THE PATHOGENESIS OF HYPERTENSION INDUCED BY RENAL CONSTRICTION*

By L. J. RATHER, M.D.

(From the Department of Pathology, Stanford University, School of Medicine, San Francisco)

(Received for publication, April 17, 1950)

In the course of experiments designed to prevent the development of collateral circulation to the renal cortex, Page (1) found that the bilateral envelopment of the kidneys of dogs, cats, or rabbits in cellophane led, after several weeks, to the development of persistent hypertension. In the same year Greenwood, Nassim, and Taylor (2) independently found that unilateral nephrectomy in dogs, combined with envelopment of the contralateral kidney in gauze-collodion, induced hypertension. The latter investigators were attempting to induce hypertension by preventing hypertrophy of the remaining kidney after unilateral nephrectomy, and they used the operative procedure of Soskin and Saphir (3) which was designed for this purpose. Page (4) showed that the hypertensive state initiated by renal constriction resembled that of the Goldblatt clamp type, in that its development and maintenance required an intact suprarenal, or substitutive cortical therapy, and was also independent of the nerve supply of the kidney. Several years later Grollman (5) found that hypertension developed when, instead of a gauze-collodion envelope, a silk thread was looped about the renal poles to form a figure-of-eight tie. The early work of Alwens (6) has been mentioned as first in this line of investigation but it was actually of a different character. Alwens compressed the kidneys of cats in an oncometer and found a slight rise in carotid artery pressure, which coincided exactly with the duration of the compression. He considered this rise to be of a mechanical nature and remarked that the rapidity in change of the pressure was not compatible with the renin mechanism of hypertension. Furthermore, he was able to produce a similar, though slighter, effect by compressing the intestine and spleen.

Those who believe that hypertension of renal origin is due to the production of a vasoconstrictor substance by the kidney consider the hypertension induced by renal constriction as a special instance of the action of this mechanism. There is some disagreement as to whether the pressor substance is released as a consequence of ischemia or of a reduction in pulse pressure in the affected kidney (7). In complete disagreement with the whole renal pressor substance hypothesis, however, is the expressed view of Grollman that, the absence of renal tissue rather than the presence of an abnormal kidney is responsible for the development of hypertension (8). Halpert and Grollman in reporting studies on structural changes in the kidneys of rats with

* This investigation was supported by a grant from the American Foundation for High Blood Pressure.

experimental chronic hypertension induced by the figure-of-eight ligature stated that the hypertension was apparently caused by damage or elimination of the renal parenchyma which reduced the number of available functioning nephrons (9).

The experimental work of Chanutin and Ferris (10) is often cited as the pioneer demonstration that the lack of a physiologically sufficing quantity of functioning renal tissue leads to the development of hypertension. It is not often noted that the operative procedure of these workers amounted to the production of renal infarction, since in their experiments the tightly ligated poles of the kidneys were usually allowed to remain *in situ*. In their first paper Chanutin and Ferris stated their belief that the hypertension which they produced was definitely dependent on renal insufficiency produced by partial nephrectomy. However, as Loomis (11) has shown hypertension develops in rats with infarcted kidneys, and partial infarction of one kidney is followed more promptly and regularly by hypertension than is total infarction of one kidney. The effect of renal infarction was undoubtedly a factor in the experimental results of Chanutin and Ferris. The question of the production of hypertension by subtotal nephrectomy is further complicated by the possibility of the development of renal lesions in the remaining stump, a possibility which has been inadequately studied. When three-quarters of the total kidney mass of young rats is operatively removed, there is rapid hypertrophy of the remainder leading to a doubling of its weight and protein content within 10 days (12). Yet hypertension and cardiac hypertrophy are absent during this period of greatest renal insufficiency (13). During a study of large numbers of three-quarters nephrectomized rats killed at varying periods after the operation Addis (14) found that cardiac hypertrophy was of minimal degree and present only after the lapse of several months. This was also the experience of Dock and Rytand (15). The immediate development of a greater degree of cardiac hypertrophy within a few days after the performance of one-stage unilateral nephrectomy and contralateral figure-of-eight renal constriction (16) is indicative of a dissimilar pathogenesis of the hypertension responsible for the cardiac hypertrophy then obtaining.

The experiments reported in the present paper were designed to clarify some aspects of the problem, in particular: (1) the time of onset of hypertension after the one-stage operation of unilateral nephrectomy and contralateral renal constriction by the Grollman technique; (2) the relation of the amount of functioning renal tissue to the development and degree of hypertension; (3) the effect of this type of constriction on renal growth, with and without contralateral nephrectomy.

Materials and Methods

Young male albino rats of the Stanford rat colony were used in these experiments in order to avoid the complication of the results by spontaneous renal disease, practically unknown in young rats of this particular colony, which was derived from the Slonaker strain about 25 years ago. The rats were kept six in a cage in a thermostatically controlled room and given a diet containing 16 per cent protein and 0.3 per cent salt. Litter mates from 70 to 90 days old, weighing about 150 gm., were chosen, and measurements of blood pressure made on five occasions prior to the time of operation. The ten rats of the unilaterally nephrectomized group

and the ten rats of the group subjected to unilateral nephrectomy and contralateral renal constriction (the latter group is referred to in the graphs as the "hypertensive group") were operated on in one-stage, within a 2 hour period. The ten rats subjected to three-quarters total nephrectomy and the twelve rats with constriction of one kidney, the other being left intact, were operated on at different times several weeks later.

Operative Procedures.—The operations were performed under ether anesthesia without aseptic technique. The right kidney of three groups was removed after ligation of the pedicle with silk. The left kidney was either, (*a*) exposed and briefly handled in rats of the unilaterally nephrectomized group, (*b*) constricted by a figure-of-eight ligature (No. 4 black silk) according to the technique of Grollman (5) in the "hypertensive group," or (*c*) subjected to removal of both poles, which were snipped off with scissors, removed, and weighed. In the rats of the fourth group the right kidney was exposed and handled, but left intact, while the left kidney was constricted in the usual way. Care was taken in the application of the figure-of-eight ligature to avoid too great constriction and subsequent extensive infarction,—which in no case occurred. Except for the procedure of three-quarters nephrectomy the operations involved the loss of little blood.

