pressure	N. P. N.	Specific gravity	Retinopathy	Glomerulitis	Productive Endarteritis		Necrotizing Arteriolitis		Tubular dilatation	Cause of death
								Kidney	Other organs	Kidney	Other organs		
		yrs.	*mm. Hg.*										
1	31–68 Ch.-H	12	260/160 200/150	Normal	1005–1020	+	Negative	Diffuse	Present	Very sparsely	Negative	Negative	Septicemia
2	32–231	45	220/130	24	1004	+	Occasional	Negative	Negative	Negative	Present in pancreas and adrenal	+	"Encephalopathy"
3	32–341	52	245/120 270/130	45–29 42–43	1010–1022	+	Occasional	Focal slight	Present in pancreas and adrenal	Negative	Negative	++	Bronchopneumonia, cerebral softening
4	33–10	24	220/140 245/140	35–56 41	1006–1022	+	Only 1 found	Moderate	Negative	Negative	Negative	++	"Encephalopathy"
5	33–264	45	260/150 240/150	30–34	1008–1022	+	Very few	Slight in some small arteries	Negative	Negative (occasional fibrinoid degeneration)	Adrenal (fibrinoid degeneration)	+	"Encephalopathy"
6	33–714	40	230/150 180/110	33–66	1010–1014	+	Occasional	Some, focal slow in type	Negative	Occasional	Occasional (fibrinoid degeneration)	++	Multiple punctate hemorrhages in brain
7	34–U20	36	260/140	23–50	1003–1009	+	Occasional	Diffuse	Adrenal severe	Very sparsely	Negative	+++	Adrenalectomy 3 weeks ago. Pulmonary embolism
8	34–84	41	250/150	33	1008–1012	+	Occasional	Some, focal slow in type	Pancreas adrenal fairly diffuse	Negative	Negative	+++	Bronchopneumonia

Table III

Malignant Hypertension. Group II

Case No.	Autopsy No.	Age	Blood pressure	N. P. N.	Specific gravity	Retinopathy	Glomerulitis	Productive Endarteritis		Necrotizing Arteriolitis		Tubular dilatation	Cause of death
								Kidney	Other organs	Kidney	Other organs		
		yrs.	*mm. Hg.*										
9	32–88	42	220/110	80 248	1007–1010	+	Occasional	Diffuse	Present in pancreas	Occasional	Present in pancreas	+++	Uremia
10	32–271	29	260/150	33–35 21–120	1005–1018	+	Frequent	Occasional		Extensive		+++	Uremia
11	32–533	45	235/120	82–190 265	1010–1016	+	Occasional	Diffuse	Present in pancreas	Negative	Negative	+++	Uremia
12	33–64	41	260/150	205 190	1010–1012	+	Frequent	Considerable	Negative	Fairly diffuse	Negative	+++	Uremia
13	33–327	45	200/120 190/120	175 165		+	Frequent	Diffuse	Present	Frequent	Present in pancreas	++	Uremia
14	33–440	43	215/155	45–67 53	1004–1009	+	Occasional	Occasional	Present in pancreas	Extensive	Negative	++++	Bronchopneumonia
15	33–514	46	250/140	?	1005–1016	+	Frequent	Diffuse	Present in pancreas	Extensive	Negative	+++	Encephalopathy ? Uremia ?
16	33–722	52	230/130	175	1015–1018	+	Occasional	Diffuse	Negative	Occasional	Negative	++++	Uremia
17	33–727	40	240/170 260/170	35–41 86–207	1006–1015	+	Occasional	Diffuse	Present	Extensive	Present only in cecum	+++	Uremia
18	34–388	41	200/120	150	1012	+	Frequent	Not diffuse	Negative	Extensive	Negative	++++	Uremia
19	S–34–3225	46	220/130	133	?	+	Occasional	Fairly extensive	?	Fairly extensive		++++	Uremia

first are scanty and irregular in distribution, combine more and more to form the histological entity or "full blown picture" of malignant nephrosclerosis. Thus, the histological diagnosis of this condition does not depend on any single specific lesion but can be made only from a consideration of the whole histological picture.

Concerning the nature of the nitrogen retention in malignant nephrosclerosis, the same arguments which were employed in benign hypertension with renal decompensation apply to the malignant type. Impaired concentrating power and tubular dilatation point to a true renal origin so that cardiac failure is only secondarily responsible, if at all, for elevation of the non-protein nitrogen of the blood.

So far we have regarded benign and malignant hypertension as two different processes, the former incident in relatively old individuals associated with varying degrees of arteriosclerosis and in some cases gradually leading to moderate renal insufficiency, the latter occurring in younger subjects and having a fulminating termination usually involving the kidney, which shows characteristic arterial lesions. The difference may be considered as one in the reaction of the arteries of the individual to the vasospastic process, young subjects being more "reactive" than older individuals.

There is a second group of *borderline or non-classical cases* which supports this idea and also might answer the question whether "benign hypertension ever becomes malignant." These cases (Table IV) represent a transition between the decompensated benign group and the malignant nephrosclerosis. Compared with the latter, they belong to a relatively later age period and have a less fulminant progress. One case showed hypertensive retinopathy characteristic of the malignant hypertension. Renal impairment is present with moderate nitrogen retention, but the "uremic process" as such plays a less conspicuous part in the terminal picture — recalling in this respect the cases in Group I. Endarteritis is found associated with arteriosclerosis and is often of the transitional type which has been described. Necrotizing arteriolitis, however, is only slight in extent being frequently associated with the change we have termed "fibrinoid degeneration." We feel that these cases represent a malignant type of hypertension incident in relatively old individuals, often superimposed on long-standing benign hypertension, and in this sense corresponding to the "Umschlag" of Volhard.

