A difficulty in studying the pathogenesis of essential hypertension is that spontaneous hypertension is not frequent in experimental animals. Most experimenters have used animals in which hypertension has been induced, usually by the production of renal ischemia. As essential hypertension in man is inheritable, an attempt was made to develop a spontaneous hypertension by selective breeding from rats with overaverage blood pressures. Eventually a strain of Wistar rats with overaverage blood pressures was obtained by Smirk and Hall; about 25 per cent of buck rats had tail blood pressures exceeding 140 mm. Hg and a few were above 160 mm. Hg. Since this article was published, the colony has improved and over 50 per cent of buck rats have systolic blood pressures exceeding 150 mm. Hg.

We are unaware of any long series of experiments on animals with spontaneous hypertension, although Alexander et al. found the response to the cold pressor test was increased in the families of rabbits with spontaneous hypertension.

Divergent conclusions have been published concerning the comparative responsiveness of hypertensives and normotensives, both human and experimental. The responses to several pressor drugs are stated to be larger in hypertensive than in normotensive rats by Sturtevant. Olsen et al. found an enhanced response to epinephrine and norepinephrine in renal hypertensive rats, whereas the responses to tyramine and phenethylamine were similar in hypertensives and normotensives. While the average responses to epinephrine and angiotensin of DCA-treated hypertensive rats were found to be slightly greater than those of control rats, Masson et al. did not consider the difference sufficiently great to be regarded as a factor in pathogenesis.

In renal hypertensive rabbits, Ogden et al. found the responses to Pitressin were markedly increased above the normotensive and there was also an increased response to fright and noise. Rothman, however, found that cerebral hypertensive rabbits showed a reduced response to epinephrine and norepinephrine, which was attributed to a dose-response phenomenon due to increased release of norepinephrine at sympathetic endings. Brown and Maegraith found that renal hypertensive rabbits showed increased pressor responses to tyramine, epinephrine, and vasopressin. Conway found little difference between the responses to norepinephrine of hypertensive and normotensive rabbits; but, when these drugs were administered after hexamethonium, the response of the hypertensives was the greater.

In dogs, Page found hypertension induced by large doses of Vitamin D to be associated with decrease rather than increase of the pressor response to epinephrine. Renal hypertension in dogs did not increase the response to angiotensin.

Increased reactivity of perfused blood vessels from renal hypertensive rats was described by Restall and Smirk and investigated in greater detail by McQueen. The exaggerated response of blood vessels from hypertensive rats was reduced when, during life, the blood pressure rise after clipping had been restrained by the long-term administration of reserpine.

In man, increased responses of hypertensives to epinephrine, angiotensin and s-methyl iso-thiourea have been described.
The responses to the latter drugs and nor-
epinephrine were appreciably greater in
hypertensives than in normotensives when the
blood pressure had been reduced previously
by hexamethonium.\(^\text{15}\) The statement has been
made\(^\text{16}\) that responses to epinephrine are
similar in hypertensives and normotensives,
but in this paper the rises of pressure were
expressed as percentages of the original
pressure.

Evidence of enhanced reactivity of the
blood vessels of human hypertensives was ob-
tained when injections of vasoconstrictor
drugs were made into brachial arteries.\(^\text{17, 18}\)
The nail-bed vessels\(^\text{19, 20}\) and conjunctival
vessels\(^\text{21, 22}\) have also been stated to exhibit
greater responses to drugs in hypertensive
than in normotensive individuals.

It was decided to examine, in some detail,
the physiological reactions of rats from the
colony bred to develop hypertension (B rats)
as contrasted with normal rats (C rats). The
B rats used all had blood pressures which
exceeded 140 mm. Hg when measured by a
tail-cuff method under light ether anesthesia
some days before the main experiment. A
study was made of the reactions to epineph-
rine, norepinephrine, angiotensin (synthetic
and biological), vasopressin (Pitressin), and
\(\text{s-methyl iso-thiourea}\). The initial study re-
vealed that although the tail-cuff method used
was satisfactory for determining blood pres-
sure levels in the absence of drug action,
methodical difficulties arise when the tail-cuff
method of blood pressure measurement is em-
ployed to study the pressor responses to some,
but not all, pressor drugs. Intraperitoneal
administration was also found to be unsuit-
able for some pressor drugs as absorption was
slow. The present study is, therefore, re-
stricted to the study of blood pressures meas-
ured directly, drugs being administered in-
travenously.

**Methods**

Indirect blood pressures were determined by a
tail-cuff method. As the pressure in the inflated
tail cuff falls below the systolic blood pressure,
expansion of the tail is recorded by a transducer.
The equipment was housed in a thermostatically
controlled room maintained at 85 to 90 F., the rats
being taken to the room not less than half an hour
before the measurement. The method is a modi-
fication of that published by Gallagher and Grim-
wood.\(^\text{23}\) Tail-cuff measurements, however, were
used only to determine the levels of the blood pres-
sures prior to experimentation.

