Experimental Renal Hypertension

Mechanism of Production and Maintenance

By Harry Goldblatt, M.D.

The evidence is reviewed that the primary cause of essential hypertension in man is intrarenal obliterative vascular disease, from any cause, usually arterial and arteriolar sclerosis, or any other condition which brings about the same disturbance of intrarenal hemodynamics.

I feel highly honored to be the first speaker on this occasion, and I am particularly delighted that there is congregated here such a large and representative group of investigators who have been working actively in the field of hypertension for so many years. Since this is the introduction to this Conference, I shall start right out by reciting my credo, which is that so-called essential hypertension is of renal origin. Note that this statement does not include a commitment as to the mechanism whereby the kidneys effect the elevation of blood pressure. In fact, I wish to emphasize that the original experiment in the artificial production of renal hypertension was designed primarily to test only whether elevated blood pressure would result from a disturbance of intrarenal hemodynamics similar to that which probably exists in the diseased kidneys usually found at autopsy in patients with essential hypertension. Essential human hypertension, as it usually is defined, signifies elevated diastolic and systolic blood pressure of unknown origin and unassociated with obvious or significant disturbance of renal excretory function. This does not mean that there is no functional disturbance of any kind; it refers specifically to the usual tests for excretory function.

Like many of you, I suppose, I was taught that the kidney does not play a primary part in the causation of the elevated blood pressure of essential hypertension. In fact, I was taught that the elevated blood pressure comes first, for some unknown reason, and that all the changes found at autopsy in such individuals are the result of the hypertension. I now contend this to be untrue, and the investigations which I am about to outline were designed to show that it is not so. If, at the end of this conference, most of us leave with the conviction that the kidneys could be the site of origin of whatever it is that brings about the elevated blood pressure in essential hypertension, I for one shall be content.

I am going to show you first, almost kaledoscopically, the background, not necessarily chronological, upon which the original experiments were based. In table 1 are listed the most important renal abnormalities found at autopsy in human beings who, with few exceptions, are usually considered clinically to have had essential hypertension if there was no significant disturbance of renal excretory function accompanying the elevated blood pressure. The hypertension that is associated with glomerulonephritis, and occasionally with some of the other conditions listed, is not considered essential hypertension, and is usually admitted to be of renal origin, even though the mechanism of its production is unknown, because it is associated with a definite disturbance of renal excretory function. I was taught that the origin of essential hyper-

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Tension, about which so much contention still exists, was definitely not renal. This is still believed by many, despite the fact that it is now 25 years since we produced, experimentally, on a definitely renal basis, a type of hypertension which we believe reproduces in every detail all the features of so-called essential hypertension in humans. As a pathologist, I was impressed by the invariable finding of renal disease, usually vascular disease, with or without accompanying pyelonephritis, in the cases of essential hypertension in which death had occurred from cardiac failure, or from a cerebrovascular lesion or, in some cases, from renal insufficiency. These kidneys varied from small, shrunken, nodular kidneys to large kidneys with finely granular surfaces, but microscopically, all were the seat of arterial and arteriolar sclerosis, with a variable amount of cortical scarring. I was taught to believe that such kidneys were the end result of the hypertension, but I finally came to believe that the hypertension does not come first, that it happens only if and when the kidneys are diseased, and most frequently when they are the seat of vascular disease. However, while this is the most common type of renal lesion associated with hypertension without functional excretory disturbance, so far as I am concerned, any other pathologic process which can produce the intrarenal hemodynamic disturbance which probably results from obliterator vascular disease can be considered the cause of the hypertension. One of the strongest supports for the idea that the hypertension is the result of renal vascular disease is the result of a study by Moritz and Oldt, in which they showed very clearly that of all the organs of the body, the kidney is the least vulnerable to this process, that evidence of severe renal arteriolar sclerosis was never found at autopsy in individuals who had had normal blood pressure, and that moderate to severe renal arterial and arteriolar sclerosis occurred in practically 100 per cent of the cases in which hypertension had existed. In the spleen, however, severe arteriolar sclerosis was almost as frequent in the normal as in the hypertensive group. This shows that, although other organs are vulnerable to this type of vascular disease, even in individuals with normal blood pressure, the one organ which is not easily affected is the kidney. The fact that, despite this lack of vulnerability of the intrarenal vessels, autopsy studies in almost 100 per cent of the cases of essential hypertension in humans showed intrarenal arterial and arteriolar sclerosis of considerable degree led Moritz and Oldt to conclude that the vascular disease comes first and that hypertension does not occur until the kidneys become involved.