TABLE IV

Malignant Hypertension. Group III. (Transitional Group)

Autopsy No.	Age	Blood pressure	N. P. N.	Specific gravity	Retinopathy	Glomerulitis	Productive endarteritis		Necrotizing arteriolitis		Tubular dilatation	Cause of death
							Kidney	Other organs	Kidney	Other organs		
	yrs.	*mm. Hg.*										
32–553	62	220/140	95	1008	Not examined	Occasional	Some focal slow type		Very sparsely		+++$^{+}$	Uremia
34–406	55	180/100	67	1014–1020	Not examined	Occasional	Negative	Negative	Occasional	Present in pancreas	+++	Cardiac failure
34–612	62	180/100	58	1004–1010	Not examined	Occasional	Negative	Negative	Occasional	Negative	++	Cardiac failure
34–707	60	260/135	52–97	1012–1018	+	Occasional	Diffuse	Present in pancreas	Negative	Negative	++$^{+}$	Uremia

The summarizing classification of benign and malignant hypertension may therefore be outlined as follows:

A. Benign Hypertension

(1) No renal involvement
(2) Extrarenal nitrogen retention } 75%
(3) Renal impairment 10%
(4) Renal decompensation (decompensated benign nephrosclerosis) 11%

Intermediate or Transitional cases ("Umschlag" of Volhard) less than 1%

B. Malignant Hypertension

(1) No renal involvement
(2) Renal impairment
(3) Renal decompensation — the "malignant nephrosclerosis" of Volhard and Fahr } 4%*

Discussion

I. Benign Hypertension

A. Hypertension and Renal Arteriosclerosis

(1) *Special Significance of Arteriolar Changes:* Our observations confirm the work of other observers on the relation of arteriosclerosis to hypertension. Although a definite parallelism exists between the two, it is in many instances imperfect. Certain authors regard arteriolar sclerosis as "morphologically characteristic" of hypertension (Herxheimer and Schulz,[9] Fahr,[1] Bell and Clawson [5]), but it appears from our data that the relationship is equally true for the medium sized vessels. Arteriosclerotic changes in some cases predominate in the arterioles, in others in the interlobular vessels. Involvement of the arterioles alone is decidedly rare. In view of the variations in statistics one should regard with caution any attempt to attribute a diagnostic significance to arteriolar changes.

(2) *Hypertension as the Cause of Renal Arteriosclerosis:* Several factors prevent us from accepting such a statement unreservedly.

* In collecting cases of malignant hypertension, the records of all services of the Boston City Hospital were drawn upon. The percentage incidence is, however, based only on those cases from the 2nd and 4th Medical Services.

Cases of renal arteriolosclerosis without hypertension, although rare, have been described (Löhlein,[10] von Monakoff,[11] Fahr,[1] Kimmelstiel [8]). We also encountered a few examples of this type. Longstanding experimental hypertension may be produced in animals by section of the aortic nerves or by kaolin injections into the cisterna magna, but apparently arteriosclerosis does not follow such hypertension (Hamperl and Heller,[12] Nordmann [13]). Graybiel, Allen and White [14] have performed muscle biopsies on the upper and lower extremities of patients with coarctation of the aorta. They failed to find any significant difference in the arterioles although there is in such cases a much higher blood pressure in the arm than in the leg. Fahr has recently pointed out that in cases of severe renal arteriolosclerosis, these changes are absent from the vessels of the kidney capsule. Since both groups of vessels originate from the same artery and are subject to the same blood pressure, it appears that hypertension *per se* cannot be regarded as the cause of the arteriosclerosis. Fahr interprets this observation as supporting his theory of the renal origin of the hypertension. Such a distribution of the arterial lesions can, however, be equally well explained on the assumption that arterial strain is proportional to functional activity in the area of supply.

The conclusion is that hypertension may be considered as an accelerating factor in the development of arteriosclerosis as Aschoff maintains and Fahr to some extent admits, but the reaction of different vascular regions to the hypertension is not uniform and is determined in some way by the functional activity of the area supplied.

(3) *Renal Arteriosclerosis as a Cause of Hypertension:* We have already referred to cases of hypertension in which renal arteriolosclerosis is absent. There is considerable difference of opinion as to the frequency of these cases. According to Herxheimer and Schulz,[9] renal arteriolosclerosis is found in 97 per cent of cases of cardiac hypertrophy with hypertension. Bell and Clawson [5] place the figure at 90 per cent. Fishberg [15] states that intact kidneys are decidedly uncommon. Such numerical values are based on a purely quantitative estimation which is open to subjective errors. If mechanical obstruction to the circulation through the kidney is to be considered as a contributory factor to the hypertension, it has to be borne in mind that less than 50 per cent of cases show a completely diffuse arteriolosclerosis. Jaffé [16] believed that dilatation of the vas afferens,

which he frequently observed in association with very early degenerative changes in the glomerulus, pointed to a primary circulatory disturbance which reflexly produced the hypertension. This finding is, however, inconstant; hence the evidence cannot be regarded as conclusive. On the positive side animal experiments undoubtedly indicate that obstruction to the kidney circulation produces hypertension (Goldblatt *et al.*[17]). In human kidneys Kimmelstiel has shown by postmortem perfusion that in certain cases of benign hypertension an actual obstruction to the circulation exists. These cases are of the type we have described above as decompensated benign nephrosclerosis. In this group, therefore, where impairment of renal function is present, one may be justified in regarding the arteriosclerotic process in the kidneys as a factor in augmenting or maintaining the hypertension. In all other cases we must regard hypertension and arteriosclerosis as undergoing a parallel development as age advances.

