Editorial

Renovascular Hypertension due to Renal Ischemia

The history of medicine is replete with examples of the experimental reproduction in animals of recognized human diseases the etiology and pathogenesis of which were not known. Such investigations usually were undertaken to put to the test an idea about the probable cause of a disease and, when successful, often led to the elucidation of its mode of development. Beriberi, scurvy, rickets, pellagra, and other diseases, now known to be due to the deficiency of a specific vitamin, are some of the more recent examples. Rarely, however, has the experimental production of a pathologic condition in animals led to the recognition of the existence of a hitherto unknown clinical entity. This is what has happened, however, as a result of the production of experimental hypertension due to renal ischemia. The original purpose of this investigation was, as usual, the reproduction in animals of a condition resembling a recognized clinical entity—so-called essential hypertension. The working hypothesis of the experiment was that this type of human hypertension might be primarily of renal ischemic origin. The obliterative, intrarenal, vascular disease (arterial and arteriolar sclerosis) so commonly found at autopsy in association with this condition was considered an indication of probable interference with the flow of blood to the functioning components of the kidneys, and the experimental method was designed to reproduce the altered hemodynamic state of such kidneys. The unexpected production of hypertension as a result of the constriction of only one main renal artery, and the prompt reduction of the elevated blood pressure as a result of excision of the corresponding, ischemic kidney, led to the discovery of human cases of hypertension associated with disease of only one kidney, most commonly chronic atrophic pyelonephritis, with the obliterative vascular disease that usually accompanies this condition. Because constriction of the main artery of one or both kidneys was the method of producing renal ischemia in animals, this led also to the recognition of stenosal, constrictive, or obstructive lesions of the extrarenal portion of the main artery of one or both kidneys in patients with hypertension previously regarded as essential. The existence of these lesions has now been demonstrated by renal arteriography, by split function tests, by biopsy, and by other methods.

The successful production in animals of a type of hypertension resembling in practically every respect the benign as well as the malignant phase of essential hypertension in man has led to the view that the pathogenesis of the two may be identical. All the constituents of the humoral mechanism...
(renin, angiotensinogen, activating enzyme and angiotensin), considered responsible for the pathogenesis of experimental renal hypertension due to constriction of one or both main renal arteries, have now been demonstrated in human essential hypertension. This has resulted from a large series of studies, in animals and man, in which many investigators have participated.6

It has been shown that in hypertensive animals the blood pressure returns to normal as a result of the development of antirenin in the blood, produced by repeated subcutaneous or intramuscular injections of heterologous renin, the substance considered primarily responsible for the elevation of the blood pressure.7 In such animals the blood pressure stays down as long as the titer of the antirenin in the blood remains adequate. It still has to be shown, however, that in essential human hypertension associated with unilateral or bilateral, intrarenal or extrarenal, vascular disease the elevated blood pressure can also be reduced to normal by the same means. Antirenin produced by injections of heterologous renin, in man or animals, is active against other animal renins, but not against human renin. In a group of hypertensive human subjects, in whom a high titer of antirenin in the blood serum, active against hog and other animal renins, developed as a result of repeated intramuscular injections of heterologous (hog) renin, the blood serum proved inactive against human renin, and the blood pressure of these patients remained elevated.8

Unmodified homologous renin is not antigenic, and does not induce the development of antirenin, but the repeated intramuscular injection of acetylated, homologous renins has resulted in the development of antirenin in the dog, rabbit, and rat,9 and even in man. Drs. Haas, Vertes, Grauel, and I have accomplished the latter, with injections of acetylated human renin, in three patients with benign essential hypertension (unpublished). The maximum titer of the antirenin to human renin that developed in the blood serum of these patients was too low, however, to produce more than a slight, but statistically detectable, effect on their blood pressure. A high titer of antirenin and a fall of the blood pressure to normal in such patients would have provided additional evidence for the renal origin of essential hypertension. An investigation on a much larger scale is therefore now in progress, but it will take a long time, because the concentration of renin in human kidneys is very low and the supply of cadaver kidneys is limited.

