PRODUCTION OF HYPERTENSION BY CONSTRICTING THE ARTERY OF A SINGLE TRANSPLANTED KIDNEY*

AN EXPERIMENTAL INVESTIGATION

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THE experimental work on hypertension which has been done during the past year in the surgical laboratory of the New York Hospital and Cornell Medical College has been undertaken to determine, if possible, what, if any, relationship exists between experimental hypertension and the glands of internal secretion, the nervous system, and the kidney. While none of these various phases of the work are in any sense completed, certain experiments of some interest have been carried forward sufficiently, perhaps, to warrant reporting. One of these concerns the production of hypertension in the dog by constricting the artery of a single transplanted kidney. It was thought that a nearer approach to the relation of the kidney to hypertension might be obtained if the kidney were removed from its normal position and completely isolated from its nerve supply.

METHOD.—A carotid loop (van Leersum) is made and the animal's normal blood pressure established by daily observations over a period of approximately one month. The left kidney is then removed from its normal position and transplanted intraperitoneally to the region of the groin, the renal artery and vein being anastomosed by circular suture to the femoral artery and vein. Following this procedure, a series of daily blood pressure observations are made over a period of approximately three weeks, to determine the effect of the operation upon the blood pressure. The opposite kidney is then removed and again blood pressure observations are made for approximately ten days. At the expiration of this period the femoral artery which has been anastomosed with the renal artery of the transplanted kidney is constricted by means of a Goldblatt clamp or other method. This procedure in eight animals has caused an elevation of blood pressure.

Operative Technic of Kidney Transplantation.—After dissecting free the femoral artery and vein in the groin, the peritoneal cavity is opened by an incision extending from Poupart's ligament to the costal margin. The kidney is freed and its vessels divided. By mobilizing the ureter throughout half its length, the kidney is easily brought down to the pelvis and its blood supply reestablished by end-to-end anastomosis of the renal and femoral vessels. The details of the procedure are arranged so as to reduce to a minimum the time during which the kidney is deprived of its circulation. The abdominal wound is closed over the transplanted kidney (Figs. 1 and 2).

Effects of Constricting the Artery of the Transplanted Kidney.—Dogs

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remain in good health with a single transplanted kidney, and several of our animals have been under observation three and four months without evidence of any abnormality. Following transplantation of the kidney, there appeared a transient elevation of blood pressure of 20 Mm. Hg. in two of the animals, which may be explained by the disproportion in size between the renal and femoral veins. The blood pressure in these two animals returned to normal before they were used for further experimentation. In one animal a transient

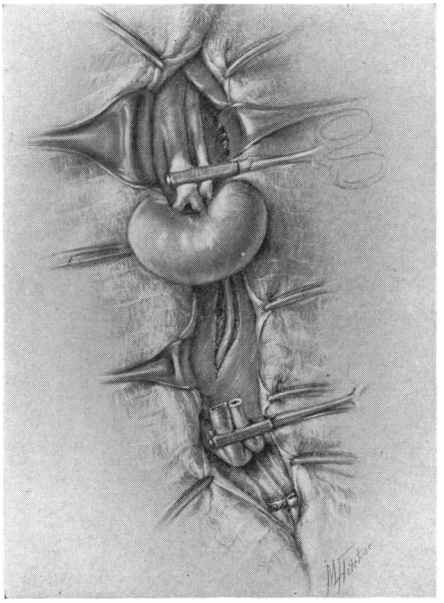


FIG. 1.—The kidney, its vessels, the ureter, and the femoral vessels dissected free preparatory to renal transplantation.

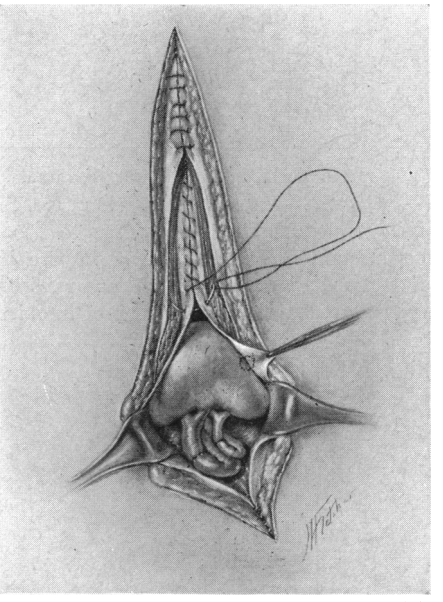


FIG. 2.—The kidney lying within the pelvis with its blood supply reestablished. Partial closure of the abdominal wound.

rise in the blood urea nitrogen followed the removal of the right kidney after the left had been transplanted. With the exception of these findings there were no changes found in the animals before the constriction of the artery of the transplanted kidney. Of the eight animals in which the artery of the transplanted kidney has been constricted, three survived and are living and five died. Brief protocols of these experiments and accompanying relevant charts are appended.