(*4*) *Functional Disturbances in Arteriosclerotic Kidneys* (*Renal Decompensation*): This group has been recognized by various observers but different interpretations have been placed upon it. Schürmann and MacMahon [18] consider the cases as transitional to malignant nephrosclerosis. Murphy and Grill [19] similarly maintain that no clear distinction exists between the two groups. Under Volhard's influence most authors incline to the opinion that when renal failure occurs in benign hypertension we should consider the disease to have entered on the malignant phase or "Umschlag" (Volhard,[3] Lange,[20] Fishberg [15]). Exception is made to this interpretation in cases where nitrogen retention is attributable to cardiac failure and disappears as the cardiac condition improves. We hope the analysis of our data clarifies the situation by establishing the decompensated benign group as a distinct entity, and by bringing out its true relation to malignant hypertension. We have pointed out the clinical and histological features which differentiate the two conditions and have contrasted these cases with those of extrarenal nitrogen retention. There is no doubt that cardiac failure may be present and may be the precipitating cause of renal failure, but the primary and most important element is the condition of the kidney itself. Although this is admitted by some writers as a possibility (Volhard,[3] Lichtwitz,[4] Fishberg,[15] Lange [20]), the frequency with which it occurs is not appreciated.

The significance and pathogenesis of the glomerular lesions in decompensated benign nephrosclerosis remain to be discussed. Are these to be regarded as the cause or the effect of renal insufficiency, or are the two manifestations attributable to a common cause? The first possibility appears extremely unlikely on account of the focal nature of the glomerulitis and the very scanty distribution of the lesion in many cases. Considering the second possibility it is obvious that nitrogen retention as such does not produce alterative glomerulitis, as the control Group 2 with extrarenal nitrogen retention clearly demonstrates. Moreover, there exist occasional cases of decompensated benign nephrosclerosis with no evidence of elevated non-protein nitrogen. Functional impairment (as indicated by diminished concentrating power and tubular dilatation) is, however, invariable and in view of the overwhelming frequency with which nitrogen retention is present in cases with glomerulitis we cannot exclude renal impairment as an etiological factor. A consideration of the third possibility — that renal insufficiency and alterative glomerulitis are attributable to the same cause — may throw further light on the matter. Can ischemia be regarded as the common cause? The common arteriosclerotic lesion of the glomeruli, produced by slow arterial occlusion, is an atrophic degenerative change. If we postulate a sudden ischemic process or spasm as the cause of the acute necrosis observed in alterative glomerulitis, a corresponding change should be discernible in the tubules. In fact, the tubular apparatus is more susceptible to vascular damage than the glomeruli. Such changes are not found. At most we encounter hyaline droplet degeneration in the tubules. Russell [21] pointed out that glomerulitis occurs in the vicinity of acute renal infarcts. Klemperer and Otani [22] also reported necrotizing arteriolitis in the same location, and regard the finding as suggestive evidence of the ischemic origin of these changes. We have examined a series of renal infarcts and have identified examples of the alterative glomerulitis already described. The corresponding tubules, however, show no acute necrosis but rather a necrobiotic process with regeneration, an observation which prevents us from ascribing the glomerular or arteriolar lesions to pure ischemia. The occurrence of glomerulitis and arteriolitis in the vicinity of acute renal infarcts suggests, indeed, a more probable explanation of their pathogenesis. We cannot escape the conclusion that in this very situation diffusible toxins are produced by the breakdown

of kidney tissue. Toxic and ischemic factors combined may produce alterative glomerulitis. The possibility, therefore, remains that in decompensated benign nephrosclerosis retained products may act as toxins on glomeruli which are already damaged by severe arteriosclerosis. Cases with no nitrogen retention are difficult to explain on this basis but we might suggest that toxic substances may be retained before the non-protein nitrogen rises appreciably, or that, owing to the fluctuant nature of the latter, it may be normal at the time of the determination. In view of the inconclusive character of the evidence, however, we still entertain the possibility of an extrarenal toxin which may produce vascular spasm with coincident renal failure and alterative glomerulitis.

II. Malignant Hypertension and Malignant Nephrosclerosis

In the presentation of cases of malignant hypertension we have briefly outlined our conception of the relation of malignant hypertension to malignant nephrosclerosis and have pointed out that borderline cases which are difficult to explain on the basis of Fahr's classification are in reality essential to an understanding of the true nature of the disease. We must now consider the new interpretation to be placed on the specific vascular lesions in relation to the clinical picture, both from the diagnostic point of view and also with reference to the pathogenesis of the condition.

In the first place we have attempted to readjust the emphasis which hitherto has been laid on specific arterial lesions in the kidney and transfer it to the clinical picture of malignant hypertension. The clinical features, which in our opinion characterize this type of hypertension, are the relatively young age incidence, the unusually high blood pressure, the occurrence of hypertensive retinopathy and the fulminating progress of the disease, with cerebral manifestations, designated, for want of greater knowledge, "hypertensive encephalopathy." Such manifestations include a variety of symptoms, among which may be mentioned severe headaches and dizziness, disorientation and loss of memory, transient paresis and paresthesias, occasionally convulsions, visual disturbances and finally coma, which may occur in the absence of gross cerebral lesions or nitrogen retention. The presence of such a clinical picture, which has been called "pseudo-uremia" by Volhard, distinguishes these cases from the benign type of hypertension. The most important inference result-

ing from our investigation is that malignant hypertension as such precedes the stage of renal involvement — the proof being based on histological as well as clinical evidence. It appears that too much emphasis has hitherto been placed on the renal end-stage — malignant nephrosclerosis. The rigid histological criteria introduced by Fahr must therefore be relaxed and extended to embrace cases which on clinical grounds should be included in the group of malignant hypertension.

