ARTERIAL HYPERTENSION IN RATS

I. METHODS

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The blood pressure of anesthetized rats has been measured in the course of several experiments. Attempts were made to produce arterial hypertension by a number of methods. These investigations were undertaken in order: (1) to learn what the normal blood pressure of rats is under anesthesia, (2) to develop methods to bring about arterial hypertension, (3) to study some of the pathological changes in animals when chronic arterial hypertension has persisted, and (4) to provide preparations for ascertaining the action of pressor and depressor substances.

Methods

Three hundred and fifty adult Norwegian white rats were used. Most were males. Blood pressures were measured with Hamilton's optical manometer, 5 per cent sodium citrate being used as an anticoagulant. All animals were anesthetized by intraperitoneal injection of pentobarbital sodium (4.5 mg. per 100 gm. body weight). The right femoral artery was exposed, and a strong solution of novocaine applied to it to prevent contraction. A curved 23 gauge needle connected to the manometer was inserted into the artery through a small incision. Heparin was injected intravenously when continuous tracings were to be taken. Operations on the kidneys were performed under ether anesthesia, as the use of pentobarbital sodium resulted in many deaths owing to strangulation from obstruction of the upper respiratory passages.

The disadvantages of this method for measuring blood pressure are: (1) animals are anesthetized and are, therefore, not under normal conditions, (2) only two or possibly three measurements can be made at different times on each animal, and (3) the rate of mortality from anesthesia alone is high (roughly 20 per cent). There are, however, several advantages: continuous records of the blood pressure can be made for as long as 2 hours, the blood pressure is probably at basal levels, and both systolic and diastolic pressures are measured with a considerable degree of accuracy.

1 The term arterial hypertension, in this study, is intended to mean a vascular disease of rats, of which one manifestation is elevation of blood pressure.
ARTERIAL HYPERTENSION IN RATS. I

The Normal Blood Pressure of Anesthetised Rats

The blood pressure of 163 “normal” rats was measured by the method described. Wide variations were found and many animals exhibited low values. It was desirable, therefore, to apply to these findings other standards of “normality.” When animals exhibiting pulse pressures of less than 25 mm. Hg were discarded (39 rats) variations were less, and the histogram of frequency was improved (Fig. 1). The mean systolic pressure of 124 rats was 128.7 mm. Hg; the mean diastolic, 91.3 mm. The median systolic pressure was 128.1 mm., the median diastolic 92.9 mm.; the extremes were between 184 and 88 mm. systolic and 145 and 58 mm. diastolic (Fig. 1).

These wide variations made it impossible to be certain of the presence of arterial hypertension in rats solely by measurement of the blood pressure under anesthesia. Another sign of its existence, hypertrophy of the heart, was, therefore, taken into account.

The method for ascertaining changes in the size (weight) of the ventricles was used by Rytand (1) based on normal standards obtained by Addis from a large series of animals. The assumption is made that persistent arterial hypertension leads to cardiac hypertrophy. Rytand’s results indicate that cardiac hypertrophy frequently accompanies renal ischemia. The hearts of 50 rats were, therefore, weighed. Care was taken to remove auricles and great vessels, and the weight of the ventricles measured to two decimal places. Changes from the expected weight of the heart were obtained from the formulas:

Males: \[ \text{Heart weight (mg.)} = 12.6 \times \text{body weight (gm.)}^{0.75} + 8 \]

Females: \[ \text{“ “ “ “ “ “} = 12.56 \times \text{“ “ “ “ “ “ “ “ 0.76} + 1.5 \]

the expected weight of the ventricles being estimated from a curve constructed from this formula. It is not unlikely that rats, especially older ones, may develop arterial hypertension spontaneously. Analysis of the blood pressures and heart weights of “normal” rats demonstrates that this is probably so, and in any consideration of what is “normal” must be taken into account. Standards constructed from this sample which exhibits two states (“normal” and “hypertensive”) must, therefore, be weighted in favor of the one to be excluded.

There was no obvious correlation between the level of blood pressure and the weight of the ventricles (Figs. 2 and 3). Cardiac hypertrophy according

3 When the upper respiratory passages remained open, or when tracheotomy had been performed, most animals exhibited levels which remained remarkably constant during periods of observation lasting 1 to 2 hours.

4 Most of the animals excluded exhibited low levels of blood pressure and were probably in a state of “shock.” Four, however, exhibited systolic pressures above 130 mm. Hg, and it is possible that errors in technique were responsible for the results obtained.