ABBREVIATED PROTOCOLS WITH RELEVANT CHARTS

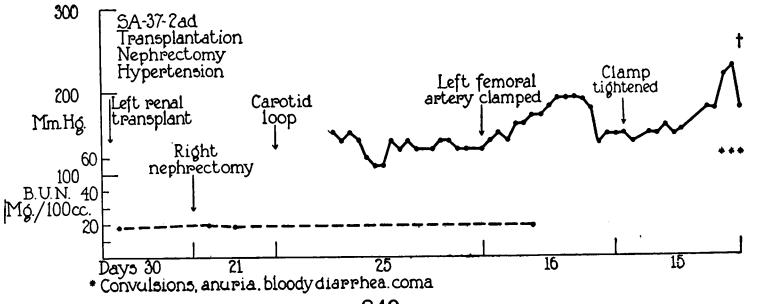
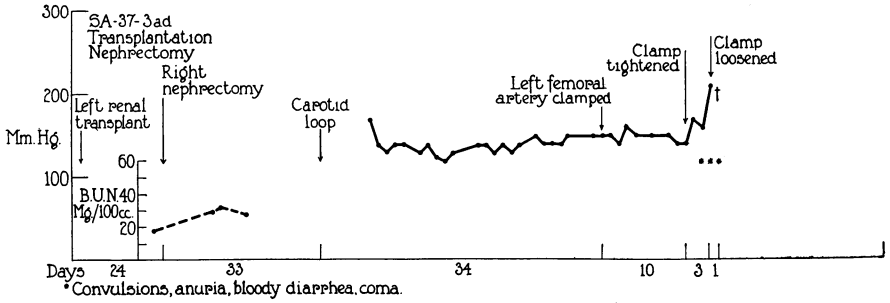
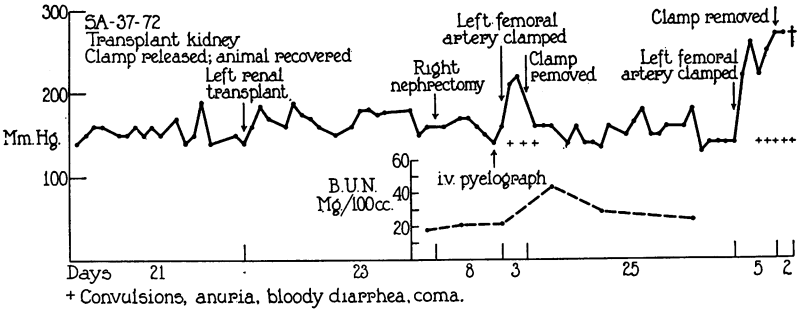


Chart 1.—Experiment I (Dog No. SA-37-2 ad): Constriction of the femoral artery; rise in blood pressure from 130 to 195 Mm. Hg.; return of blood pressure to normal; further constriction of the femoral artery with a slow rise in pressure (over a period of ten days) from 140 to 230 Mm. Hg. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*



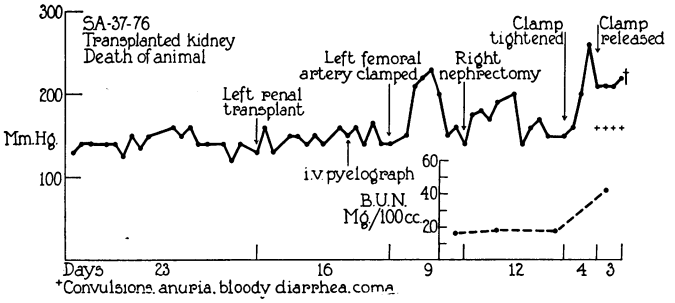
*Convulsions, anuria, bloody diarrhea, coma.

Chart 2.—Experiment II (Dog No. SA-37-3ad): Constriction of the femoral artery; rise in blood pressure from 130 to 160 Mm. Hg.; return to 140 Mm. Hg.; further constriction of the artery with a rise in blood pressure from 140 to 210 Mm. Hg. Symptoms of acute intoxication necessitated release of the constriction. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*



+ Convulsions, anuria, bloody diarrhea, coma.

