HIGH ARTERIAL PRESSURE AS A PRIMARY CAUSE OF HYPERTENSIVE VASCULAR LESIONS*

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GULL and Sutton[1] in 1872 defined the concept of the primacy of "arterio-capillary fibrosis" as the cause of hypertension in the "forbid state called chronic Bright's disease with contracted kidney." They based their conclusions primarily on studies at necropsy. Mahomed,[2] in 1879, reported the opposite conclusion. He was primarily a clinician, and was one of the first to measure arterial pressure and to correlate it with clinicopathologic changes. He[3] considered that there were "three stages of chronic Bright's disease: first, the *functional stage,* which is limited to the condition of high arterial pressure without organic changes in either the vascular system or the kidneys; second, the *chronic Bright's disease without nephritis,* the stage of organic changes in the vascular system and in the kidney (for which, if thought desirable, the term 'arterio-capillary fibrosis' might be employed); third, *chronic Bright's disease with nephritis,* the natural, but by no means the invariable, termination of the disease." Unfortunately, Mahomed died while still a young man, and was thus prevented from convincing the medical public by further demonstrations of the natural history of the disease; the authority of the older, presumably wiser, men prevailed.

The demonstration by Goldblatt, Lynch, Hanzal, and Summerville,[4] in 1934, that in dogs, partial occlusion of the main renal artery could cause hypertension of varying severity, seemed to support the view that primary nephrosclerosis, if not diffuse "arterio-capillary fibrosis," might be the true event in hypertension. This concept received further support in 1937 from the observations of Moritz and Oldt[5] that people who died of complications of hypertension, consistently showed signs of nephrosclerosis, and that, whereas in previously normotensive subjects, extrarenal arteriolar lesions were frequently present, renal arteriolar lesions were conspicuously absent. More than 25 years of further clinical, experimental, and pathologic studies of hypertension have not resolved the issue.

The experiments of Wilson and Byrom,[6,7] Wilson,[8] Floyer,[9] and Selye and Stone[10] represent a large body of evidence that, in rats, hypertension will cause, and relative normotension or hypotension will tend to prevent, nephrosclerotic

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lesions. These data concur in supporting the thesis that high arterial pressure per se is a primary, if not the only significant, factor in the pathogenesis of these lesions. The design of these experiments unfortunately was such that the associations observed for the most part were definable only in qualitative rather than in quantitative terms. A direct approach to the problem by forced intraarterial injections was made by Byrom and Dodson,[11] by us,[12] and by Schaffenburg and Goldblatt,[13] but with discordant results. These are considered next.

Quantitative associations have been reported[14] between the degree of arterial hypertension and the severity of hypertensive vascular disease in small groups of rats with hormonal (desoxycorticosterone) hypertension, which were treated with hydralazine hydrochloride, or reserpine, or with both agents. Koletsky[15] controverted these associations in rats that had renal hypertension; he injected dibenamine, a relatively ineffective antihypertensive drug. More recently, a quantitative association of high arterial pressure and arterial lesions has been defined[16] from results in rats with hypertension due to partial renal infarction, some of which were treated with hydralazine hydrochloride. In those experiments we demonstrated the presence of a specific hypersusceptibility of the renal vascular bed to the development of nephrosclerosis, even when arterial pressures were not conspicuously or continually elevated.

Some investigators still are not convinced of the association between elevated pressure and lesions, or of the primacy of high pressure in causing lesions. They believe that other factors, as for example the presence[17] or absence[18] of intact renal tissue, partly or wholly determine the occurence of hypertensive vascular disease, particularly that which is acute, fulminant, and severely destructive. Perera[19] believes that he has demonstrated clinically a condition of "hypertensive disease without hypertension." The controversy spans more than 80 years, and has followed various trends—often accompanied by more conviction and acerbity than evidence.