The Specific Arterial Lesions

We have already stated that the cases described under malignant hypertension were primarily separated on the basis of "specific" arterial lesions — productive endarteritis or necrotizing arteriolitis. The distribution of these lesions throughout the group, however, is not consistent with the significance attributed to them by Volhard and Fahr. We shall now attempt to elaborate a fuller conception of the nature of these changes.

(*1*) *Productive Endarteritis:* Diffuse endarteritis in the small or medium sized arteries of the kidney is an unmistakable diagnostic criterion of malignant hypertension. In several of our cases, however, it is either entirely absent or inconspicuous, so that it cannot be regarded as an invariable feature of the disease. We agree with Klemperer and Otani [22] that productive endarteritis should be regarded as an accelerated form of arteriosclerosis. The transitional type of lesion we have already described supports this view and makes it difficult to regard the change as inflammatory (Evans [23] and Fahr [1]). Productive endarteritis differs from the purely degenerative arteriosclerosis in one important respect however, namely, that in the diffuse form it is invariably associated with high blood pressure. We may, therefore, justifiably regard it as a response to a particularly severe type of hypertension. The rate of development of the endarteritic process may be extremely rapid. Weiss, Parker and Robb [24] described a case of malignant nephrosclerosis in which one kidney was removed at operation 67 days before death. Through their courtesy we have been able to examine sections of both kidneys and observed a striking increase in the extent and severity of productive endarteritis during this interval. We may state, therefore, that productive endarteritis may be absent in the early stages of malignant hypertension, develops rapidly during the course of the

disease, is present as a diffuse lesion in the kidney and other organs in fully developed cases, and in the diffuse form is never seen in the absence of hypertension. We cannot, however, explain the lesion simply as a reaction to a severe type of vascular spasm. Prinzmetal and Wilson [25] have shown that the vasospastic process in malignant hypertension is universally distributed. The incidence of endarteritis is, however, by no means universal — usually being confined to the organs of the splanchnic area. We therefore make the assumption that the vessels in certain regions are more susceptible to the vasospastic process, a susceptibility which may be in some way related, as we have already suggested in discussing arteriosclerosis, to the functional activity of the area of supply. This view is consistent with the observation made by Fahr that endarteritis and arteriolitis are not found in the vessels in the kidney capsule. It is necessary, however, to mention the paper by Kernohan, Anderson and Keith [26] who describe thickening of the arterial wall in the voluntary muscles in hypertension. It is surprising that similar investigations (Graybiel *et al.*[14]) in cases of coarctation of the aorta did not reveal any difference in the arterioles in the arm and leg. In order to explain this discrepancy we may point to the recent experiments one of us [25] has made in which it was shown that the mechanism of arteriolar constriction in generalized hypertension is apparently different from that in coarctation of the aorta. The former has to be interpreted as intrinsic vascular spasm whereas the latter has been shown to be vasomotor in origin. Graybiel, Allen and White [14] suggest a similar explanation although experimental support was not available at that time.

(2) *Necrotizing Arteriolitis:* Since necrotizing arteriolitis in the kidney may be slight or even absent in cases with malignant hypertension we cannot justifiably regard it as causing the hypertension. Arteriolitis differs from productive endarteritis in its relation to renal failure. Cases which show a fulminating uremic termination with gross nitrogen retention (Group II), in general show severe necrotizing arteriolitis. In the pre-renal stage, however (Group I), this feature is slight or absent. The extent and severity of the focal glomerulitis also show a parallel relationship with the renal function. The pathogenesis of the arteriolar necrosis presents a similar problem to that of the origin of alterative glomerulitis in decompensated benign nephrosclerosis. The inconstancy of the lesion prevents us from re-

garding it as the cause of renal insufficiency. Its occurrence with alterative glomerulitis in the vicinity of acute infarcts suggests the association of toxic and acute ischemic factors in its production. We have referred above to evidence of vascular spasm in malignant hypertension. Such spasm has been observed in the retinal vessels and its existence is indicated on the pathological side by cases of cortical necrosis of the kidney and by the occurrence of "Fleckmilz" and "Fleckpancreas" in malignant nephrosclerosis.

That spasm alone does not cause arteriolitis is evident from the absence of this lesion in Raynaud's disease and acute eclampsia where vascular spasm is undoubtedly present. Klemperer and Otani [22] suggest that endarteritis in larger radicles may produce ischemic damage in the corresponding arterioles, thereby precipitating arteriolar necrosis. Since, however, necrotizing arteriolitis occurs in the absence of endarteritis (see also our Case 2), these authors were led to subdivide malignant nephrosclerosis into two types: one in which arteriolar necrosis is assumed to follow endarteritis ("accelerated arteriosclerosis"), the other in which true necrotizing arteriolitis is regarded as the primary lesion. Schürmann and MacMahon similarly attempted to distinguish two forms of malignant nephrosclerosis — an exogenous and an endogenous form — on the basis of a difference in distribution of the arteriolar lesion. We feel that the evidence is insufficient to justify such distinctions. In the first place the separation of arteriolar necrosis and necrotizing arteriolitis is unjustifiable since transitions frequently occur from one to the other. Secondly there is no constant relation between endarteritis and arteriolar necrosis or arteriolitis. The distribution of the lesions in the arterioles is indeed very irregular and we feel cannot be regarded as an adequate basis for subdivision of cases. Such variations as occur are attributable to the different stages of development of the disease rather than to differences in pathogenesis. It is impossible to escape the fact that in malignant hypertension the development of both arteriolitis and glomerulitis is closely related to renal insufficiency. By analogy with decompensated benign nephrosclerosis it seems reasonable to regard the renal failure as the direct result of acute functional ischemia. Whether some toxin, producing the vascular spasm, produces also the glomerulitis and arteriolitis, or whether, alternatively, the combination of acute ischemia and retained toxic substances be regarded as the cause remains an open