Chart 3.—Experiment III (Dog. No. SA-37-72): Constriction of the femoral artery; rise in blood pressure from 150 to 220 Mm. Hg. Symptoms of acute intoxication; removal of clamp; complete recovery. Second constriction of the artery with rise in blood pressure from 140 to 270 Mm. Hg.; symptoms of acute intoxication; removal of the constriction. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*



+Convulsions, anuria, bloody diarrhea, coma.

Chart 4.—Experiment IV (Dog. No. SA-37-76): Constriction of the femoral artery; rise in blood pressure from 140 to 230 Mm. Hg.; return of blood pressure

to normal. Further constriction of artery; rise in blood pressure from 140 to 260 Mm. Hg. Symptoms of acute intoxication; clamp loosened. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*

Chart 5.—Experiment V (Dog No. SA-37-73): Constriction of femoral artery; rise in blood pressure from 140 to 240 Mm. Hg.; blood pressure maintained at 240 Mm. Hg. for eight days, then sudden fall to 130 Mm. Hg. Roentgenologic examination showed that the clamp had slipped off of the artery. Further constriction of the femoral artery; rise in blood pressure from 130 to 230 Mm. Hg.; return to 160 Mm. Hg. Animal living and well four months after transplantation of the kidney.

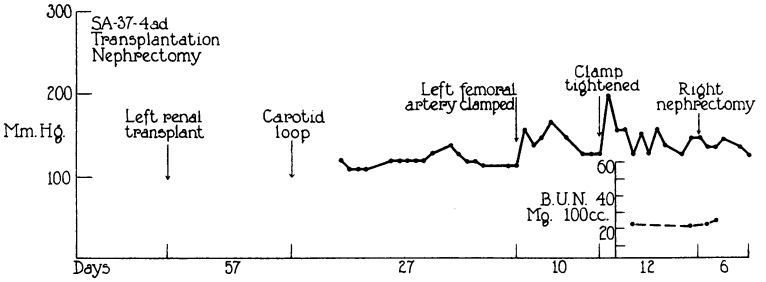


Chart 6.—Experiment VI (Dog No. SA-37-4 ad): Constriction of the femoral artery; rise in blood pressure from 120 to 170 Mm. Hg.; return of blood pressure to 130 Mm. Hg. Further constriction of the femoral artery; rise in blood pressure from 130 to 200 Mm. Hg.; return of blood pressure to 130 Mm. Hg. Animal living and well four months after transplantation of the kidney.

Chart 7.—Experiment VII (Dog No. SA-37-77): Constriction of the femoral artery; rise in blood pressure from 140 to 180 Mm. Hg.; return to 150 Mm. Hg. Further constriction of the femoral artery with rise in blood pressure from 150 to 200 Mm. Hg.; return of blood pressure to 160 Mm. Hg. Further constriction of the femoral artery with rise in blood pressure from 160 to 270 Mm. Hg. Animal blind due to bilateral detached retinae. Symptoms of acute intoxication. Animal died at operation while an attempt was being made to remove the constriction. Death with symptoms and autopsy findings of intoxication associated with acute hypertension.*

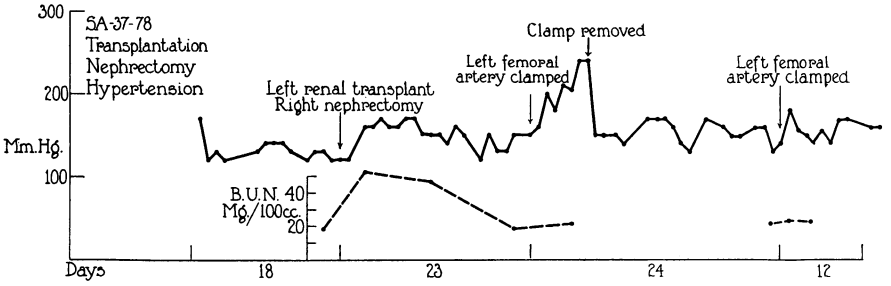


Chart 8.—Experiment VIII (Dog No. SA-37-78): Constriction of the femoral artery; rise in blood pressure from 130 to 260 Mm. Hg.; symptoms of acute intoxication necessitated the removal of the constriction; complete recovery. Further constriction of the femoral artery; rise in blood pressure from 140 to 180 Mm. Hg.; return to 150 Mm. Hg. Animal living and well three and one-half months after transplantation of the kidney.