The data that we now report, together with the previous experience of Corcoran, Dustan, and Page,[20] and with observations on the course of severe human hypertension as affected by long-term treatment with effective antihypertensive drugs[21] serve to convince us of an association between elevation of pressure and lesions, and of the primacy of high arterial pressure in causing lesions in various hypertensive states. This relationship does not preclude the participation of other factors, such as the apparent generalized sensitization to lesions produced by nephrectomy, whether or not there are subsequent vividialyses,[17, 22] administration of sodium-rich electrolyte solutions [23] or injections of renin.[24]

Effects of Increased Arterial Pressure

As noted above, results of direct experiments have not been concordant. Byrom and Dodson[11] reported that in rats, forced, manual, intracarotid injections of 2 ml. of saline solution, repeated from 10 to 15 times, caused, at the time of injection, widespread focal spasms of renal arteries, as evidenced by blanching of

the kidney. A few days later at necropsy they observed focal arterial necrosis, especially in the renal vascular bed. Arterial pressure, registered by a mercury manometer, increased as much as from 80 to 90 mm. of Hg during the injections. Using a mechanical device* we[12] confirmed these findings. They were briefly presented earlier, and are described here in detail.

The injection apparatus consisted of a 50-ml. syringe enclosed partly in an air-tight glass cylinder connected by a regulating valve with a container of compressed nitrogen. It was possible to regulate accurately the pressure in the air chamber and, therefore, the flow of Ringer's solution from the syringe. A three-way stopcock permitted easy filling or evacuation of the Ringer's solution through a No. 22 needle inserted into the carotid artery. The critical pressure was 2 kg. per square centimeter at a flow rate of 240 ml. per minute: with a higher rate, fatal hemorrhages occurred in the aorta. Since a mercury manometer was ill-adapted to the exact measuring of arterial pressure at the time of injection, we used a capacitance manometer that was cannulated to the femoral artery. Our mechanical device yielded equal, reproducible increases in pressure.

Immediately at the time of each injection there was a rapid rise in arterial pressure *(Fig. 1)*. Since the rise was not maintained throughout the injection, we

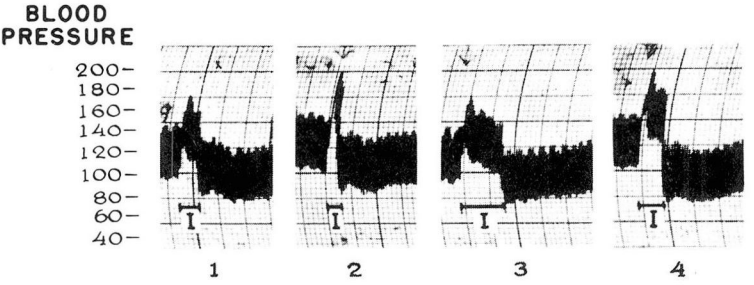
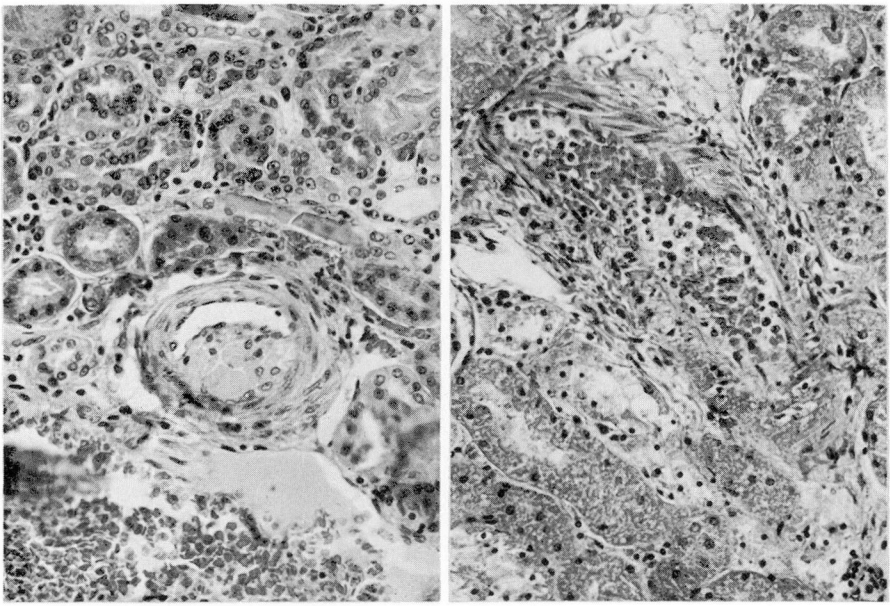