4 According to Rytand (1), cardiac hypertrophy is present when the weight of the heart is 12 per cent or more than that expected from this formula.
to the criteria just provided was present in seven "normal" animals; two of these exhibited elevation of the diastolic pressures to more than 110 mm. Hg,

![Abnormal rats with cardiac hypertrophy](image1)

![Normal rats](image2)

Fig. 1. Histograms of the blood pressures of 124 "normal" and 54 abnormal rats. The cross-hatched areas in the normal systolic histogram represent animals exhibiting diastolic pressures greater than 110 mm. Hg; those in the diastolic represent animals with systolic pressures greater than 150 mm. Hg. In every case the pulse pressure was greater than 24 mm. Hg. The abnormal rats all exhibited cardiac hypertrophy.

and four to more than 100 mm. On the other hand the diastolic pressures of six were more than 110 mm.; four of these being larger animals (350 to 500 gm.).
Since the presence of arterial hypertension is probably dependent upon the level of the diastolic pressure more than on the systolic, an attempt was made to ascertain in this series the upper limit of the normal diastolic pressure. When larger animals were excluded, as well as those with cardiac hypertrophy,
the diastolic pressure of all but one of the remainder lay below 110 mm. Hg and of one other animal between 100 and 110. When these results are compared with those obtained in animals subjected to procedures designed to produce arterial hypertension (see below), many of which exhibited diastolic pressures greater than 100 or 110 mm. Hg, it will be seen that it is safe to regard 110 mm. Hg as the upper limit of "normal" (Fig. 1). In the same animals the upper limit of the "normal" systolic pressure was somewhere between 140 and 150 mm.; the more extreme variations make it desirable to regard 150 as the upper limit.

As the level of the blood pressure is easily influenced by experimental procedures (anesthesia) at the time of measurement, the size of the heart appears to be a more reliable index of the presence of chronic hypertension (Fig. 3). In this study rats exhibiting cardiac hypertrophy\(^6\) alone will, therefore, be considered to be "probably hypertensive;" rats exhibiting cardiac hypertrophy and elevation of the diastolic pressure to a level greater than 110 mm. Hg to be "certainly hypertensive." Those animals with diastolic pressures greater than 110 mm. Hg without cardiac hypertrophy will be considered to exhibit elevation of the blood pressure due to certain experimental conditions, and not to chronic arterial hypertension.\(^6\)

The Production of Arterial Hypertension by Renal Injury

(a) Partial Constriction of One Renal Artery.—

Seventy-two rats were anesthetized and the left kidney found through a mid-abdominal incision. By retracting the kidney to the right of the midline, the origin of the renal artery was brought into view where it left the aorta. By careful dissection it was freed from the vein. A wire, 0.46 to 0.52 mm. in diameter, was placed along the artery and a ligature tied tightly around both the artery and the wire (1). When the wire was removed the artery was left partially constricted. Care was taken to see that the kidney was not completely anemic. In 14 instances the opposite kidney was removed (Fig. 4). Nine died after operation. The hearts of 56 were weighed.

Cardiac hypertrophy occurred in 39 of 56 animals. Blood pressure was elevated in 12. In 13 the affected kidney was completely infarcted. There

\(^6\) Although cardiac hypertrophy was believed to exist when the weight of the ventricles was more than 12 per cent of that expected, this value is probably a little high for this series. The arithmetical mean variation in ventricular weight from the calculated mean was \(-0.4\) per cent; when those animals with cardiac hypertrophy were excluded, the mean variation (43 rats) was \(-3.1\) per cent. The standard deviation of fifty rats was \(\pm 9.0 \pm 0.6\) per cent, the mean 0 \(\pm 0.9\) per cent.

\(^6\) "Arterial hypertension" when used in this report means, therefore, (1) diastolic pressure of 111 mm. Hg or more, and (2) enlargement of the heart 12 per cent or more than that expected.
was no difference in the degree of hypertrophy after (a) constriction of one renal artery and (b) constriction plus nephrectomy of the opposite kidney, although the result in (b) was more constant (Table I).

When animals with an intact kidney were allowed to survive for 8 weeks or more, a few (5 of 15) lost weight and died. Elevation of urea nitrogen in the blood was found in 2, and there were vascular lesions in some of the organs, including the kidneys. One animal died after delivery of a litter. There was no evidence that hypertension, once established, was transient (Fig. 8).

(b) Unilateral Hydronephrosis.—

The left ureter of fifteen rats was cut close to the bladder and brought through the skin of the flank. In six the ureter was occluded; in nine the kidney continued to function and to discharge urine through the side of the animal (2). The wounds healed well.