TABLE I

Mean and Standard Deviation of Range of Four Readings

	A	B	C	D
Preoperative	10.9 ± 7.5	9.3 ± 6.6	7.1 ± 4.3	8.2 ± 5.3
Postoperative	12.2 ± 10.3	13.3 ± 8.1	8.6 ± 6.8	8.2 ± 6.0

A, Unilateral nephrectomy and contralateral renal constriction.
B, Unilateral nephrectomy.
C, Three-quarters (of total) nephrectomy.
D, Unilateral renal constriction.

Operative and Postoperative Mortality.—None of the rats died during the operations. One of the "hypertensive group" died on the 2nd postoperative day and two failed to develop hypertension, as judged by measurements of blood pressure and terminal heart weight. These two are not included in the charts and graphs. One of the unilaterally nephrectomized group died under ether on the 9th postoperative day during a measurement of blood pressure. Two of the three-quarters nephrectomized rats died on the 2nd and 28th postoperative days, respectively. The cause was not ascertained.

Blood Pressure Measurements.—These were made with the microphonic manometer of Friedman and Freed (17) using the following procedure: The rat was placed in an ether bottle until relaxation occurred, then removed and the tail microphone and cuff adjusted. Four readings were taken in quick succession, two with a beaker containing ether-soaked cotton over the rat's nose, and two after removal of the beaker. The four readings thus obtained were usually quite closely grouped, though in some cases there was a wide range. The mean and standard deviation of the ranges for all groups is shown in Table I. This procedure was adopted for the sake of uniformity since the depth of the anesthesia could not be conveniently controlled. The average time required to process a rat in this fashion was about 4 minutes. The unilaterally nephrectomized group of rats and the group subjected to contralateral renal constriction in addition, underwent measurement of blood pressure on twenty occasions, always within the same 2 hour period, during the 50 days following the operations.

Final Disposition.—Fifty days after the time of operation all the rats were killed by ex-

sanguination from the aorta under ether anesthesia. The hearts were removed and weighed to the nearest milligram on a torsion balance, after opening the chambers and blotting with filter paper. The kidneys were removed, capsular tissue and thread, if present, were carefully dissected off, and the renal tissue then blotted after sagittal section. The renal tissue was then weighed to the nearest milligram on a torsion balance. Representative sections were taken from various organs and fixed in Bouin's fluid. Individual determinations of creatinine were made with the Coleman spectrophotometer, according to the technique of Bonsnes and Taussky (18). Hematocrit determinations were carried on on all rats at the time of the kill.

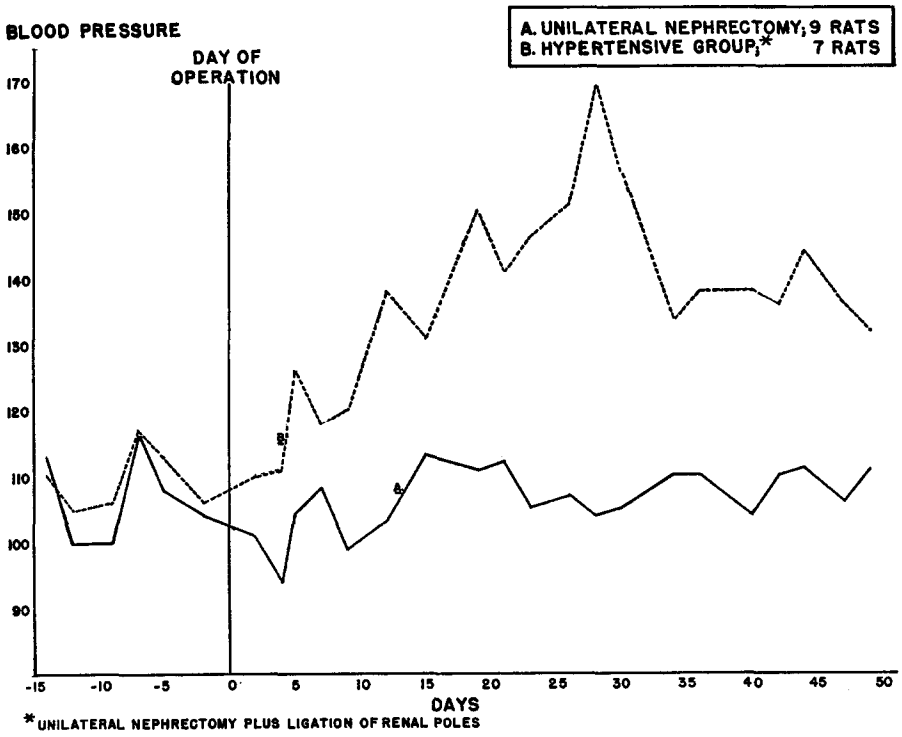

FIG. 1

RESULTS

(*a*) *Alterations in Systolic Blood Pressure.*—Fig. 1 shows the means of the preoperative and postoperative systolic pressures in the unilaterally nephrectomized group and the "hypertensive" group (unilateral nephrectomy plus contralateral renal constriction by the Grollman ligature). As previously stated the rats in these two groups were operated on in one-stage during a 2 hour period and all readings of blood pressures were made under similar conditions within a 2 hour period, in order to make the results as closely comparable as possible. Preoperatively the lines are remarkably close but immediately after

the day of operation the mean pressure of the hypertensive group rises sharply. The value of "P," calculated according to the method of Fisher (19) for the significance of the difference of the two means, is <0.02 >0.01 on the 2nd postoperative day. This is of borderline statistical significance; however, from the 4th postoperative day on the value of "P" is less than 0.01, which is significant. Prior to the operation the values of "P" did not drop below 0.3. The increase in blood pressure seems to be clearly established by the 4th day and is probably initiated within the first 2 days. This substantiates some previous