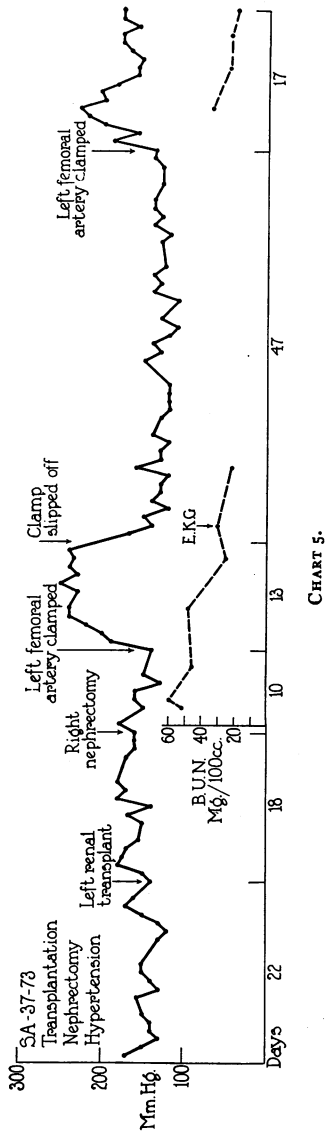


CHART 5.

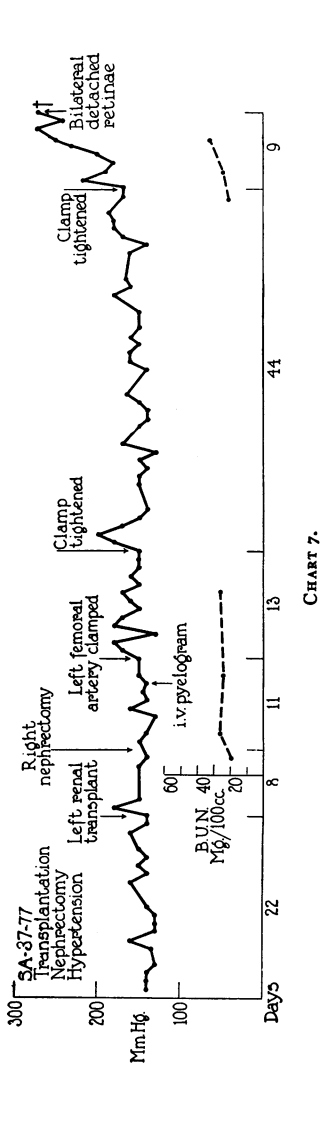


CHART 7.

* Since the initial presentation of this paper, microscopic studies of the kidneys of the animals that died following constriction of the femoral artery have been completed. The picture in each case has been one of diffuse necrosis.

No.	Normal	After transpl.	1st Constriction	2nd Constriction
1		130	130 → 195 → 140	140 → 230 → †
2		130	130 → 160 → 140	140 → 210+ → †
③	150	150	150 → 220+ → 140	140 → 270+ → †
4	130	140	140 → 230 → 140	140 → 260+ → †
⑤	140	140	140 → 240● → 130	130 → 230 → 160
6		120	120 → 170 → 130	130 → 200 → 130
7	140	150	140 → 180 → 150	150 → 200 → 160
8	130	130	130 → 260+ → 140	140 → 180 → 150

● Clamp slipped + Clamp removed

CHART 9.—Composite representation of blood pressure changes produced in the preceding eight experiments.

SUMMARY.—The protocols show that hypertension may be produced in dogs by the constriction of the artery of the transplanted kidney. It will be noted that thus far we have not produced a permanent hypertension as may so readily be done by constricting both renal arteries in the dog. It is well known that it is more difficult to produce a sustained hypertension in the dog after unilateral nephrectomy; it appears even more difficult to produce a sustained hypertension after unilateral nephrectomy and renal transplantation.