Fig. 1. Recorded graph of effects of intracarotid injections on femoral arterial pressure. Injections of 2.5 ml. of Ringer's solution under pressures of (1) 0.7 kg., and (2) 2 kg. per square centimeter. Injections of 5 ml. of Ringer's solution under pressures of (3) 0.7 kg., and (4) 2 kg. per square centimeter. Interval I represents duration of injection. *Published through the courtesy of the Revue Canadienne de Biologie.*[12]

believed it to be more important to increase the number rather than the volume of the injections. We injected doses of from 2.5 ml. to 5 ml. every two minutes up to a total volume of 80 ml. Rats were sacrificed from 8 hours to one week after each series of injections. Blood pressure of some as recorded by plethysmography of the tail was regularly increased up to 180 mm. of Hg from a base line of about 100 mm. of Hg during the succeeding five days, followed by an abrupt decline that was fatal.

**The mechanical device was constructed by Mr. Frederick Olmsted of the Division of Research.*

The lesions were restricted to the kidneys; they consisted of hemorrhages, excessive distention of arteries and arterioles, edema of the intima, which resulted in partial obliteration of the lumen, and focal fibrinoid necrosis of the muscularis *(Fig. 2, A and B)*. There was no evidence that these injections caused lesions of



A B

Fig. 2. Photomicrographs of sections of renal tissue after intracarotid forced injections. A, Arteriole, with evidence of distention and focal swelling of the endothelium, hemorrhage, and edema of interstitial tissues. Masson's trichrome stain; magnification x 200. B, Wall of an artery with evidence of hemorrhages and fibrinoid necrosis, also necrosis of the tubules. Masson's trichrome stain; magnification x 200. *Published through the courtesy of the Revue Canadienne de Biologie.*[12]

splanchnic arteritis, such as occur in rats with severe hypertension. These observations are essentially in accordance with those of Byrom and Dodson,[11] but differ from the more recent ones by Schaffenburg and Goldblatt,[13] who, like Byrom and Dodson injected fluid manually in amounts of 2 ml., repeated at intervals of one minute, up to a total volume of 30 ml. They reported maximum rises in arterial pressure to 194 mm. of Hg above the base, which are considerably higher than those that we observed. However, since their measurements were made with a mercury manometer connected to the aorta, the high values may reflect in part the momentum of the mercury column. Thus, although the conditions of their experiments are similar to those of Byrom and Dodson[11] allowing for differences in manually controlled injections, Schaffenburg and Goldblatt[13] did not detect any pathologic vascular changes.

Effects of Lowered Arterial Pressure

A clear demonstration of the relationship between pressure and vascular disease has been provided by our results with antihypertensive agents in rats with experimentally produced renal infarcts. Renal infarction was produced in one kidney by the method of Loomis,[25] and was associated with contralateral nephrectomy. Sham-operated, uninephrectomized rats served as control animals. Hydralazine hydrochloride* (hereinafter termed "hydralazine") was selected as a potent hypotensive agent. A series of preliminary experiments established that it would cause sustained hypotension when given in drinking water. That a maximally effective dose was thus given was confirmed by the absence of a further decrease in arterial pressure when, after seven days of oral treatment, a test dose of hydralazine was given by gavage.