In those cases (nine) in which the kidneys continued to function, hydronephrosis of mild degree developed; there was cardiac hypertrophy in all and
# TABLE I
## Summary of Results

<table>
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<th>Procedure</th>
<th>Total No. rats</th>
<th>Deaths within 24 hrs</th>
<th>Deaths after 24 hrs</th>
<th>Hearts enlarged</th>
<th>Deviation, significant, from normal</th>
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<th>Diastolic pressure</th>
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* = spontaneous. † = by comparison of means. § = pulse pressure < 25 mm Hg, systolic pressure > 88 mm. || = excluding those in "shock." ** = one week or more after procedure.
arterial hypertension in seven. In those (six) with total occlusion of the ureter there were large hydronephrotic sacs and no hypertension (Fig. 5).

(c) Unilateral Renal Trauma.—

The left kidneys of 21 anesthetized rats were isolated in a fold of skin in the flanks and injured with light strokes of a hammer. Five animals died from rupture of the kidney and hemorrhage.

Cardiac hypertrophy resulted in six of fourteen, the mean variation being significantly greater than the normal. It lasted 4 months in three cases (Fig. 8) which exhibited arterial hypertension (Fig. 5). The left kidneys of the six with cardiac hypertrophy were scarred and contracted with small healed infarcts in the cortices.

(d) Perinephritis.—

The left kidneys of 22 anesthetized rats were covered with a sac of cellophane loosely tied about the renal pedicle (4). In four others a rayon sac was used instead.

The results (changes in the weight of the hearts) were examined statistically by a method found in Pearl (3), p. 343). The mean of the variation of heart weight from that expected was 10.3 ± 1.1 per cent. In comparison with the mean of the series of normal rats this change was significant.
Cardiac hypertrophy developed in sixteen rats, and arterial hypertension in four (Fig. 5). Infection in the sac was present in nine, of which six showed cardiac hypertrophy. Measurements indicated that the systolic pressure tended to be elevated more than the diastolic, especially during the first 30 days after operation (Fig. 6). When rayon was used there was no enlargement of the heart.

(e) Rats with Destruction of One Kidney.—In 20 instances among those previously cited the left kidneys were either totally infarcted by the procedure or completely destroyed by infection. Infarction occurred thirteen times on constriction of the left renal artery, and once after the kidney had been injured;
cardiac hypertrophy was observed 7 to 129 days later in ten. In two infection destroyed the kidney; the heart of one was enlarged. The weights of the hearts of two the kidneys of which were destroyed by infection in the cellophane sac were within normal limits. Two died of renal insufficiency 3 days after infarction of their left kidneys and removal of the right ones; their hearts were enlarged. The mean variation from normal of the weights of the hearts was significantly increased.

Attempts to Produce Arterial Hypertension by Chemical Methods

(a) Pitressin and Female Sex Hormone.—

Seven female and thirteen male rats were given by intramuscular injection $\alpha$-estradiol (1500 to 2000 rat units) in divided doses during 10 days, and then given
pitressin (6 to 8 units per 100 gm. body weight). The procedure of Byrom (5) was followed, except that adult rats were used. Blood pressures were measured up to 70 days later.

Cardiac hypertrophy occurred in four animals but the statistical change for the series was not significant. The diastolic pressure was elevated in three on more than one occasion, one of which could be said to exhibit arterial hypertension (Fig. 5). All but two rats weighed less than 325 gm.

(b) Adrenalin.—

A single dose of adrenalin in oil, 1.0 mg. was injected intramuscularly into each of eighteen rats. Eight died within 24 hours. The remainder were observed up to 20 days.

Cardiac hypertrophy occurred in seven and the mean enlargement for the whole series was significant.8 Diastolic pressures became elevated in three (Fig. 5). Only one could be said to have developed arterial hypertension. Cardiac hypertrophy was present in four of the eight dying soon after the procedure, and many hemorrhages were seen in the kidneys.

(c) Dihydroxyphenylalanine.—

The intravenous injection of dihydroxyphenylalanine resulted in an immediate and prolonged pressor response, the curves obtained resembling those produced by renin. In each of ten rats, the injection of 3 to 10 mg. of this amino acid was followed by a rise in the level of diastolic blood pressure from 20 to 60 mm. Hg, the height of the reaction occurring 2 to 7 minutes after injection. It continued to be elevated from 12 to 40 minutes. Injection of tyrosine did not occasion this response. Six rats, therefore, were given 20 mg. of this substance intraperitoneally, and six, 10 mg. intravenously. Blood pressures were measured up to 27 days.

Cardiac hypertrophy occurred only in two, not a significant change for the series (Fig. 5). In nine, however, the blood pressure rose (Fig. 7). Two of the remainder were in a state of shock when measurements were made.