DISCUSSION.—The interest in this experiment lies chiefly, perhaps, in the observation that hypertension may be produced by constricting the artery of a kidney completely isolated from its nerves. The application of Goldblatt clamps to the renal artery may not interrupt nerve impulses to and from the kidney; indeed, gross dissections of the renal artery from one week to four months after the application of Goldblatt clamps suggest that the renal nerves are not interrupted. Further work, however, on this point is in progress. Page,[1] by careful dissection, removed the renal nerves from the artery and vein and found that the exclusion of the renal nerves did not affect the level of hypertension produced by renal ischemia. Collins,[2] about a year later, employing a technic for constricting the renal artery different from that of Goldblatt, also found that denervation of the kidney is without effect on the expected rise in blood pressure. Some doubt has been expressed as to the adequacy of this method. It is asserted that following renal denervation, regeneration of the nerves may take place in three months and that these regenerated nerves may play an important rôle in the permanency of the hypertension produced by this experimental method. By experiments upon the transplanted kidney, the possible rôle of the renal nerves in hypertension may more nearly be determined. These experiments indicate that they play no part in the initiation of this type of hypertension. They suggest, however, that, because of our failure to produce a permanent hypertension, they may play a rôle in maintaining the hypertension. But this is only a supposi-

tion; and whether our failure thus far to produce a permanent hypertension by the method described is due to complete absence of the renal nerves, to some unknown abnormality of the transplanted kidney or simply to our inability thus far to secure the proper degree of arterial constriction we shall, we hope, be able to determine in the near future.

REFERENCES

[1] Page, I. H.: Relationship of Extrinsic Nerves of the Kidney to Origin of Experimental Hypertension. Am. Jour. Physiol., **112**, 166, 1935.

[2] Collins, D. A.: Hypertension from Constriction of Arteries of Denervated Kidneys. Am. Jour. Physiol., **116**, 616, 1936.

DISCUSSIONS OF THE PAPERS BY DOCTORS PHEMISTER, GRIMSON, HEUER, GLENN AND CHILD

DR. ALFRED ADSON (Rochester, Minn.): The essayists have proved conclusively that constriction of one or both renal arteries results in increased blood pressures. By inference, one assumes that some pressor substance is not eliminated or is created during that period when the renal artery is constricted. Again by inference one has to assume that conditions may occur in the human being such as have been produced experimentally in dogs. We do know that glomerulonephritis invariably results in increased blood pressures but we still are unable to give the explanation. We also know that extensive sympathectomy fails to lower these pressures when it appears that they have resulted from renal destruction, all of which raises the question, "Is hypertension of nephritic origin the same as that of familial origin?" Thus it is obvious that physiologists as well as clinicians have innumerable problems to solve.

In our attempt to offer something towards relief of the symptoms resulting from hypertension, we have chosen patients that had a progressive disease, uncontrollable by medical measures, which appeared to be of familial origin and which was uncomplicated by other diseases. At first we were compelled to select patients for extensive sympathectomy by trial and error, but of late we have selected only those whose preoperative blood pressures could be lowered to normal readings by rest in bed, by administration of sodium amytal or by intravenous injection of pentothal sodium. We prefer not to operate upon patients who have had irreparable damage to the kidneys, heart or arterial system, since our results have shown that the advanced sclerotic, hypertensive patient will not receive any benefit from sympathectomy.

There are numerous borderline cases which one is justified in accepting for surgery but the results will not be as good as those obtained if the individual appears to present an uncomplicated vasospastic problem.

In attempting to carry out an extensive sympathectomy a number of procedures have been proposed. Our original attempt consisted of a rhizotomy which included division of the ventral roots on both sides, from the sixth thoracic to the second lumbar, thus interrupting all vasomotor impulses that might travel over the lower end of the sympathetic thoracolumbar outflow. We realized, of course, that laminectomy extensive enough to accomplish this wide sympathectomy was a formidable procedure and that sooner or later other technics effecting a similar sympathetic denervation would be introduced.

The technic that we are now employing at The Mayo Clinic, which has been used for more than two years, consists of bilateral resection of all three splanchnic nerves, a portion of the celiac ganglion and the first and second lumbar ganglions through a subdiaphragmatic, extraperitoneal approach. The

incision is very similar to a high kidney incision except that we attempt to follow anatomic lines and to resect a portion of the twelfth rib in order to secure additional exposure. The operation is divided into two stages, with an interval of about ten days between a right and a left operation.

The results of the operation depend on the degree of vasospasm present and on the extent of the disease. The younger patients, who respond favorably to preoperative studies, have obtained excellent clinical results as well as marked drops in systolic and diastolic pressures, which have remained low for intervals of more than two years. The borderline group of patients may obtain some material drop in blood pressure but do not obtain the same and continued drop that the younger patients receive who have less advanced disease. However, curiously enough, in these borderline cases there often results complete relief of symptoms, which consist of headache, cardiac consciousness, dyspnea and similar phenomena. In advanced cases, in which there are sclerotic changes, little or no result is obtained. Temporary or partial relief may be obtained but sooner or later symptoms and preoperative pressure readings return.