Two series of experiments were performed. In Series I, we were concerned with the effects of hydralazine-induced control of hypertension on the acute lesions that developed during the first seven to 15 days after operation; and in Series II, on the effects over periods of one and two months, including the effects of one month of hydralazine treatment on lesions that had developed in the absence of treatment during the first month.

Series I. Effects of hydralazine on acute vascular lesions (Table 1). Particular attention was paid to changes in the extrarenal vascular bed, because of the possibility

Table 1.—*Effects of hydralazine during acute renal hypertension (Series I)*

Group	No. of rats	Treatment	Duration of experiment, days	Percentage with extrarenal vascular disease, %	Heart wt. as percentage of body wt., %
1	14	0	7	66	.34
2	22	+	7	18	.32 (.28—.38)
3	22	0	15	68	.30 (.25—.39)
4	21	+ †	15	57	.34 (.28—.40)
5	10	0 ‡	7	0	.26 (.23—.28)

† Hydralazine started on the seventh day.

‡ Sham-operated control.

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**Apresoline (hydralazine) hydrochloride was generously provided by Ciba Pharmaceutical Products Inc.*

of confusing renal lesions consequent to infarction with those attributable to hypertensive disease. In the absence of treatment, extrarenal vascular lesions, primarily splanchnic, were present in about two thirds of the animals. During continuous treatment with hydralazine from the time of operation, the arterial pressure was maintained within normal limits in most animals, and the incidence of extrarenal lesions decreased from 66 per cent to 18 per cent. No lesions were found in the uninephrectomized sham-operated control animals; however, in these experiments, as in those of Series II, the administration of hydralazine did not prevent the development of myocardial hypertrophy.

Series II. Effects of hydralazine on chronic vascular lesions. In these experiments, as in those of Series I, hydralazine administered orally prevented the otherwise expected rise of arterial pressure for periods as long as two months *(Fig. 3)*.

Fig. 3. Graph of changes in blood pressure in the six groups of animals listed in Table 2.

When, at the end of one month of treatment, the administration of hydralazine was discontinued, arterial pressures rose promptly to hypertensive levels, and lesions, which had been inhibited, developed in florid form by the end of the second month.

Animals continuously under treatment for either one or two months had a smaller number of lesions as compared with untreated hypertensive control animals *(Table 2)*. Gross splanchnic arteritis was present only in the untreated (one or

Table 2.—*Effects of hydralazine during chronic renal hypertension (Series II)*

Group	No. of rats	Treatment	Duration of experiment, mos.	Mortality	Percentage with extrarenal vascular disease, %	Heart wt. as percentage of body wt., %	Gross arteritis
1	10	0	1	4	100	.43 (.32—.64)	+
2	10	+	1	1	22	.32 (.33—.43)	0
3	10	0	2	2	85	.36 (.27—.49)	+
4	8	+	2	1	20	.37 (.33—.43)	0
5	10	+*	2	2†	70	.35 (.28—.46)	+
6	10	+‡	2	3†	90	.34 (.31- .41)	+

*Treatment was terminated on the thirtieth day and animals sacrificed one month later.

†Mortality occurred after operation (group 5), or before initiation (group 6) of treatment.

‡Treatment was initiated on the thirtieth day and animals were sacrificed one month later.

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two months) hypertensive control animals, and in animals that had been treated for one month and then left untreated during the second month *(Fig. 4, A and B)*. Healed lesions occurred in animals allowed to be hypertensive for the first month and treated during the second month *(Fig. 4, C)*.

Throughout, as in the short-term experiments (Series I), there was a strong association between blood pressure, as measured by plethysmography of the tail, and the presence, absence, state of regression, or activity of the extrarenal vascular lesions.