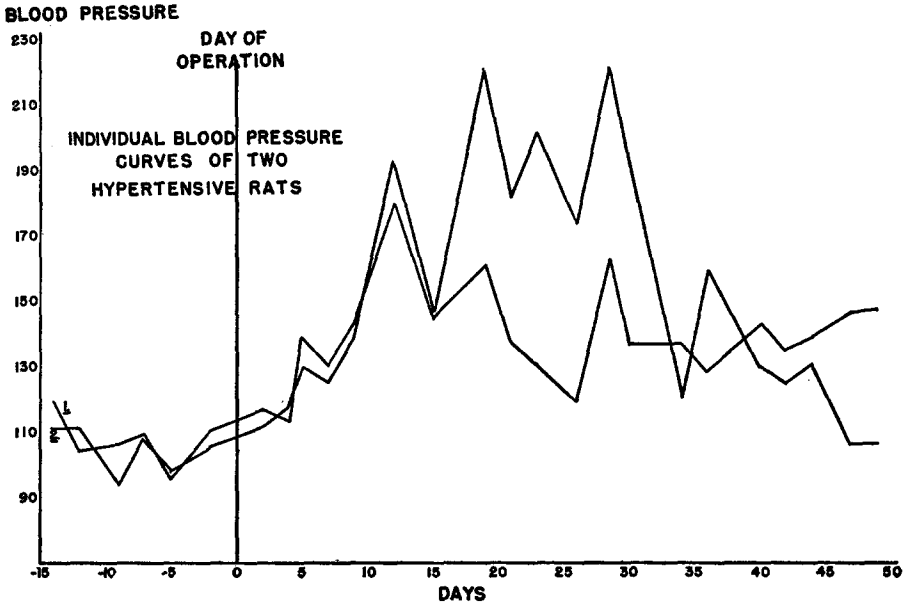

FIG. 2

work on the rate of development of cardiac hypertrophy after unilateral nephrectomy and contralateral renal constriction in which it was shown that a definite increase in heart weight was present in animals killed 5 days postoperatively (16). Such early development of cardiac hypertrophy and hypertension had not previously been demonstrated

Fig. 2 shows the wide swings of systolic pressure which were found in individuals of the hypertensive group. It was because of these that the investigation was put on a statistical basis. These wide variations of pressure seem to be a feature of developing hypertension in the rat. After the passage of several months of hypertension they are not so prominent.

Fig. 3 shows the means of the systolic pressures in the two groups subjected to unilateral renal constriction (the other kidney being exposed and handled

but left intact) and three-quarters nephrectomy (the mean of the amount actually removed was 73 ± 2 per cent), respectively. It is clear that whatever significance be attached to a slight upward trend in the last 25 days the curves are quite different from that of the hypertensive group. The measurements of blood pressure were taken at different times in the two groups, so that the curves are not as closely comparable as those shown in Fig. 1.

Since the use of a mean may conceal a significant spread of data, frequency distribution curves (Figs. 4–7) were constructed from all the readings of blood

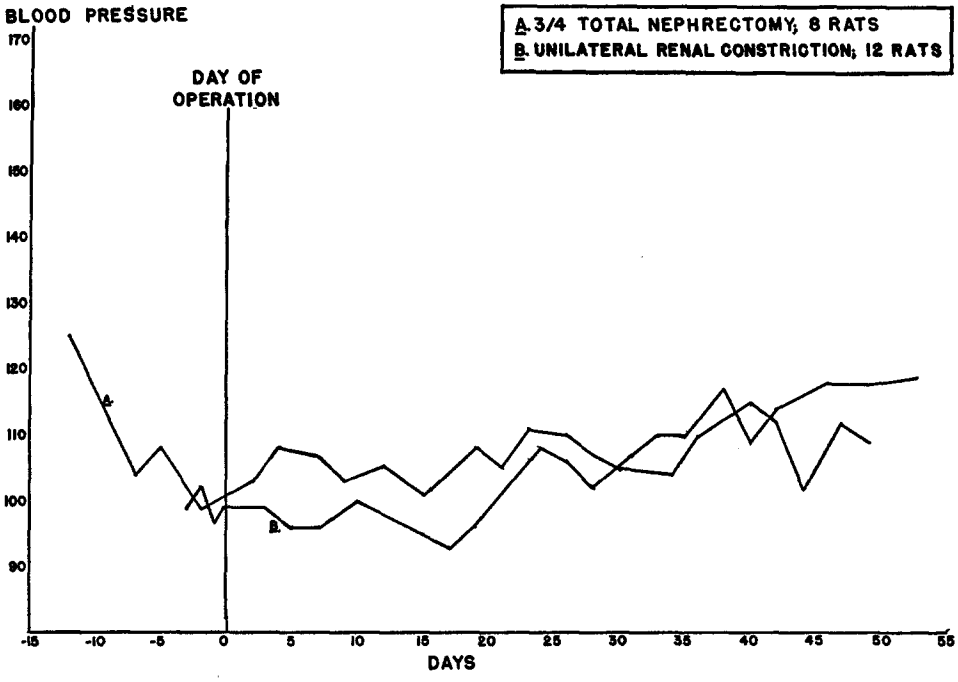

FIG. 3

pressure obtained. In the preparation of the curves the four readings taken on each rat at each occasion of measurement were charted separately. The curve for normal rats shown in Fig. 6 was constructed from measurements made on all the rats, plus a few others of the same age and body weight, prior to the operations. It will be noted that the frequency distribution curves for the unilaterally nephrectomized group, the unilaterally constricted group (the other kidney remaining intact), and the three-quarters nephrectomized group, all fall within the field of the normal curve. There is some evidence that the mode of the readings in the last two groups is shifted to the right, *i.e.* to higher readings, but this is of doubtful significance. The breakdown of the data into two

equal postoperative periods (Figs. 4 and 5) shows that the shift to higher readings, such as it is, occurs in the second period.