The postoperative sequelae of the extensive sympathectomy that we are employing at present are not contra-indications. There is an additional dryness of the skin below the first lumbar segment. There is a corresponding increase in cutaneous temperature. There is some increase in peristalsis which is of value to constipated patients and which is not troublesome enough to produce diarrhea. The extensive sympathectomy does not alter menstrual cycles or interfere with pregnancy nor does it alter potentia of the male or libido of either sex but there is a loss of ejaculatory power. Consequently, men are usually sterile following operation.

The experimental work of Phemister and Grimson does not coincide with the clinical results; patients who have undergone extensive sympathectomy, as we perform it, nearly always present marked postural influences. That is, the pressure may drop, when the patient stands, to such a degree that he may collapse. Usually this alteration of pressure adjusts itself but does not completely disappear. In a few instances we have been compelled to apply an abdominal support in order to control postural hypotension.

DR. EDWIN BEER (New York): Although the evidence is very clear that constriction of the renal circulation will produce the results that have been depicted today, it seems to me the next step in the experiment must be the determination of the pressor substance in the circulation. Within the last year, Doctor Prinzmetal, who was quoted by one of the readers today, has called attention to the fact that by animal experimentation on the denervated ear of the rabbit, he has been able to show in the circulating blood in hypertensive seizures in a case of pheochromocytoma the pressor substance, and he has been able to counteract that effect by the use of its antagonist ergotamine. It seems to me the most important thing to determine in these experiments is whether the pressor substance is circulating in the blood following constriction of the renal artery, and what the pressor substance is.

DR. ALFRED BLALOCK (Nashville, Tenn.) closing: An important step would seem to be to prove whether or not there is any relationship between the type of hypertension produced by causing renal ischemia and that which is encountered in any of the hypertensive states in man. That is probably going to be a very difficult undertaking.

I should like to say that we draw no conclusions concerning the treatment of hypertension in man from the experiments that have been reported.

DR. GEORGE J. HEUER (New York) closing: I agree with Doctor Blalock that it is desirable if possible to relate the hypertension produced in dogs by the Goldblatt method with the hypertension as it occurs in the human subject.

We, too, have been interested in this relationship. In experimental hypertension it has been shown by the experiments of Phemister and Grimson, and by destruction of the spinal cord as done by ourselves, that no method of procedure thus far directed at the sympathetic nerves will serve permanently to lower the blood pressure in hypertension produced by the Goldblatt method.

The human subject with hypertension appears to react to bilateral splanchnicectomy in much the same way as does the dog with experimental hypertension. In a small group of cases of hypertension in which we have performed bilateral splanchnicectomy and which have been observed over periods of more than a year, the blood pressure reduction as a result of the operation has returned to or now exceeds its previous level. Similar experiences are reported in the literature.

In a group of 25 cases of hypertension treated by rhizotomy, 15 have been followed for periods from one and one-half to three years. In these the results with respect to the blood pressure are as follows: In three out of six cases of mild hypertension, three out of six cases of severe hypertension, and one out of five cases of malignant hypertension, the blood pressure has been greatly reduced and shows no tendency to rise after one to three years. In three additional cases the blood pressure was reduced and showed no tendency to rise during the period of observation, but the patients died from nine to 16 months after operation.

In three cases of mild hypertension, one case of severe hypertension and one case of malignant hypertension, the blood pressure reduction resulting from the operation has shown a tendency to rise anywhere from three to 15 months after operation, and now after one and one-half to three years, has risen to its preoperative level in three cases, but is still considerably below its preoperative level in two cases. This experience, you will observe, is not exactly similar to that in experimental hypertension in animals. In one case of hypertension, I performed a bilateral renal denervation which did not affect the blood pressure. This observation is similar to observations made in dogs. In one case of rapidly advancing malignant hypertension, symptoms of complete transverse myelitis appeared before the anterior roots were divided. The blood pressure remained normal for one and one-half years. Recently, however, at the expiration of two years, his blood pressure is showing, I think, a tendency to rise.

This is the experience which I have had to date with hypertension in the human subject. While in some respects it resembles the experience in dogs, in other respects it does not. Such as it is, it suggests to me that there is a similarity between the hypertension produced in dogs by the Goldblatt method and essential hypertension as seen in the human subject.