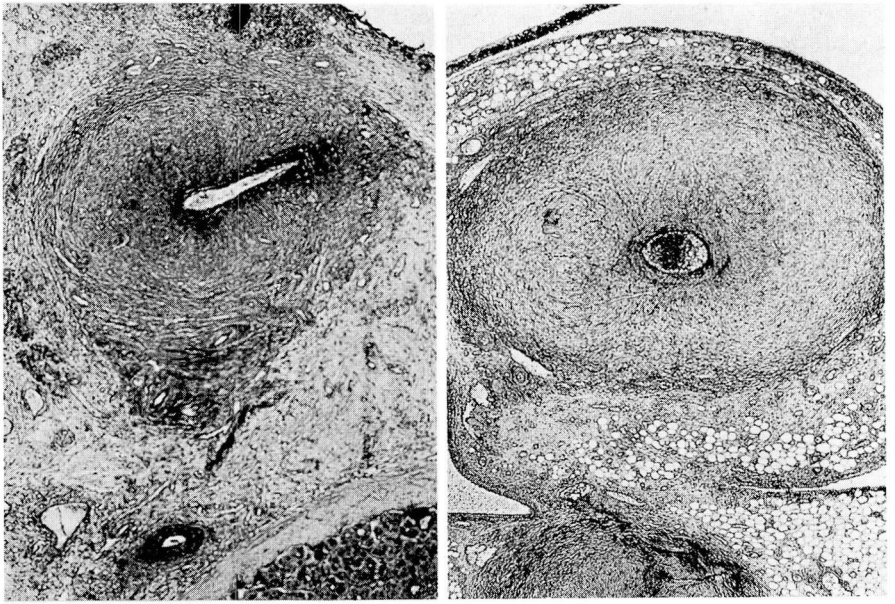
The sensitivity of the renal vascular bed was demonstrated by the presence of unexpected lesions consisting of progressive damage to large arterioles and small arteries in the kidneys of the animals maintained under continuous treatment, with blood pressures with the range of normal *(Fig. 4, D)*. Possibly some of these may have been transiently hypertensive at some time during treatment. The results of our direct injections suggest that only from 20 to 30 such episodes, each lasting less than a minute, might result in renal lesions. Such transient episodes could be easily missed in the course of biweekly determinations of arterial pressure by plethysmography. As in Series I, cardiac hypertrophy was not prevented by such treatment. In this respect the experience is similar to that of the clinical treatment of hypertension with hydralazine.[26] Possibly this may reflect the tendency of hydralazine to cause tachycardia. Some states of tachycardia, as for example hyperthyroidism, are associated with cardiac enlargement.

Neurogenic Hypertension

One disturbing inconsistency in the association between hypertension and arterial lesions is the fact that most workers have not seen such lesions in the course of neurogenic hypertension due to buffer nerve resection in dogs.[27-29] However, lesions have been described by Dammin, Goldman, Schroeder, and Pace,[30] in dogs that were made hypertensive by bilateral buffer nerve section and were then maintained for periods as long as three and one-half years. The lesions occurred primarily in the glomerular basement membranes. They do not seem to us to be characteristic of diffuse nephrosclerosis. Furthermore, it should be remembered that dogs with moderate degrees of renal hypertension may be maintained for periods as long as six years without the occurrence of recognizable renal vascular lesions in the kidney contralateral to that causing the hypertension.[17] Thus, it appears that dogs are more resistant to the nephrosclerotic effects of arterial hypertension than are rats. Therefore, induction of chronic, neurogenic hypertension in rats should represent a better approach to this problem. From our experience with other forms of hypertension in rats one might expect it to be associated with nephrosclerosis and with the splanchnic vascular disease characteristic of hypertension in this species.

Summary and Conclusions

The controversy as to the primacy of high arterial pressure in the pathogenesis of hypertensive arterial disease has continued for 80 years and has not been resolved by the past 25 years of study of various experimental types of hypertension. A body of evidence indicates that factors other than pressure participate in the pathogenesis of certain acute necrotizing lesions. However, recent clinical remissions in patients with severe hypertensive disease who were given antihypertensive drugs, indicate that high arterial pressure must be a primary factor in the causation of hypertensive vascular disease.