Direct measurements of pressure were made
from a cannulated femoral artery, with kymo-
graphic recording using a small volume mercury
manometer. Cannulation of blood vessels and of
the trachea was made under light ether anesthesia
and followed by chloralose (50 mg./Kg.), given
intravenously, which served to maintain anesthesia
during experimentation. Drugs were administered
into a cannula inserted into a femoral vein.

**Results**

**COMPARISON OF BLOOD PRESSURES BY THE TAIL-CUFF METHOD WITH MEAN PRESSURES RECORDED DIRECTLY FROM A FEMORAL ARTERY**

In 28 experiments, measurements were
made of tail blood pressures and intra-arte-
rial pressures were recorded simultaneously
with a cannula in a femoral artery. In rats
anesthetized with ether or with pentobarbi-
tal, it was found that the tail pressure was
recorded as 5 to 10 mm. higher than the mean
pressure recorded directly. A difference is
to be expected as the blood pressure by a cuff
method should be approximately equal to the
systolic pressure and the mean pressure meas-
ured directly is somewhat lower. In the ab-
sence of drug administration, the agreement
between tail-cuff and direct femoral blood
pressures was good both in normotensive and
hypertensive rats.

**EFFECT OF SURGICAL PROCEDURES AND ANESTHESIA UPON THE TAIL PRESSURES OF INHERITED HYPERTENSIVE AND CONTROL RATS**

While the levels of the femoral mean pres-
sure and indirectly measured tail pressure

\*A table containing the regression data for re-
sponse to pressor drugs has been deposited as
document number 6954 with the American Documen-
tation Institute Auxiliary Publications Project, Pho-
to-duplication Service, Library of Congress, Wash-
ington 25, D. C. A copy may be obtained by citing the
document number and by remitting $1.25 for photo-
prints, or $1.25 for a 35 mm. microfilm. Advance
payment is required. Make checks or money orders
payable to: Chief, Photoduplication Service, Library
of Congress.
remain closely related, if measured simultaneously, the necessary surgery under ether anesthesia usually led to falls in both, the falls being larger in the B rats. However, when surgical trauma was reduced and chloralose anesthesia used, the rat blood pressures were preserved at levels close to those observed preoperatively.

In a series of 25 B rats, the mean tail blood pressure measured under light ether anesthesia with no surgical procedures was 152.4 mm. Hg and a series of 24 C rats under corresponding conditions had mean tail blood pressures of 115.1 mm. Hg. The blood pressures of these rats were measured at a later date with a cannula in a femoral artery. The mean femoral blood pressures of the 25 B rats was 140.9 mm. Hg, and of the 24 C rats was 119.1 mm. Hg. This tendency for the difference between the blood pressures of B and C rats to diminish when blood pressures are measured directly under chloralose anesthesia occurs also under ether anesthesia and has been a feature of subsequent experiments.

**EFFECT OF NOREPINEPHRINE ON THE BLOOD PRESSURE OF RATS WITH INHERITED HYPERTENSION AND CONTROLS**

Because, as will be seen later, the responses of rats to intravenous injections of norepinephrine (0.35 µg. of base/Kg.) differed from the responses to other pressor drugs, an extensive study was made of the effect of norepinephrine in 59 C and in 42 B rats. It is evident in figure 1 that there is no significant difference between the responses of C and B rats in that the magnitude of the responses appears to be independent of the preinjection level of the blood pressure. The regression lines drawn in figure 1 are not significant.

**EFFECT OF EPINEPHRINE ON THE BLOOD PRESSURE OF RATS WITH INHERITED HYPERTENSION AND CONTROLS**

Intravenous administration of epinephrine (1.65 µg. of base/Kg.) was made in 21 experiments on B and in 38 on C rats. Blood pressure rises occurred shortly after the administration and were succeeded by blood pressure falls. It will be seen in figure 2 that in B rats, higher initial blood pressure levels were associated with smaller blood pressure increases. The regression line for hypertensives in figure 2 is significant (0.01 < P < 0.05). This relationship could not be established for the controls.

The regression data show that there is a significant difference between the blood pressure rises for B and C rats (P < 0.01) between initial blood pressure levels of 110.0 and 143.1 mm. Hg, the rise being greater in the B rats. This difference is particularly well marked when the blood pressures of B rats had fallen during experimentation into the normotensive range. Because of the significant relationship between initial blood pressure level and response to epinephrine among the B rats, we were surprised at the absence of such a relationship among C rats. However, the same absence of a significant relationship was noted when the experiment was repeated on an additional series of controls.