(*b*) *Correlation of Means of the Five Highest Postoperative Blood Pressures of Individual Rats with the Corresponding Kidney Weights, Heart Weights,*[1] *and*

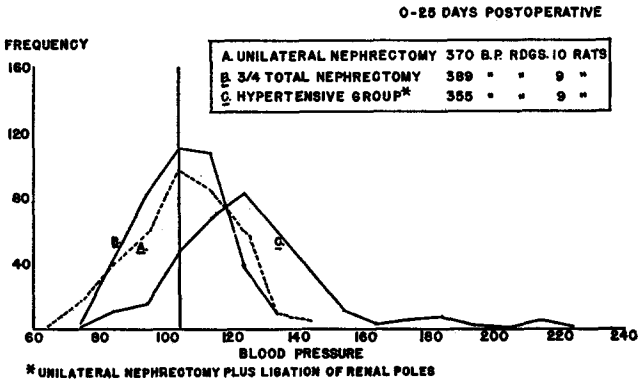

FIG. 4

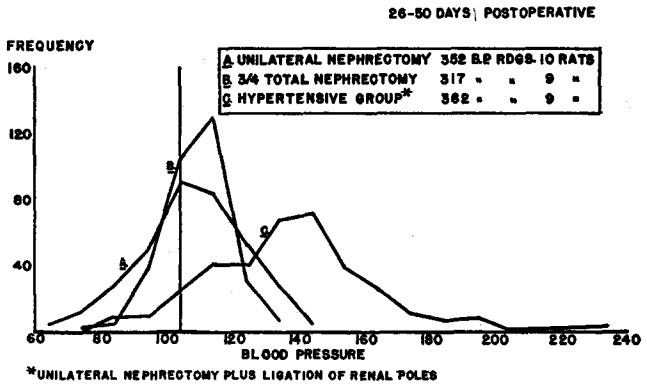

FIG. 5

Terminal Serum Creatinine Levels.—It has been shown that rats of the three groups subjected to unilateral nephrectomy, unilateral renal constriction, and

[1] The heart and kidney weights are expressed as percentages of a normal figure calculated from the body weight according to the equations of Gray and Addis (20, 21) based on the study of a large number of rats of the Stanford colony. The relationship of the organ weights to the body weights takes an exponential form, (organ weight) = (constant) $\times$ (body weight)^k where the exponent k is less than unity. The accuracy with which organ weights can be predicted from body weights in growing rats is shown in some previously reported data (16), in which the mean of the actual heart weight of ten rats killed 20 days after a sham operation was 98.8 per cent of the predicted value with a standard error of ± 1.4.

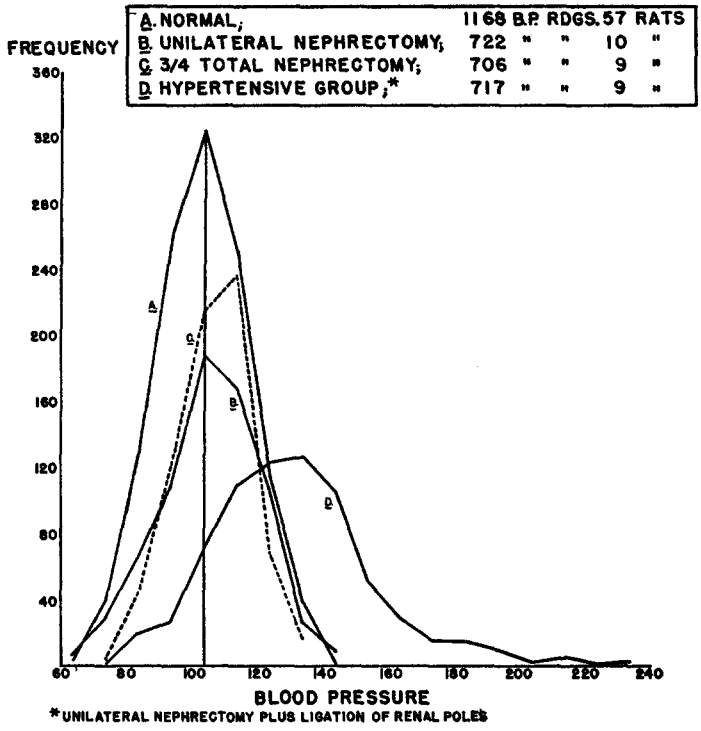
A. NORMAL; 1168 B.P. RDGS. 57 RATS
B. UNILATERAL NEPHRECTOMY; 722 " " 10 "
C. 3/4 TOTAL NEPHRECTOMY; 706 " " 9 "
D. HYPERTENSIVE GROUP;* 717 " " 9 "
FREQUENCY
360
320
280
240
200
160
120
80
40
A
C
B
D
60
80
100
120
140
160
180
200
220
240
BLOOD PRESSURE
*UNILATERAL NEPHRECTOMY PLUS LIGATION OF RENAL POLES

FIG. 6

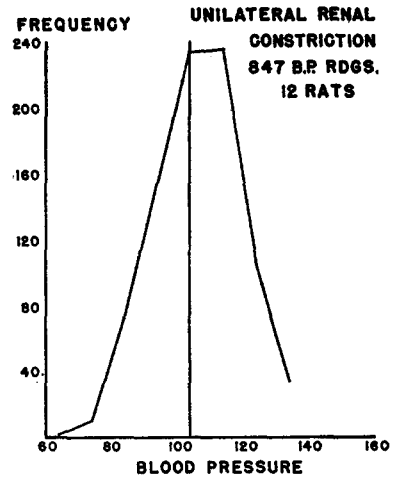
FREQUENCY
UNILATERAL RENAL CONSTRICTION
847 B.P. RDGS.
12 RATS
240
200
160
120
80
40
60
80
100
120
140
160
BLOOD PRESSURE

FIG. 7

three-quarters nephrectomy, respectively, did not develop hypertension, whereas unilateral nephrectomy combined with contralateral renal constriction led to its rapid development.