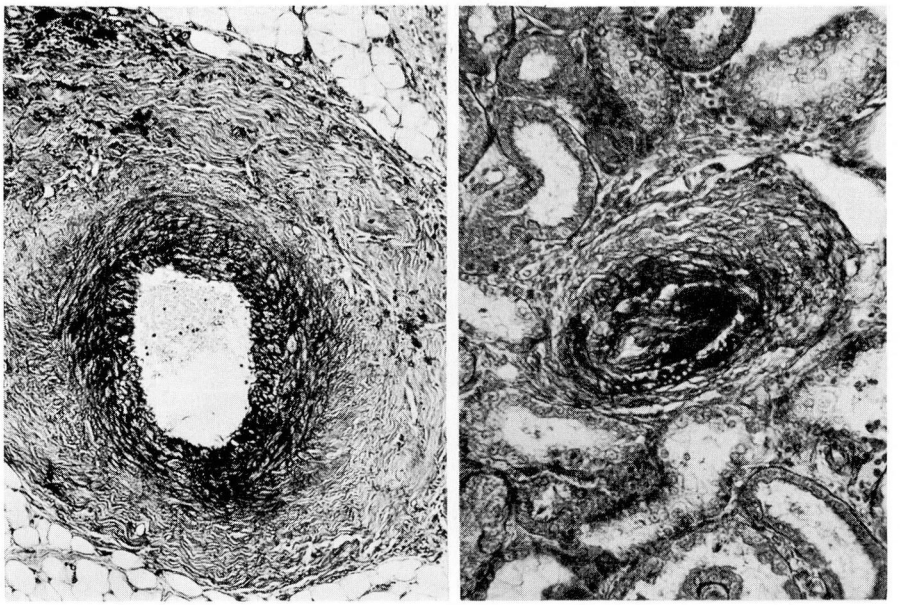


A B

Fig. 4. A, Photomicrograph of a section of an acute arteritic lesion in a rat with renal infarction maintained without treatment for one month. Periodic acid—Schiff stain; magnification x 45. *Published through the courtesy of The American Journal of Pathology.*[16] B, Photomicrograph of section of acute arteritic lesion similar to the one of A in a rat with renal infarction treated with hydralazine during the first month, then maintained without treatment during the second month. Periodic acid—Schiff stain; magnification x 40.

This clinical view has experimental support: (1) in rats, forced, brief rises of arterial pressure evoke acute fibrinoid necrosis of renal vessels; (2) rats with renal infarction, given hydralazine as an antihypertensive agent, demonstrate a close association between levels of pressure and the incidence, degree, state of healing, or activity of extrarenal, hypertensive, vascular lesions. Renal vascular lesions were found in treated, apparently normotensive animals, but these, in view of the lesions caused by forced rises of arterial pressure, may be attributed to repeated, brief, undetected "escapes" from the effect of hydralazine.

The absence of hypertensive vascular disease in dogs with neurogenic hypertension is noted; attention is drawn to the dog's resistance to chronic hypertensive vascular disease, and it is suggested that experiments in the rat may resolve this



C D

Fig. 4. C, Photomicrograph of a section of a healed lesion of arteritis from a rat with renal infarction, untreated during the first month then treated with hydralazine during the second month. It can be assumed that at the end of the first month this artery was similar to the one indicated in Fig. 4 A. The central dark core represents the limits of the original normal artery; it is surrounded by sclerosed tissue in which dark spots representing pigments of blood can be distinguished. Periodic acid—Schiff stain; magnification x 100. *Published through the courtesy of The American Journal of Pathology.*[16] D, Photomicrograph of a section of a small renal artery with evidence of progressive occlusion due to deposition of periodic acid—Schiff positive material. This section is from a rat with renal infarction, which was treated with hydralazine for two months. There were no extrarenal vascular lesions. Periodic acid—Schiff stain; magnification x 220. *Published through the courtesy of The American Journal of Pathology.*[16]

single inconsistency in the otherwise rather uniform causal association between high arterial pressure and hypertensive vascular disease.

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