I am often accused of thinking that there is no such thing as hypertension that is not renal, but of course this is not true. I am certain that there is a "psychoneurogenic" type or an "endocrinogenic" type of hypertension that is not on a renal basis. Who would not admit the latter, after observing the return of the blood pressure to normal as soon as the tumor had been removed in a case of pheochromocytoma of an adrenal gland associated with hypertension? As I said, I even admit that there is such a thing as a "psychoneurogenic" factor in essential hypertension, but not that it is the exclusive cause. Many years ago, Dr. Saunders of Western Reserve University, who was involved in a geographic survey of the Virgin Islands, observed an extraordinary incidence of hypertension in the Negro population, which constitutes about 95 per cent of the total. To account for the greater incidence in the Negro population of the large cities in the United States, he had been taught to believe that the stress and strain of living, the competition with the white man, and the insecurity in which the Negro lives, account for

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**Table 1. — Renal Diseases Associated with Hypertension**

<table>
<thead>
<tr>
<th>No.</th>
<th>Disease</th>
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<tbody>
<tr>
<td>1</td>
<td>Arterial and arteriolar nephrosclerosis</td>
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<tr>
<td>2</td>
<td>Glomerulonephritis</td>
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<tr>
<td>3</td>
<td>Pyelonephritis</td>
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<tr>
<td>4</td>
<td>Hydronephrosis</td>
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<td>5</td>
<td>Polycystic disease</td>
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<tr>
<td>6</td>
<td>Glomerulosclerosis</td>
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<tr>
<td>7</td>
<td>Periarteritis nodosa</td>
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<tr>
<td>8</td>
<td>Lupus</td>
</tr>
<tr>
<td>9</td>
<td>Amyloidosis</td>
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this greater incidence. But Dr. Saunders had observed that the Negro people of the Virgin Islands are actually unusually secure. They are under no special emotional stresses or strains that account for this unusual incidence of hypertension. I told him that I would be very pleased to see sections of the kidneys of some of those patients with hypertension, and I did have that opportunity, later, in two cases. I was greatly relieved to find in the kidneys of both of these patients the most profound preglomerular arteriolosclerosis.

All this serves as a background for a rapid survey of the experiments in which we attempted to produce hypertension by doing something to the kidneys. In order to try to reproduce the disturbance of intrarenal hemodynamics which probably exists in the kidneys with intrarenal arterial and arteriolar sclerosis, we were obliged to retreat to the main renal artery and to constrict it by means of a special clamp which we devised because we knew of no way of reproducing the intrarenal arterial and arteriolar sclerosis which occurs in the kidneys of human hypertensive patients. The rest of the story you are so familiar with, I am sure, that it is hardly necessary to repeat much of it in detail. We showed that there was a definite immediate reduction of blood flow to the kidney, as a consequence of moderate to severe constriction of the main renal artery. I thought that constriction of only one main artery would not result in elevation of the blood pressure and that it would be necessary to do it to both. The blood pressure did rise, however, when only one renal artery was constricted, but in the dog it did not stay up for more than about 6 weeks, as a rule. In an occasional dog it did remain up longer, and in one it remained elevated for 9 months and came down only when the ischemic kidney was removed. Later, it was shown that in the rabbit, the rat, the goat, and the sheep, a persistent type of hypertension, lasting many months, may occur as the result of the constriction of only one main renal artery.