The next question to be considered is the problem of the relation of the amount of functioning renal tissue to the development and degree of hypertension. In Fig. 8 the means of the five highest postoperative readings of blood pressure on individual rats are plotted against the corresponding kidney weights in a scatter diagram. There is neither positive or negative correlation between

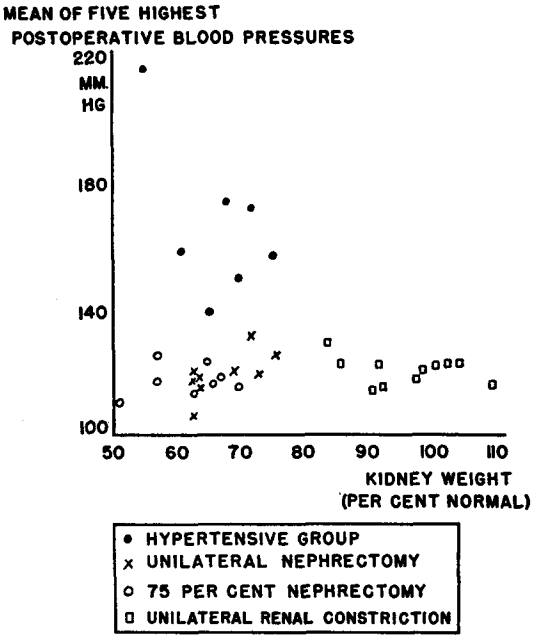

FIG. 8

these means and the corresponding amount of renal tissue as measured by the wet weight. An objection may be raised to the use of this weight as an index of the amount of functioning kidney present, on the ground that the amount of non-functioning tissue, due to atrophy in the neighborhood of the constricting thread or from other causes, is not specified. This is a valid objection, although the amount of such "dead weight" appeared to be small. This will be discussed later in connection with the histological findings. Another method of determining the amount of functioning renal tissue has been worked out by Addis (12), who has shown that the serum creatinine level in the rat is a quite accurate measure of kidney mass. In Fig. 9 the means of the five highest pressures are plotted against the terminal serum creatinine levels and it is again

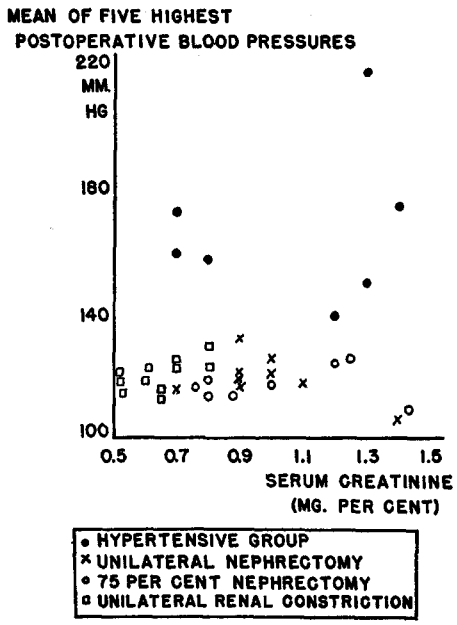
MEAN OF FIVE HIGHEST
POSTOPERATIVE BLOOD PRESSURES
220
MM.
HG
180
140
100
0.5
0.7
0.9
1.1
1.3
1.5
SERUM CREATININE
(MG. PER CENT)
• HYPERTENSIVE GROUP
× UNILATERAL NEPHRECTOMY
∘ 75 PER CENT NEPHRECTOMY
□ UNILATERAL RENAL CONSTRICTION

FIG. 9

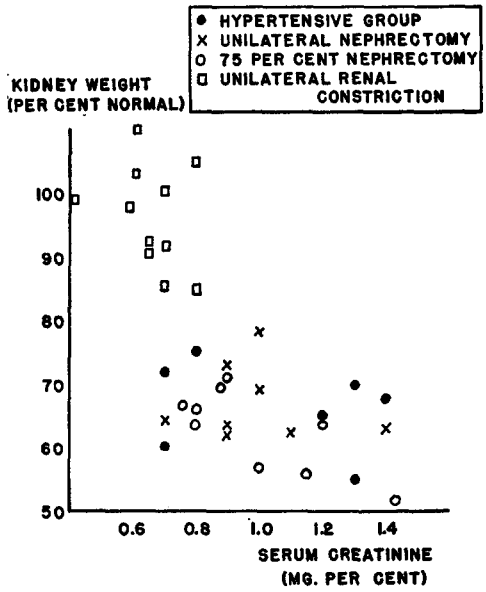
• HYPERTENSIVE GROUP
× UNILATERAL NEPHRECTOMY
∘ 75 PER CENT NEPHRECTOMY
□ UNILATERAL RENAL CONSTRICTION
KIDNEY WEIGHT
(PER CENT NORMAL)
100
90
80
70
60
50
0.6
0.8
1.0
1.2
1.4
SERUM CREATININE
(MG. PER CENT)

FIG. 10

apparent that there is no correlation between the blood pressure and this measurement of the amount of functioning renal tissue. In Fig. 10 the individual kidney weights of all groups are plotted against the corresponding serum creatinine values and a good negative correlation shown. In Fig. 11 the relationship of the degree of cardiac hypertrophy to the height of the blood pressure is clearly indicated. This positive correlation between heart weight and height of the postoperative pressure occurs whether the blood pressure mean used is based on five, ten, or all the postoperative measurements.

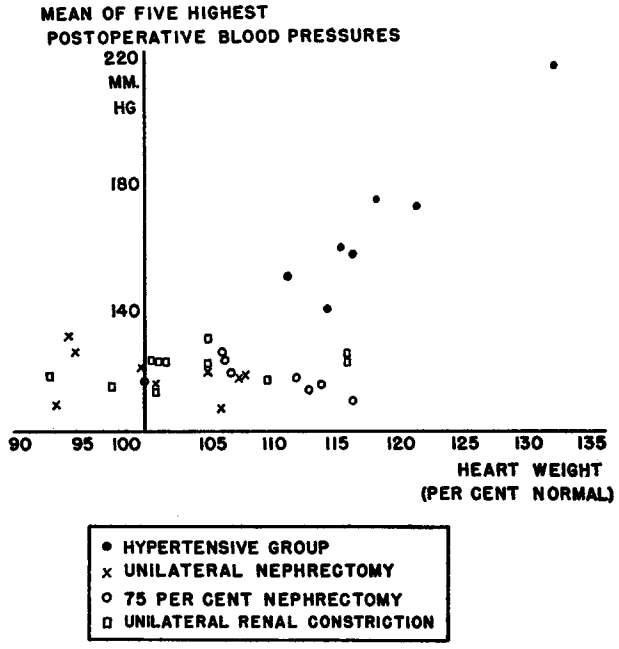

FIG. 11

(*c*) *Correlation of Heart Weight with Kidney Weight and Terminal Serum Creatinine Levels.*—Figs. 12 and 13 show these relationships. As would be expected from previous considerations there is no correlation between heart weight (a measure of the degree of hypertension) and serum creatinine or kidney weight (measures of functioning renal mass).