question. Whatever their pathogenesis, these manifestations must be considered as essentially characteristic of the acute renal end-stage of malignant hypertension, independent of the endarteritis and in certain cases appearing before the latter has developed. When death occurs before this end-stage is reached (Group I) necrotizing arteriolitis may be entirely absent.

Malignant Hypertension

Etiology: We have been led to postulate both a toxic and a spastic factor to explain the characteristic lesions of malignant hypertension. The only exogenous toxin of known etiological significance is lead. Recent work has shown, however, that other conditions may act as precursors of malignant hypertension and lead ultimately to malignant nephrosclerosis. Such are basophil adenoma of the pituitary [27] and eclamptic toxemia of pregnancy.[28] This suggests that any hypertensive state may give rise to the malignant form of hypertension. There is considerable evidence that acute glomerulonephritis, the most common cause of hypertension in young subjects, may similarly act as a precursor of malignant hypertension. Persistent hypertension has been reported to follow acute glomerulonephritis even though the renal lesion has apparently healed (Longcope,[29] Van Slyke [30]). It might be expected that hypertension of such an origin could pass over to the malignant form. Volhard [3] has reported a case of glomerulonephritis which suggests this sequence of events (case Joh. Ei., p. 1439). The histological diagnosis of malignant nephrosclerosis was made, although from the description it is not clear whether terminally the glomerular lesion was focal or diffuse. The following case is an example of acute nephritis in which apparently the diffuse glomerular lesion healed, and which was followed later by malignant nephrosclerosis.

CASE 1. E. S., first admitted May, 1924, aged 8 years, with 2 days history of bloody urine followed by headaches and convulsions coming on after an attack of acute tonsillitis. *Urine:* Specific gravity 1010 to 1015; albumin, slight trace.

Well until second admission August, 1933. Three months pregnant.* Blood pressure 228/158. *Urine:* Specific gravity 1006; large trace of albumin; occasional white and red blood cells in sediment. Pregnancy terminated.

Third admission December, 1934. Two and a half months pregnant. Blood

* In view of the early stage of pregnancy it is unlikely that a hypertension of such severity could be attributable to a pregnancy toxemia.

pressure 230/100. *Urine:* Specific gravity 1009; large trace of albumin. Therapeutic abortion and sterilization performed.

Final admission February, 1935, complaining of increasing dyspnea and abdominal swelling. *Physical Examination:* Orthopneic, pale, signs of heart failure. Fundi not well seen. Blood pressure 270/165. *Urine:* Specific gravity 1008; large trace of albumin; granular casts and occasional red cells in sediment. Non-protein nitrogen 150 mg. per cent rising to 325. Developed pericardial friction rub and died in uremic coma.

Histological Findings in the Kidney

Multiple areas of fresh anemic infarction with a broad hemorrhagic border in the cortex.

Arteries: Severe diffuse endarteritis of large, medium and small vessels. Extensive necrotizing arteriolitis. Fibrin thrombi are present in necrotic vessels within the substance of the infarcts but are not seen outside these areas.

Glomeruli: Majority are normal. Remainder show increase in nuclei, necrosis of capillary walls, occasional adhesions, a few polymorphonuclear leukocytes present.

Tubules: Considerable tubular hyperplasia.

The conception that acute glomerulonephritis may act as a precursor of malignant hypertension is consistent with the occurrence of arteriolitis and endarteritis in the kidney in chronic glomerulonephritis. The high blood pressure which develops in the later stages of diffuse glomerulonephritis is usually moderate in degree, but cases are not infrequently encountered, especially in young subjects where the blood pressure is extremely high. In such cases hypertensive retinopathy is frequently present and the rapid downhill course of the disease is more characteristic of malignant hypertension than of chronic glomerulitis. The following is a typical example.

CASE 2. J. P., male, aged 27 years, admitted Nov. 8, 1932, with a 2 years history of "kidney trouble." Frequency day and night and hematuria. There was a history of severe headache, shortness of breath, swelling of face and misty vision for 1 week following a cold in the head.

Physical Examination: This revealed a pale, ill-looking man, orthopneic and coughing up blood-stained sputum. Retinal examination showed papilloedema with extensive exudates and hemorrhages. Blood pressure 240/140 mm. Hg.

Urine: Specific gravity maximum 1012; large trace of albumin; many red cells and leukocytes in sediment.

Blood: Non-protein nitrogen 130 mg. per 100 cc.

Patient died in uremia on day after admission.

Macroscopic Examination of Kidneys: Combined weight 160 gm. Capsule strips with difficulty from yellowish gray, coarsely granular surface. Cut surface boggy. Cortex diminished in size.