Other measures were used to cause the elevation to become permanent in the dog; one was to constrict both renal arteries, another was to clamp one main renal artery, and later, when the blood pressure was elevated, to remove the other kidney. That the elevated blood pressure resulting from a constriction of the renal arteries is true hypertension was shown by the demonstration that in the dog and the monkey, at least, both diastolic and systolic blood pressures were elevated. In some animals, when there was a tendency for the blood pressure to return to a lower level even when both renal arteries were constricted, we wrapped a fishskin condom around one or both kidneys to reduce the accessory circulation which had developed (not with the idea of producing a membrane to compress the kidney). As a matter of fact, the development of such a membrane did not occur when a fishskin condom was used. Dr. Page and his collaborators later, did wrap kidneys in silk or cellophane and in time observed the development of hypertension, presumably as the result of ischemia induced by compression of the renal parenchyma by the thick membrane of connective tissue which usually develops under the silk or cellophane. This is frequently referred to as the peri-nephritis type of hypertension.

There were two working hypotheses for the experiments which I have been describing: (1) that there would be elevation of blood pressure, and (2) that there would be no significant disturbance of renal excretory function, as a result of constriction of the main renal arteries. Had a definite reduction of renal excretory function occurred, and been proved necessary, the contribution would not have been great for it would have reproduced the hypertension of glomerulonephritis, or any other condition that impairs renal excretory function, and not true benign essential hypertension. Fortunately, the hypertension which usually did develop was not accompanied by a significant disturbance of renal excretory function, but it was soon found that a type of hypertension like that of the malignant phase of essential hypertension could be produced at will merely by great constriction of both main renal arteries. The typical necrotizing arteriolar lesion of ma-
E X P E R I M E N T A L  R E N A L  H Y P E R T E N S I O N

Lignant hypertension also developed in such animals, so that the resemblance to human malignant hypertension was complete. In the rat, the naked, necrotic arteriole characteristic of the malignant phase of hypertension is being confused with periarteritis nodosa, to which the rat is unusually susceptible and which develops even in the absence of hypertension or of impaired renal excretory function. This matter requires clarification. In the dog, periarteritis nodosa is a rare occurrence, but in the rat it occurs spontaneously or as a result of many experimental procedures. If the pathogenesis of the necrotizing arteriolar lesion and of periarteritis nodosa should prove identical, the significance of the necrotizing lesion as an indicator of malignant hypertension would vanish, at least insofar as the rat is concerned.

Finally, we come to the question of the pathogenesis of experimental renal hypertension. I am not going into detail about this phase of the investigation, but I should at least refer to it. The first question to be answered is: Is it the kidney, after all, that is responsible for the elevation of blood pressure when the renal arteries are constricted? Briefly, the release or removal of the clamp, when only one main renal artery was constricted, resulted in a prompt fall of the blood pressure to normal. Bilateral nephrectomy in an animal with previously normal blood pressure did not result in elevation of the blood pressure unless, as has been shown by Dr. Grollman and his associates, artificial means of prolonging the life of the animal were used. This treatment consisted of peritoneal or gastrointestinal lavage or the use of the artificial kidney which results in a disturbance of fluid and electrolyte balance. The indication is, therefore, that you have to have the kidneys in the body, or disturb the fluid and electrolyte balance in some way in order to bring about the hypertension.

The observation of a prompt fall of blood pressure to normal as a result of excision of the kidney in an animal which is hypertensive, because of constriction of the main artery of only one kidney, led to the recognition of the association of hypertension and unilateral renal disease in man, and to the deliberate performance of unilateral nephrectomy to cure the hypertension. This operation was first performed by Butler and associates, in 2 children, at the Children’s Hospital in Boston. The patients had unilateral pyelonephritis, with the usual associated vascular disease. The blood pressure promptly returned to normal after the nephrectomy. Recently Dr. Homer Smith published a compilation of all the cases reported in the literature up to December 1956, in which unilateral nephrectomy had been performed for the possible cure of hypertension. He found that about 25 per cent of the patients were cured; that is, the blood pressure remained normal for at least one year and up to about 18 years in 149 of 375 patients. In January 1957, Dr. J. E. Thompson reported the results of similar cases treated at the Mayo Clinic. In the group in which the kidney proved to be a shrunken, atrophic one, probably the seat of pyelonephritis and vascular disease, the cure rate was 50 per cent. In his cases, too, the blood pressure had remained normal for at least one year.