(*d*) *Effect of the Constricting Thread on Renal Enlargement with and without Contralateral Nephrectomy.*—In Tables II and III are summarized data which show,—when a comparison is made with the growth of the remaining kidney in the unilaterally nephrectomized group,—that the constricting thread did not interfere with enlargement of the kidney after contralateral nephrectomy was carried out. The meaning of the kidney weights is given confirmation by the

terminal serum creatinine levels. If the contralateral kidney is left in after renal constriction in growing rats, however, there is a preferential growth of the unconstricted kidney. The rats of the group subjected to unilateral constriction alone grew from a mean weight of 156 gm. to 251 gm. At the end of this period the mean weight of the constricted kidneys had increased only 17 ± 6 per cent over the estimated original weight, while the mean weight of the unconstricted

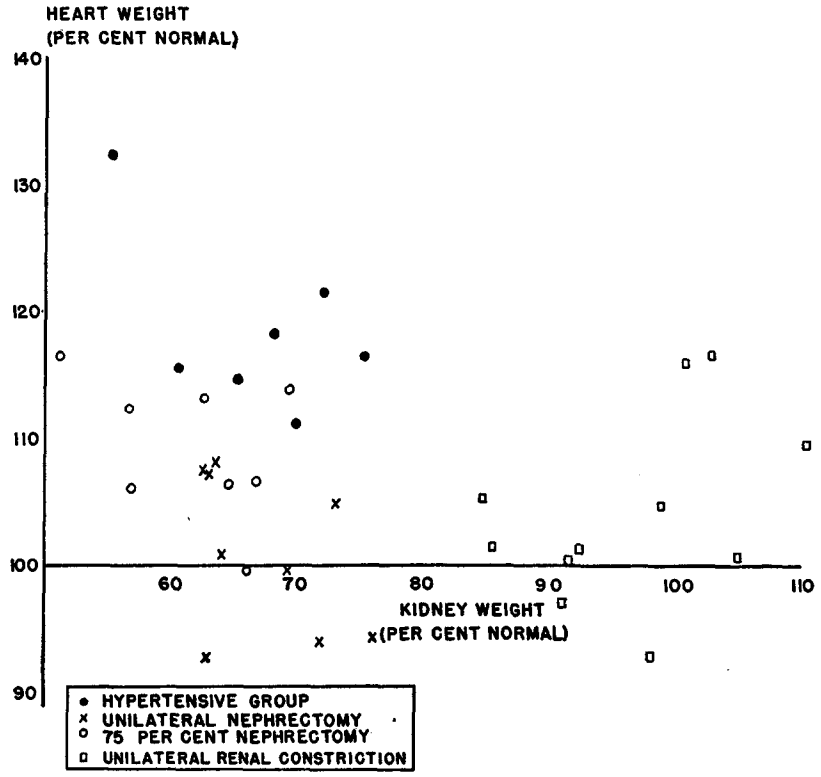

FIG. 12

kidneys had increased 50 ± 3 per cent. It is clear that interference with renal enlargement is not the factor which determines the development of hypertension.

(*e*) *Heart Weight in the Three-Quarters Nephrectomized Group.*—The mean heart weight of this group shows a significant increase (Table II, column C) which is not accompanied by an increase in blood pressure. The hematocrit level is distinctly low in this group and it seems quite probable that the cardiac enlargement is related to this finding, since mild to moderate hypertrophy of the heart is a frequent accompaniment of anemia.

(f) Structural Alterations in the Kidneys and Other Tissues.—

Gross: At autopsy the constricting figure-of-eight silk ligatures were easily removable, along with the irregularly thickened capsule which was slightly adherent to the cortex. A shallow groove in the cortex then marked the site of the renal ligature. In two animals a small infarct occupied a portion of a renal pole but in no case was there any extensive infarction. Suppurative perinephritis

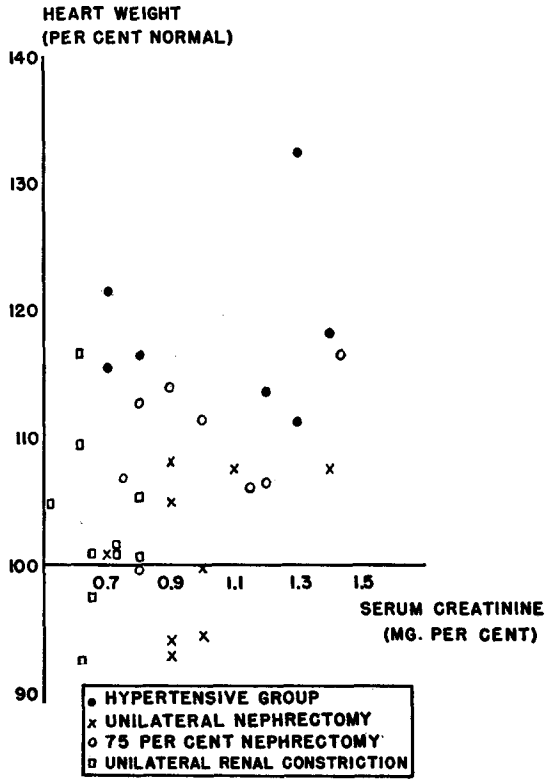

FIG. 13

or the formation of a thick fibrous hull was not observed. Externally and on section the kidneys were not otherwise remarkable. There was no significant difference, except in size, between the constricted kidneys of the group of rats subjected to contralateral nephrectomy and of the group in which the opposite kidney was left intact. The kidney tissue of the three-quarters nephrectomized animals was devoid of a true capsule, this having been removed previously when the poles were snipped off; but the stumps were covered by a thin layer of fibrous tissue.