DISCUSSION

It is probable that the standards adopted as representing the range of blood pressure of normal rats anesthetized with pentobarbital sodium are somewhat rigid. The extreme variability of blood pressure and the possibility that arterial hypertension may be present in “normal” animals makes it necessary, however, that the upper limits be high. The presence of cardiac hypertrophy

8 The mean change for the whole series was +8.3 ± 1.7 per cent. The standard deviation was 10.9 ± 1.2 per cent. When this mean was compared with that of the normal series, it was found that the change was a significant one. The coefficient of variation of this series, as with the others, was naturally large.
is probably a better index of hypertension (1). The fact that normal rats may exhibit cardiac hypertrophy, elevation of blood pressure, or both, and that abnormal rats may have cardiac hypertrophy with or without elevation of blood pressure makes the whole matter confusing. It is likely that hypertrophy of the ventricles is associated with chronic arterial hypertension whatever the level of the blood pressure may be under anesthesia—a—it is almost certain that rats with hypertrophied hearts and elevated blood pressures under anesthesia are hypertensive.

When the different procedures here discussed are reviewed, it is seen that rats, or at least some of them, are susceptible to arterial hypertension. Of four operative methods involving unilateral renal injury, all resulted in cardiac hypertrophy of significant degree. The heart was large even when the affected kidney was functionless and totally infarcted, as in the case of rats subjected to the Goldblatt technique. The persistence of its enlargement was not dependent upon ischemic and functioning renal tissue.

There is little doubt that injury to one kidney is often followed by persistent chronic arterial hypertension (Fig. 8). This condition is usually associated with vascular lesions in the opposite kidney (6). In those cases where the affected one is destroyed by infarction or infection, arterial hypertension probably persists because of the presence of vascular disease in the other, secondary to the initial renal damage.

Attempts were made at producing hypertension by chemical methods in the hope that these substances might set in motion an irreversible process which would lead to chronic arterial hypertension. The method failed in those animals injected with pitressin, for only one was definitely hypertensive 10 weeks later though four exhibited cardiac enlargement in 7 days. When adrenalin was injected cardiac hypertrophy occurred to a significant degree, but in no case did it persist more than 14 days after injection, and in only two cases more than 3. The injection of dihydroxyphenylalanine (9) resulted in cardiac hypertrophy only twice; these animals were considered to be "certainly hypertensive." Although rats frequently exhibit hypertension after one kidney is damaged, single injections of these pressor substances brought about little prolonged effect.

An interesting observation is the rapidity with which cardiac hypertrophy occurred. The injection of large doses of adrenalin, of pitressin (in three cases) and of injury to a single kidney after partial constriction of a renal artery, often resulted in enlargement of the ventricles in 1 to 3 days. The increase in weight was not due to the presence of edema; the hearts felt firm, the left ventricles were thick, and there was no evidence of general edema in the weight of the animals.

Wilson and Byrom (8) found that the blood pressure of rats exhibiting "malignant" hypertension was extremely variable.
Fig. 8. The relation of the production and persistence of hypertension to the number of days after renal injury. Notations same as in Figs. 3, 4, and 5. (a) Variations in the weights of the hearts. The hearts of many animals became enlarged very soon after the procedures designed to produce arterial hypertension. (b) The diastolic blood pressure of rats with cardiac hypertrophy. There is no obvious tendency for the blood pressure to become lower. (a) includes all rats exhibiting enlarged hearts and also those killed within 10 days after injury.
It is obvious, therefore, that rats are susceptible to arterial hypertension, even when only one kidney is injured. The relation of this condition to disease in the blood vessels of the opposite kidney will be discussed in a subsequent communication (6).

**SUMMARY**

Normal standards for the blood pressure of rats under pentobarbital sodium anesthesia have been ascertained. Arterial hypertension did not consistently follow the injection of estradiol and pitressin in adult rats, and only transient hypertension occurred after the injection of dihydroxyphenylalanine. The injection of adrenalin in oil, however, was followed by cardiac hypertrophy, and it also resulted from (a) partial constriction of one renal artery, (b) the production of unilateral hydronephrosis, (c) traumatic injury to one kidney, (d) inducing unilateral perinephritis with a cellophane membrane. The blood pressure in many of the animals became elevated.

In rats the weight of the heart is probably a more reliable index of the presence of the hypertensive state than is one measurement, or two, of blood pressure under anesthesia. The latter is extremely variable, both in normal and in hypertensive animals. Rats are, however, liable to hypertension under natural circumstances, and it can be easily induced in a number of ways. The weight of the heart may then become rapidly increased. To judge from the findings in this species, rats are very susceptible to the production of the hypertensive state, in comparison with other animals.

The author is indebted to Dr. J. Murray Steele who developed this technique for measuring blood pressure of rats, and who kindly made available for use in this study the measurements of blood pressure of 39 normal animals.

**BIBLIOGRAPHY**