The one procedure which has interfered with the development of hypertension from constriction of the main renal arteries has been complete removal of both adrenals. Removal of the medulla alone did not interfere with the phenomenon. Renal denervation, splanchnic section, section of anterior nerve roots from the sixth dorsal to the second lumbar inclusive, total sympathectomy and even pithing of the cord all failed to interfere with the development of hypertension as a result of constriction of the main renal artery; therefore a nervous reflex from the ischemic kidney could not be the cause. The first indication that the elevation of the blood pressure might have a humoral basis came when we tied off the renal veins of an animal which should have had an elevation of blood pressure from great constriction of both main renal arteries; azotemia developed, of course, and the animal died within a few days, but there was no elevation of the blood pressure during the survival. The recognition of a possible humoral mechanism involved in the
pathogenesis of hypertension led to the rediscovery of renin and the simultaneous discovery of a vasoconstrictor substance, called hypertensin by the South American group of which Dr. Braun-Menéndez was a member, and angiotensin, by Dr. Page and collaborators. It was found that this substance resulted from the action of renin upon a substrate in the blood which has been called hypertensinogen. This finally led to the view that there may be a humoral mechanism of renal origin in the pathogenesis of human essential hypertension and to the finding by Dr. Skeggs and Dr. Kahn of a significant increase in the amount of hypertensin in the blood of hypertensive humans, in both the benign and malignant phases, but especially in the latter. The fact that the blood pressure of a dog hypertensive for months or years on the basis of constriction of the main renal arteries can be returned to normal by repeated subcutaneous or intramuscular injections of renin resulting in the development of antirenin in the blood, should be convincing evidence that, even at this stage, the humoral mechanism is mainly responsible for the elevated blood pressure. Dr. Wakerlin and collaborators were the first to produce antirenin.

We have found that 2 units of antirenin per milliliter of blood appears to be the critical level. When this level is reached, the blood pressure definitely falls and continues to fall as long as the antirenin level remains at this height or higher. When renin injections are discontinued and the amount of antirenin in the blood decreases definitely below 2 units of antirenin per milliliter, the blood pressure rises again to the previous hypertensive level.

While these experiments indicate that the mechanism of experimental renal hypertension is mainly humoral (the renin-hypertensin mechanism), the work of Ogden and his collaborators with yohimbine, indicates that in the later stage of the benign phase another mechanism, probably neurogenic, may be involved. Dr. Erwin Haas and I have performed some unpublished experiments which fit in with their experiences with yohimbine. If pentolinium (Ansolsyens), 150 mg per Kg. of body weight per minute, is infused for
about 8 minutes into a normal, unanesthetized dog, there is either no change in the blood pressure, or a very slight rise, during or after the injection. If an elevated blood pressure is induced experimentally by the constant infusion of renin, and the same dose of Ansolysen is given while the infusion of renin continues, the blood pressure becomes even more elevated. The same dose of Ansolysen given to a dog with experimental renal hypertension during the first 4 weeks of the hypertension also results in a further increased blood pressure. At this time the animal reacts to an infusion of Ansolysen like a normotensive dog with renin infused into the blood, that is, the blood pressure rises still higher; but the same quantity of Ansolysen infused into dogs hypertensive for more than a month invariably results in a fall of blood pressure. This is an enigma which requires an explanation. It may be explainable on the basis of some other, perhaps neurogenic, mechanism as Ogden has suggested. I have no answer at this moment.

Finally, the similarities between experimental renal and essential human hypertension are quite complete. Some of the most important observations on human essential and experimental renal hypertension are shown in table 2. The identity between the 2 columns is obvious; therefore I still believe in the primary renal origin of human essential hypertension. I also subscribe wholeheartedly to the theory of an involved pressor mechanism playing an important, if not exclusive, part in the initiation and early stage of experimental renal hypertension. It may also play a part in chronic experimental renal hypertension. I do not know how far one can go at present in applying these mechanisms to explain the pathogenesis of human essential hypertension, however, I reiterate my credo that human essential hypertension is primarily of renal origin, no matter what the nature of the mechanism of the elevation of the blood pressure may prove to be. Problem number one, however, is still the pathogenesis of the renal vascular disease, the most common pathologic change found in the kidneys of patients with essential hypertension. This remains to be elucidated in the future.

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