The evidence for the renal ischemic origin of benign essential hypertension has been convincing in the cases associated with unilateral renal disease capable of producing ischemia because, as in animals with hypertension due to unilateral renal ischemia,5 this type of human hypertension can be cured in many patients, as a result of surgical removal of the diseased kidney,2,3,10,11 provided the other kidney is not ischemic. As in animals, in which the experimental renal hypertension can be cured by the release or removal of the clamp on the main renal artery, so also in humans, with hypertension associated with unilateral or bilateral, stenotic or obstructive lesions of one or both main renal arteries, the hypertension can be cured by surgical correction of the vascular lesions12-15 provided there is no intrarenal cause of ischemia in either kidney.4 Endarterectomy, for an obstructive arteriosclerotic plaque, or partial thrombosis; excision of a stenotic lesion, with anastomosis of the severed renal artery, or anastomosis of the artery with the aorta, at a new site, if the lesion is at, or close to, the origin of the renal artery; or excision of a considerable portion of the artery, with replacement by a portion of a vein, or by a prosthesis; or the creation of a bypass of the stenotic or obstructive lesion by means of a vein, or a prosthesis (most commonly a Dacron tube) are the most common surgical procedures that have been employed.10

If the elevated blood pressure were the primary event in essential hypertension, as some still believe, and the vascular disease were merely a consequence of the hypertension, the blood pressure should not fall
as a result of bilateral nephrectomy. Also, the transplantation of one normal kidney to replace the diseased ones would not be logical, because the transplanted normal organ should be subjected to the same conditions that presumably brought about the original bilateral renal disease. It has been found, however, in a small number of patients in the terminal stage of the malignant phase of essential hypertension, that bilateral nephrectomy does result in a fall of the blood pressure to normal, and that it remains down as a result of the successful transplantation of a normal kidney from a living person\textsuperscript{16–19} or even from a cadaver.\textsuperscript{20, 21} Unfortunately, permanently successful transplantation, even of a surgically removed kidney, from an unrelated or even closely related individual, except an identical twin,\textsuperscript{16–19} is still infrequent. In those bilaterally nephrectomized, hypertensive patients in whom the transplantation of a surgically removed or cadaveric kidney has proved successful, the blood pressure has fallen to normal and remained normal for several years.\textsuperscript{19–21} The problems of securing and transplanting cadaveric kidneys, under the most favorable conditions, soon after the death of the donor, and of insuring adequate function of the transplanted kidney are still unsolved. Progress is being made, however, and a few successful cases have been reported.\textsuperscript{22, 23}

Again, if the elevated blood pressure, in essential hypertension, comes first, and the arterial and arteriolar sclerosis, including that of the kidney, is a consequence of the hypertension, as some other investigators believe,\textsuperscript{25–27} one would expect such vascular lesions to develop in animals with benign experimental renal hypertension for many years. This has not occurred in animals with persistent hypertension for as long as 8 years.\textsuperscript{5} Only in those animals with hypertension and greatly impaired renal excretory function, usually for only a period of a few days, before death, does a vascular lesion occur, but this lesion is plasmatic arteriolosclerosis,\textsuperscript{28, 29} not arteriolar sclerosis, and resembles the so-called necrotizing arteriolar lesion of the malignant phase of essential hypertension in man. This should not be confused with the obliterative, hyaline, arteriolar sclerosis characteristic of the benign phase of essential hypertension, the origin of which is still unknown.

Despite all the convincingly suggestive evidence that has accumulated during the past 30 years in favor of the renal ischemic origin of essential hypertension, this view has not yet gained general acceptance, although there are those, like Stamey,\textsuperscript{2} who include it in the category of renovascular hypertension due to renal ischemia. Why correctable renovascular hypertension, associated with occlusive disease in the extrarenal portion of the main artery of one or both kidneys, is now generally regarded as of renal ischemic origin, while the hypertension associated with diffuse, intrarenal, obliterative, vascular disease is not, is neither clear nor logical. In recent years, however, because of the recognition of the clinical entity, correctable renovascular hypertension, the number of cases of hypertension classified as essential has been shrinking, and it is becoming increasingly difficult to reject the view that essential hypertension is primarily of renal ischemic origin.\textsuperscript{24}


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Hypothesis and Experiment

A research problem is not solved by apparatus, it is solved in a man's head. . . . The laboratory is the means by which it is possible to do the solving after the man has the idea clarified in mind.—CHARLES F. KETTERING.
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