Microscopic: In relation to the plane of excision of the renal poles in the three-

quarters nephrectomized group there were nephrons whose glomeruli were bloodless and whose tubular lumina were small and lined by flat or cuboidal cells lacking the abundant pink cytoplasm characteristic of the proximal con-

TABLE II

Mean	A	B	C	D	*P* (A − B)	*P* (C − B)	*P* (D − B)
Heart weight (per cent normal)	118.5	101.1	109.3	104.2	<0.01	<0.01	<0.4 >0.3
Kidney weight (per cent normal)	66.7	67.5	61.8	96.6	<0.7 >0.6	<0.1 >0.05	
Initial body weight, *gm.*	151	149	165	156			
Final body weight, *gm.*	238	253	226	251			
Gain in weight, *per cent*	58	70	36	61			
Creatinine, *mg. per cent*	1.05	0.98	1.00	0.66	<0.6 >0.5	<0.5 >0.4	
Hematocrit	53	54	36		<0.01		

A, Unilateral nephrectomy and contralateral renal constriction.
B, Unilateral nephrectomy and contralateral sham operation.
C, Three-quarters (of total) nephrectomy.
D, Unilateral renal constriction and contralateral sham operation.
P (A − B), "*P*" value indicating significance of difference of means A and B.
P (C − B), "*P*" value indicating significance of difference of means C and B.
P (D − B), "*P*" value indicating significance of difference of means D and B.

TABLE III

Mean and Standard Error of Weight Gain of Kidney Remnant

Mean	A	B	C	Dc	Du
Weight gain of kidney tissue remaining after operation, expressed as per cent gain above estimated original weight	86 ± 11	93 ± 6	188 ± 31	17 ± 6	50 ± 3

A, Unilateral nephrectomy and contralateral renal constriction.
B, Unilateral nephrectomy.
C, Three-quarters (of total) nephrectomy.
Dc, Unilateral renal constriction: constricted kidney.
Du, Unilateral renal constriction: unconstricted kidney.

voluted tubule. There were scattered areas of scanty lymphocytic infiltration in the same region. No lesions were seen elsewhere in the kidneys. In relation to the constricting thread there were similar groups of atrophied nephrons and foci of lymphocytic infiltration. The small infarcts noted in the gross were microscopically characteristic.

Vascular Changes: Neither fibrinoid arteritis of the periarteritis nodosa type nor arteriolonecrosis of the malignant hypertensive type occurred in the kidney or other tissues of any of the animals. The medial layer of some of the medium sized and small renal arteries of the hypertensive group appeared distinctly thickened, though most were in the range of the other groups. Measurements of the ratio of the wall diameter to the lumen diameter were carried out on 174 renal arteries and arterioles of the hypertensive group and on 69 of the unilaterally nephrectomized group, revealing a small but distinct difference. The frequency distribution curves of these ratios were of approximately normal distribution and overlapped widely, but the mean wall to lumen ratio of the hypertensive group was (24.3 ± 0.4) (10^{-2}) and for the unilaterally nephrectomized group (21.9 ± 0.6) (10^{-2}) giving a critical ratio of 3.3 for the difference of the means, which is highly significant. The change in size of the vessels appears more striking when one considers that the wall to lumen ratio dealt with is a unidimensional index of a three dimensional object. The fact that this medial hypertrophy occurred in the constricted kidneys of the hypertensive group suggests that these kidneys were not protected against the effect of hypertension by the ligature, as the kidneys distal to a Goldblatt clamp are said to be.

DISCUSSION

Page (1, 4) believed that the persistent arterial hypertension produced in his experiments was due to the development of a fibrous constrictive perinephritis which interfered in some way with the hemodynamics of the kidney and led to the production of a renal pressor substance. In the rat there is no development of perinephritis after the application of a silk figure-of-eight ligature and the early onset of the hypertension demonstrated here clearly antedates the development of the minimal degree of renal capsular thickening occurring. Goldblatt (22) states that the elevation of blood pressure considered due to perinephritis and the compression of the kidneys by a fibrous hull has not been shown to be due to renal compression *per se* and suggests that it may be due to scar tissue forming around and constricting the renal pedicle. In our experiments, however, such constriction of the pedicle was not observed and the fact that hydronephrosis did not occur is good evidence against its existence, since the ureter would surely be more easily compressed than the renal artery. Furthermore the onset of the hypertension took place too early to be accounted for in this manner and, as previously stated, the silk thread was applied in such a way as to avoid the pedicle completely.

Greenwood, Nassim, and Taylor (2) considered that the development of hypertension after unilateral nephrectomy and the envelopment of the remaining kidney in gauze-collodion wrappings was due to interference with compensatory renal hypertrophy. Their data did not show to what extent such interference was present or whether it was actually necessary for the development

of the hypertension. In the rat the figure-of-eight ligature does not interfere with the growth of the kidney after contralateral nephrectomy, as judged both by the weight increase of the tissue and the terminal serum creatinine levels. On the other hand, if the opposite kidney of young rats is left in after unilateral figure-of-eight ligature there is a very definite interference with the growth of the ligated kidney. The data supporting these conclusions are shown in Tables II and III.

According to Halpert and Grollman (9) and Grollman (8) the hypertension of rats after figure-of-eight ligation is due to a reduction in the number of functioning nephrons and the latter worker has extended this hypothesis to cover renal hypertension in general. The histological evidence of widespread destruction of renal tissue described by Halpert and Grollman was not seen in our studies; evidently they were dealing with the effect of long standing hypertension with or without the added factor of infection. It is certainly true that rats with hypertension of many months' duration may develop destructive renal lesions and uremia. We have observed typical arteriolonecrosis in such rats in association with serum creatinine levels round about 5 mg. per cent. It is equally true, as the data presented here show, that such lesions are not necessary for the development of hypertension. A reduction in the amount of renal tissue cannot be the determining factor in the development of the type of hypertension under discussion since, as judged by weight of renal tissue, terminal serum creatinine levels, and histological examination of the kidneys, the rats of the unilaterally nephrectomized group as well as those of the three-quarters nephrectomized group had amounts of functioning renal tissue equivalent to those of the unilaterally constricted, contralaterally nephrectomized group which alone developed hypertension. It is true that hypertension did not occur in those rats subjected to unilateral renal constriction alone, the other kidney being left intact. In general, after unilateral operative procedures and in the presence of unilateral renal disease hypertension does not develop, although there may be exceptions to this rule. There is evidence that it is due to inactivation of a pressor substance by the intact kidney (23). Only in this limited sense does the contention of Grollman seem valid.