Histological Examination of Kidneys: Chronic diffuse glomerulonephritis. Every glomerulus involved. Fairly extensive necrotizing arteriolitis and productive endarteritis affecting small vessels only.

The difficulty in making a histological diagnosis in such cases arises from the simultaneous occurrence of diffuse glomerulonephritis and the arterial lesions — endarteritis and necrotizing arteriolitis. Two theories have been suggested:

(1) The arterial lesions are regarded as secondary to the glomerular inflammation. This explanation, which is maintained by Fahr, is apparently supported by the fact that the vascular lesions are confined to the kidney. If, however, the arteriolitis and endarteritis are regarded as part of a generalized vascular disease their occurrence only in this situation can be explained on the basis of the excessive vascular strain in an already damaged kidney. In pure malignant nephrosclerosis the vascular lesions may similarly be found only in the kidney. Hence the fact that arterial and arteriolar changes in glomerulonephritis are not found outside the kidney does not disprove the theory that they depend on a generalized vascular disturbance.

(2) There remains the possibility that we are dealing with coincident malignant nephrosclerosis and chronic glomerulonephritis. The frequency of this association, however, suggests a closer relation between the two conditions. It has frequently been stated that arteriolitis also occurs in acute nephritis (Löhlein,[31] Fishberg [32] and others) and the explanation has been offered that the same toxin produces both the glomerulonephritis and the arteriolitis. Such a toxin may be allergic in origin (Masugi [33]). It appears moreover that acute nephritis is not to be regarded as a purely renal disorder but rather as a general vascular disturbance which may manifest itself before the kidney shows signs of involvement. Assuming that one toxin (? allergic) may produce both the arteriolar and glomerular lesions in acute nephritis, the same explanation may hold for the lesions found in chronic glomerulonephritis. The acute stage of the disease may be regarded as resulting in a hypersensitive state of the general arterial system as well as of the glomeruli. In its progress the disease may involve either the glomeruli or the blood vessels, or both. Accordingly we may encounter any of the above mentioned sequelae of acute glomerulonephritis, *i.e.* chronic diffuse glomerulonephritis, malignant nephrosclerosis, or chronic glomerulonephritis with vascular lesions in the kidney.

Periarteritis Nodosa and Malignant Nephrosclerosis

The close similarity between these conditions in many instances led Fahr to the opinion that malignant nephrosclerosis might be regarded as a special form of periarteritis nodosa in which the arteriolar lesions were for the most part confined to the kidney — a view which agreed with his theory of the renal origin of malignant hypertension. If, however, we are correct in regarding malignant hypertension as a primary generalized vascular disturbance, and the renal vascular lesions as secondary, it is necessary to find an explanation for the association of malignant hypertension and periarteritis nodosa, especially since Volhard states that in these cases the hypertension is of the so-called "pale" type. Since the summarizing articles on periarteritis nodosa do not discuss in detail the relation of kidney involvement to hypertension, especially in its malignant form, we have made an analysis of the original case reports in the literature.

Cases with insufficient information concerning blood pressure, heart weight or kidney involvement were eliminated. Where a diagnosis of diffuse glomerulonephritis was made or where kidney involvement was definitely stated to be focal the case was also excluded. There remained some 75 cases with a diffuse distribution of the arterial lesion in the kidney — so-called "infarcted contracted kidneys." Forty-seven cases (62 per cent) showed evidence of hypertension (in 5 cases based on cardiac hypertrophy at autopsy). In 28 cases (37 per cent) a normal blood pressure was observed (in 5 cases no note was made of the blood pressure but the heart weight was normal at autopsy). Eighteen of the cases with hypertension showed a systolic pressure at or above 200 mm. Hg.

Relation of Hypertension to Kidney Involvement: We have pointed out that the majority of cases (62 per cent) with diffuse arterial lesions in the kidney showed hypertension. Where diffuse lesions in the kidney were absent no elevation of blood pressure was found. On the clinical side complete renal function tests were only occasionally available, hence the occurrence of red blood cells, albumin and casts in the urine had to be taken as clinical evidence of renal involvement. Eighty-four per cent of cases with hypertension showed such involvement but similar findings were also present in 37 per cent of cases without hypertension. Thus, as has previously

been stated, there appears to be no rigid relation between hypertension and renal involvement in periarteritis nodosa.

The Nature of the Hypertension: We usually find that the elevation of blood pressure in periarteritis nodosa is gradual in development, moderate in severity and, in cases where a full description is given, appears to be preceded by the renal involvement. This suggests that we are in fact dealing with a renal hypertension. Cases are, however, observed where extensive arterial lesions are present in the kidney with death in uremia but with no hypertension. It is possible that the diffuse involvement of the heart muscle frequently observed in periarteritis nodosa may in such cases prevent the blood pressure from rising.

An attempt to separate cases of the malignant type was made by paying special attention to the ophthalmoscopic findings. In 15 cases with hypertension where examination of the fundus occuli was reported, 7 were normal, in 6 of these [34-39] at a time when signs of renal insufficiency were already present (*i.e.* diminished concentrating power of the urine or raised non-protein nitrogen). Eight cases showed signs of retinopathy, but whether or not this could in all cases be considered of the malignant type is doubtful. The reports of these cases were, however, analyzed in an attempt to determine whether the hypertension was preceded by renal involvement. We came to the conclusion that such was not invariably the case. In 5 cases [40-44] hypertensive retinopathy and renal insufficiency were already present on the patient's admission to the hospital. In 2 cases, however, there was a history of high blood pressure preceding the periarteritis nodosa by 7 years [45] and 5 years.[46] In only 1 case did retinopathy appear while renal insufficiency was developing.[47] It may be of interest to notice that in 2 cases [48, 49] a previous history of lead poisoning is mentioned.

