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Pathogenesis of Arteriolar Necrosis of Malignant Hypertension.* (23497)

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Fibrinoid degeneration and necrosis of the walls of small arteries and arterioles, typical of the malignant phase of hypertension, have been observed in various tissues and organs of dogs with experimental renal hypertension which is accompanied by impairment of renal excretory function(1,2). The necrotizing arteriolar lesions occur in the rat also, when impairment of renal excretory function accompanies experimental renal hypertension(3). Various views concerning the pathogenesis of the necrotizing lesion, based mainly upon studies carried out on the rat, have been published, and these have been the subject of recent reviews(3,4). One concept of the pathogenesis of arteriolar necrosis which has won wide acceptance is that it is due solely to elevated blood pressure(5-9). Byrom and Dodson(7), have even asserted that sudden, intermittent increases of intra-arterial pressure, induced for only a short period, in normal rats, by a series of rapidly repeated, sudden, forcible, intracarotid injections of warm Ringer's solution, resulted in the production, in a few days, of what they interpreted as arterial and arteriolar necrosis, in the kidneys. It did not occur in kidneys the vascular bed of which had been protected from the sudden rise in intravascular pressure by occlusion of the main renal artery just prior to and during the injections. They expressed the view that, although the necrotizing arteriolar lesions are the result of elevated blood pressure alone, yet, once produced, they might lead to a vicious circle whereby the damaged kidney could perpetuate the existing hypertension. Although these results of Byrom and Dodson (7) have not been confirmed(4), nevertheless this concept has been invoked to explain the pathogenesis of malignant hypertension. It seemed of importance, therefore, to repeat their experiments and, in order to make the test more rigid, it was decided to attempt to produce even greater sudden increases of arterial pressure than were attained by them. The maximum rise reported by Byrom and

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Dodson† was 90 mm Hg.

Method. In this study, young, female, albino rats varying from 170 to 220 g were used. The rises of blood pressure in the lower abdominal aorta caused by a series of sudden injections of Ringer's solution through needles of various gauges from #22 to #19 were first determined in a number of rats anesthetized with ether which were sacrificed immediately after completion of the injections. In these rats the left carotid artery was first cannulated with a blunt hypodermic needle and the abdominal aorta was cannulated just below the origin of the main renal arteries with a glass cannula measuring 0.8 mm in internal diameter at the tip. The cannula in the aorta was connected by plastic tubing with a mercury manometer (1.5 mm bore) and the animal was then heparinized. The intracarotid needle was connected by means of a three-way stopcock to a 2 cc insulin-type syringe and to a bottle of sterile Ringer's solution kept at 40° C. This arrangement permitted the filling of the syringe for rapidly repeated injections. The injections were made by hand, with as great force as possible, and the consequent rises of pressure in the lower abdominal aorta at the level of the origin of the renal arteries was observed by another person. It was found that the sudden, forcible injection of 2 cc of saline through needles of increasing gauge, gave increasing maximum elevations of blood pressure, but the maximum recorded with any needle smaller than a #19 gauge was 86 mm, whereas with a 19 gauge needle, the maximum attained in any animal was always well above 100 mm Hg above the basal level. In 8 rats in which a 19 gauge needle was used and the rises in pressure were determined, the maximum rises varied from 138 to 194 mm Hg. In all the rats the rise in pressure was immediate and it began to drop even before the injection was completed. The injection of larger amounts of fluid (5 and 10 cc) caused smaller rises. It was decided, therefore, to use the 19 gauge needle and 2 cc of Ringer's for this experiment.

† Determined in only one rat. Personal communication.

Experiments. For the definitive experiment, which required the survival of the animals for four days, the procedure described above was followed, except that the aorta was not cannulated for the determination of the blood pressure, and the blood was not heparinized. Thirty female albino rats were used, and every animal received 15 intracarotid injections of 2 cc of sterile Ringer's solution, through a #19 gauge needle, with an interval of 1 minute between injections. Upon completion of the injections, the needle was withdrawn from the carotid artery, the vessel was ligated, and the incision in the neck was closed by means of interrupted stitches. The animals recovered quickly from the operation and were sacrificed with ether at the end of the fourth day after the injections.

Results. At autopsy, in the gross, there were no significant changes in any of the organs. Pieces of tissue from the heart, stomach, duodenum, pancreas, mesentery, kidneys and, in some instances, brain, liver and adrenals were fixed in 10% formalin in normal saline, sectioned and stained with hematoxylin and eosin, for microscopic examination. More sections of the kidneys were made than of any other organ or tissue, because this was the main organ studied by Byrom and Dodson. Microscopic examination of these sections showed that in none of the 30 rats was there a single instance of fibrinoid degeneration, necrosis or inflammation of large or small arteries or arterioles in any organ or tissue, and even periarteritis nodosa did not occur in any of these animals. The findings were essentially negative.

Discussion. The results of this experiment make no positive contribution to the elucidation of the pathogenesis of arteriolar necrosis. We believe, however, that they tend to negate one of the most widely accepted views of the pathogenesis of fibrinoid necrosis of arterioles, namely, the mechanical effect of elevated blood pressure alone. In experiments similar to the present one, Johnston and Marples(4) also failed to observe necrotizing arterial and arteriolar lesions, but their failure to obtain them can be attributed to inadequate rises of blood pressure produced because they used a

#21 gauge needle. Similarly, the vascular lesions observed in a few animals by Masson and collaborators(10) certainly cannot be attributed to great increases in intravascular pressure (their recorded maximum is about 60 mm Hg), because they used a #22 gauge needle. By the use of a 19 gauge needle, however, although we succeeded in producing great rises of pressure, yet we failed to find any degenerated or necrotic arterioles in any of our 30 rats. Fortunately, also, in not a single rat did periarteritis nodosa occur to complicate the result and confuse the issue. Byrom and Dodson(7) claimed to have observed what they called renal arteriolar necrosis in 10 out of 23 rats. Their illustrations, however, suggest that they were dealing with periarteritis nodosa, and even these vascular lesions were few in number. The illustrations of Masson *et al.*(10) are also of periarteritis nodosa. The question of the identity of periarteritis nodosa and the necrotizing vascular lesion of malignant hypertension has been a source of confusion and this will not be discussed further here because we failed to observe any such lesions in our rats. If it should be established eventually that the two conditions are identical, then the significance of the necrotizing vascular lesion, at least insofar as hypertension in the rat is concerned, will greatly diminish, because in some strains of rat periarteritis nodosa occurs even in the absence of hypertension(3,11), or of impairment of renal excretory function. It is probable, however, that they are not identical, and it is therefore equally probable that the experimental conditions, as outlined by Byrom and Dodson, had nothing to do with the development of the vascular lesions which they observed in their rats.

Summary. Repeated intracarotid injections of warm, sterile, Ringer's solution, carried out under high pressure in control rats, caused transient rises of intra-aortic (lower abdominal) blood pressure, up to 194 mm Hg above the basal level. Thirty rats thus treated failed to show the development of arterial or arteriolar lesions of any kind, in the kidney or any other organ or tissue, when they were sacrificed at the end of 4 days after the completion of the injections. The results of this study fail to confirm the finding of Byrom and Dodson of necrotizing arterial and arteriolar lesions in the kidney as a result of repeated sudden increases of systemic intra-arterial tension, and do not lend support to their contention that elevated blood pressure alone is a sufficient condition for the production of the arteriolar lesions characteristic of malignant hypertension.

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