That unilateral nephrectomy does not cause hypertension in healthy animals is supported by many observations in addition to our own. Grollman (24) at one time claimed that unilateral nephrectomy led to a slight, though statistically significant, rise in blood pressure. Later (8) he stated that though such elevation might be dependent on the presence of lesions in the remaining kidney, nevertheless his main contention still held, since the effect of the lesion would be simply to reduce the amount of functioning renal substance. This seems to be an erroneous assumption since the lesions might have positive effects, such as the liberation of pressor substances. In the experiments of Loomis (11) the effects of renal infarcts were shown to be more than simply negative

ones due to reduction in the amount of functioning renal tissue. Then, too, the findings in the rats subjected to three-quarters nephrectomy in our experiments did not fit in with this hypothesis, since hypertension did not develop within the 50 day postoperative period. It is agreed by all observers that hypertension following subtotal nephrectomy is a late development, rarely seen until 2 months after the operation. If it were a consequence of the elimination of renal substance it would be expected to develop during the time of greatest deficiency; *i.e.*, immediately after the operation. There is some reason to doubt whether hypertension would develop at all in the absence of disease in the remaining stump.

In conclusion, the data presented and analyzed here give no support to the hypothesis that renal constrictive hypertension in rats is due either to reduction in the amount of functioning renal tissue, to interference with compensatory renal hypertrophy after contralateral nephrectomy, or to constriction of the renal pedicle simulating a Goldblatt clamp. It does not require the development of fibrous perinephritis, although this may be a factor in other animals and with modifications of the operative technique. The experimental results are most compatible with the hypothesis that there is some disturbance of hemodynamics or perhaps of tissue tension with the liberation of a pressor substance by the affected kidney, although the data presented yield no information as to the nature of the disturbance or pressor substance.

SUMMARY

Blood pressures were determined on forty-two young male albino rats and a basal level established. The rats were then divided into four groups and subjected to one of the following operations: (*a*) unilateral nephrectomy with exposure and handling of the opposite kidney; (*b*) unilateral nephrectomy and constriction of the remaining kidney with a silk figure-of-eight ligature; (*c*) unilateral renal constriction with a silk figure-of-eight ligature, the other kidney being left intact after exposure and handling; (*d*) unilateral nephrectomy and removal of the poles of the contralateral kidney (three-quarters nephrectomy). The animals were followed for 50 days, during which blood pressures were measured on twenty occasions, then killed by exsanguination under ether anesthesia. The organs were weighed according to a standardized procedure and studied histologically. Individual determinations of serum creatinine and of the hematocrit levels were made. Mean lines and frequency distributions of blood pressure were subjected to statistical analysis. A definitely significant increase in blood pressure developed in the group subjected to operation (*b*) within 4 days postoperative. In none of the other groups did hypertension develop. Analysis of the individual renal weights and creatinine levels indicates the independence of the development of hypertension from the total mass of functioning renal tissue. Nor is it dependent on the prevention of renal hypertrophy

or the presence of fibrous perinephritis. The effect is probably due to the production of a disturbance of hemodynamics or tissue tension with the liberation of a pressor substance by the injured kidney.

The author wishes to acknowledge the invaluable technical assistance of Miss Elizabeth Snead in this investigation.

BIBLIOGRAPHY

1. Page, I. H., *Science*, 1939, **89,** 273.
2. Greenwood, W. F., Nassim, R., and Taylor, N. B., *Canad. Med. Assn. J.*, 1939, **41,** 443.
3. Soskin, S., and Saphir, O., *Am. J. Physiol.*, 1932, **101,** 573.
4. Page, I. H., *J. Am. Med. Assn.*, 1939, **113,** 2046.
5. Grollman, A., *Proc. Soc. Exp. Biol. and Med.*, 1944, **57,** 102.
6. Alwens, W., *Deutsch. Arch. klin. Med.*, 1909, **98,** 137.
7. Braun-Menendez, E., Fasciolo, J. C., Leloir, L., Muniz, J., and Taquini, A. C., Renal Hypertension, Springfield, Illinois, Charles C. Thomas, 1946, 199.
8. Grollman, A., Factors regulating blood pressure, *Tr. 2nd Conf.*, New York, Josiah Macy, Jr., Foundation, 1948.
9. Halpert, B., and Grollman, A., *Arch. Path.*, 1947, **43,** 559.
10. Chanutin, A., and Ferris, E. B., *Arch. Int. Med.*, 1932, **49,** 767.
11. Loomis, D., *Arch. Path.*, 1946, **41,** 231.
12. Addis, T., Glomerular Nephritis, New York, Macmillan Co., 1948.
13. Rytand, D., personal communication.
14. Addis, T., personal communication.
15. Dock, W., and Rytand, D., *Proc. Soc. Exp. Biol. and Med.*, 1937, **36,** 196.
16. Rather, L. J., *Am. J. Physiol.*, 1949, **159,** 153.
17. Friedman, M., and Freed, S. C., *Proc. Soc. Exp. Biol. and Med.*, 1949, **70,** 672.
18. Bonsnes, R. W., and Taussky, H. H., *J. Biol. Chem.*, 1945, **158,** 581.
19. Fisher, R. A., Statistical Methods for Research Workers, London, Oliver and Boyd, 10th edition, 1948.
20. Walter, F., and Addis, T., *J. Exp. Med.*, 1939, **69,** 467.
21. Gray, H., and Addis, T., unpublished data.
22. Goldblatt, H., The Renal Origin of Hypertension, Springfield, Illinois, Charles C. Thomas, 1948, 25.
23. Rodbard, S., and Katz, L. N., *J. Exp. Med.*, 1941, **73,** 357.
24. Grollman, A., *Special Pub. New York Acad. Sc.*, 1946, **3,** 9.