From the literature, therefore, it appears that the hypertension associated with periarteritis nodosa is only occasionally of the malignant type. More often it is in the nature of renal hypertension — moderate in severity, late in development, and lacking the retinal signs which characterize malignant hypertension. Malignant nephrosclerosis and periarteritis nodosa differ therefore in certain important respects. In the former, hypertension is of primary vascular origin, is malignant in type and terminates in renal failure. Histologically productive endarteritis is the most characteristic

arterial lesion and is regarded as the result of a severe prolonged vascular spasm. Arteriolitis on the other hand appears to be a terminal manifestation and is related more closely to renal insufficiency than to hypertension.

In periarteritis nodosa inflammatory lesions of the vessels occur as the primary event and, as in malignant nephrosclerosis, appear to be more closely related to some toxic factor than to hypertension. In fact hypertension only arises in the majority of cases when destruction of the kidneys by vascular changes has resulted in renal insufficiency. The inflammatory lesions in the vessels predominate and endarteritis, as Volhard points out, is irregular in distribution. Hypertension of the malignant type occurs in relatively few instances and in these some additional factor appears to be present; thus antecedent hypertension was present in 2 cases in the literature and in 2 others a history of lead poisoning was obtained.

We are led to the conclusion that the etiological agent (allergic or otherwise) which produces the inflammatory lesions in the arteries in periarteritis nodosa is not *per se* responsible for the malignant character of the hypertension but only when acting on arteries which show an abnormal reactivity. We were previously led to postulate a difference in reactivity of the arteries to explain the different character of malignant hypertension in young and old subjects; and we suggested above that the blood vessels might be "sensitized" by an attack of acute diffuse glomerulonephritis. The whole evidence leads us to the conclusion that two factors are necessary for the development of malignant nephrosclerosis — a preëxisting hyperactivity or "sensitization" of the arteries on which is superimposed some precipitating factor, allergic or otherwise.

Summary and Conclusions

(*A*) Benign hypertension and benign nephrosclerosis may show a parallel development but in the early stages are not causally related. In the later stages, however, there may be a reciprocal relationship, *i.e.*:

(1) Hypertension acts as an accelerating factor on the development of arteriosclerosis.

(2) Arterial and arteriolar sclerosis of the kidney, when severe enough to produce impairment of renal function, may give rise to

"renal" fixation of the hypertension. Such cases are termed "decompensated benign nephrosclerosis" since clinical and histological evidence shows that the impairment of function is of true renal origin.

(*B*) Malignant hypertension and malignant nephrosclerosis, on the other hand, show a definite correlation.

(1) On clinical and histological grounds malignant hypertension is to be regarded as a primary generalized vascular disease of which malignant nephrosclerosis represents the "renal end-stage." Cases are described in which death occurs from malignant hypertension before the renal end-stage is reached.

(2) When malignant hypertension progresses to the stage of malignant nephrosclerosis, the condition is clinically and histologically characteristic, as described by Volhard and Fahr. The main objection to their classification is the existence of so-called "borderline" cases, which are neither clinically nor histologically characteristic. Of these cases, in our interpretation, one group consists of cases of malignant hypertension in which death occurs before the renal phase develops, the other group comprises older subjects in whom the malignant hypertension is less fulminant and may be superimposed on benign nephrosclerosis.

(3) Endarteritis in its diffuse form is regarded as the most characteristic histological sign of malignant hypertension. Arteriolitis (arteriolar necrosis) is more closely related to the terminal renal failure than to the hypertension itself.

(4) Various hypertensive states may act as precursors of malignant hypertension. Evidence is presented that diffuse glomerulonephritis may similarly be associated with or followed by malignant hypertension, thereby explaining the occurrence of the "specific" vascular lesions in the kidney in diffuse glomerulonephritis.

(5) A study of the relation of periarteritis nodosa to malignant nephrosclerosis provides suggestive evidence that two factors are necessary for the development of malignant hypertension, namely, a preëxisting hyperactivity or "sensitivity" of the arteries, on which is superimposed a precipitating factor, allergic or otherwise.

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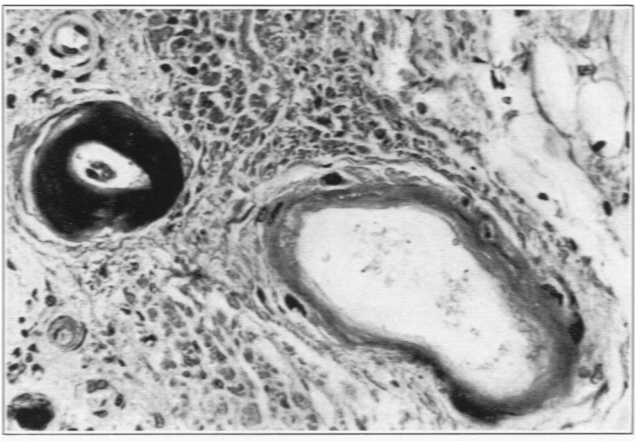
DESCRIPTION OF PLATES

PLATE 7

FIG. 1. Fibrinoid degeneration in the small vessel staining dark purplish blue with eosin-methylene blue. Wall of large vessel shows hyalinization only. Stains red.

FIG. 2. Similar fibrinoid degeneration showing irregular, flake-like appearance of fibrinoid material in hyaline mass. Eosin-methylene blue.

FIG. 3. Early alterative glomerulitis showing necrosis of swollen epithelial cells with adhesion to Bowman's capsule at this point. Eosin-methylene blue.



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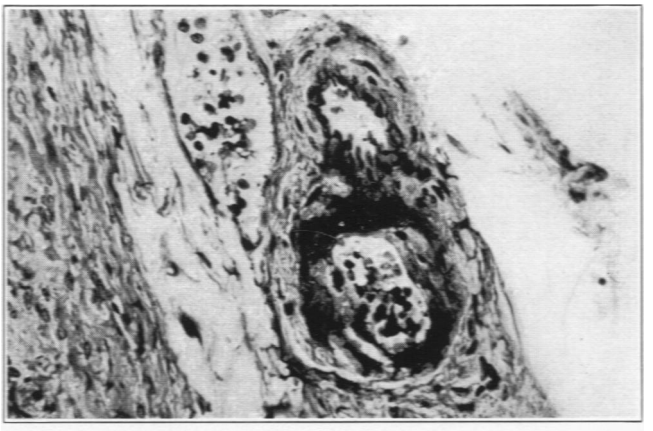

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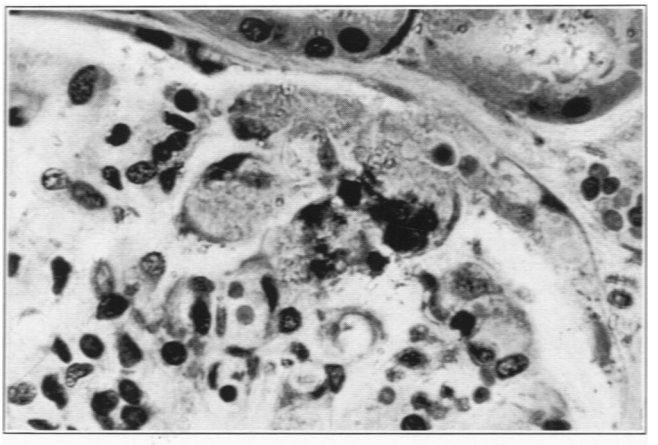

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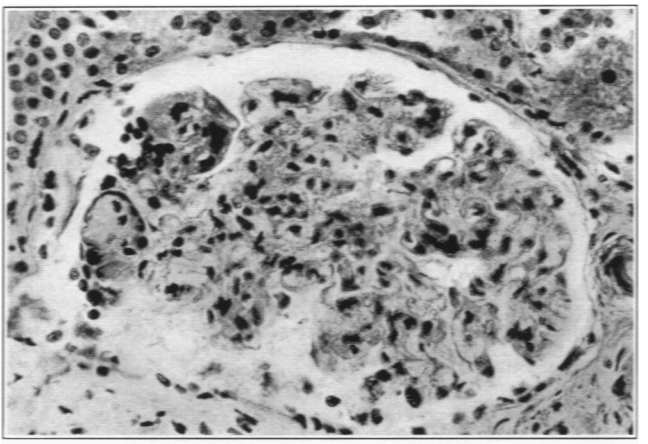
PLATE 8

FIG. 4. Early alterative glomerulitis; several loops show necrotizing processes. There seems to be a slight increase of nuclei in these areas. Eosin-methylene blue.

FIG. 5. Alterative glomerulitis showing acute necrosis at one point (dark area which stains purplish). Several old adhesions. Eosin-methylene blue.

FIG. 6. Extensive necrotizing glomerulitis; several loops involved simultaneously. Eosin-methylene blue.



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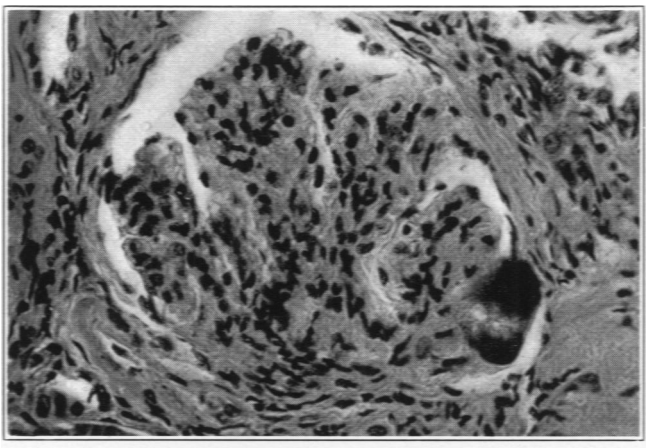

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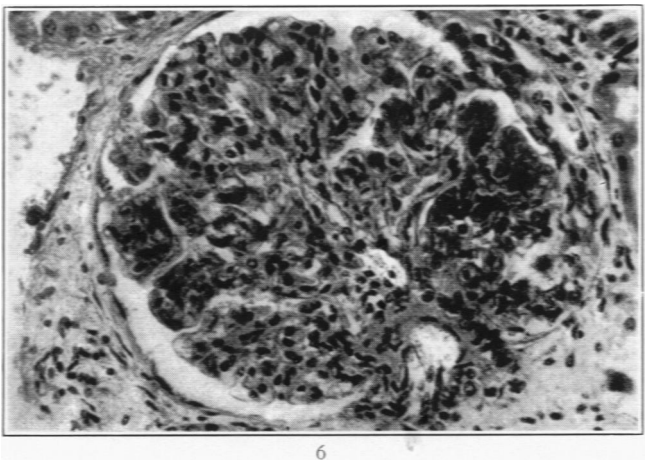

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