In general, the falls of blood pressure which followed the blood pressure rises were larger in the rats with higher than average initial blood pressure levels (34.0 mm. Hg fall) than in those with lower than average initial blood pressures (24.79 mm. Hg fall). The difference was not significant.
Relation between blood pressure and rise in blood pressure with injected epinephrine. Symbols as in figure 1. For B rats, the regression line is significant ($r = -0.494, P < 0.02$) but is not significant for C rats.

Relation between blood pressure and rise in blood pressure with injected biological angiotensin. Symbols as in figure 1. The regression lines for B rats ($r = -0.695, P < 0.001$) and C rats ($r = -0.503, P < 0.01$) are both significant.

Relation between blood pressure and rise in blood pressure with injected synthetic angiotensin. Symbols as in figure 1. The regression lines for B rats ($r = -0.539, P < 0.001$) and C rats ($r = -0.441, P < 0.01$) are both significant.

The effects of intravenous injections of the two angiotensins (synthetic: 0.167 μg./Kg.; biological: 3.3 units/Kg.) were not unlike quantitatively in their pressor effects. The 3.3 units/Kg. of the biological angiotensin had a larger effect than 0.167 μg./Kg. of the synthetic. In rats, the synthetic angiotensin had approximately twice the potency of noradrenaline. The responses of B rats and C rats to these two preparations are shown in figures 3 and 4. It will be seen that comparing B rats with B rats and C rats with C rats, the rises in blood pressure are smaller if the initial level of the blood pressure is high than if it is low.

The regression lines in figures 3 and 4 are significant both for hypertensives ($P < 0.001$) and for controls ($0.001 < P < 0.01$). The regression lines for B rats lie above those for C rats, but the difference between them is only significant in the case of biological angiotensin between initial blood pressure levels of 110.0 and 137.1 mm. Hg ($P < 0.01$).

Rats 39 C and 40 B were used in the experiments with biological angiotensin. Rats 52 C and 53 B were used in the experiments with synthetic angiotensin.

**EFFECT OF ANGIOTENSIN ON THE BLOOD PRESSURE OF RATS WITH INHERITED HYPERTENSION AND CONTROLS**

Two types of angiotensin were used: the first prepared biologically in the Eli Lilly Laboratories and the second synthetically in the Ciba Laboratories, Basle.
DRUGS AND HYPERTENSION

821

K

I

II

IO

90

80

70

60

50

40

30

20

10

0

FIGURE 5

Relation between blood pressure and rise in blood pressure with injected vasopressin. Symbols as in figure 1. The regression lines for B rats \(r = -0.811, P < 0.001\) and C rats \(r = -0.832, P < 0.001\) are both significant.

EFFECT OF VASOPRESSIN ON THE BLOOD PRESSURE OF RATS WITH INHERITED HYPERTENSION AND CONTROLS

Intravenous injections of 0.133 units/Kg. were made into a femoral vein. When hypertensives are compared only with hypertensives and controls only with controls, it will be seen in figure 5 that the blood pressure rises are greater in the animals with the lower initial blood pressures. The regression lines are significant \(P < 0.001\) and the regression line for hypertensives lies significantly above that for the controls between initial blood pressure levels of 115.0 and 162.2 mm. Hg \(P < 0.01\). Evidently when a correction is made for initial blood pressure level, B rats exhibit larger blood pressure rises than C rats. The experiments were made using 32 C and 34 B rats.

EFFECT OF S-METHYL ISO-ThIOUREA ON THE BLOOD PRESSURE OF RATS WITH INHERITED HYPERTENSION AND CONTROLS

Intravenous injections of s-methyl iso-thio-urea sulphate (2.2 mg./Kg.) also led to appreciably larger femoral blood pressure rises in B rats with comparatively low than in B rats with high initial blood pressure levels. The regression line for the 25 B rats in figure 6 is significant \(0.01 < P < 0.05\). The regression line for the 47 C rats has a similar slope but is not significant \(0.1 < P < 0.2\).

The responses of the B rats are clearly larger than those of the C rats used in this experiment and the regression lines of hypertensives and controls are significantly different between initial blood pressure levels of 110.0 and 153.0 mm. Hg \(P < 0.01\).

EFFECT OF HEXAMETHONIUM ON THE BLOOD PRESSURE AND RESPONSE TO PRESSOR DRUGS OF RATS WITH INHERITED HYPERTENSION AND CONTROLS

The mean femoral blood pressure of 13 rats bred for hypertension was 141.3 mm. Hg immediately before the administration of hexamethonium, and that of 19 controls was 122.1 mm. Hg; the difference between the blood pressures was highly significant \(P < 0.001\). After 5 mg. hexamethonium bromide was given intravenously, the mean femoral blood pressure of inherited hypertensive rats was 67.54 mm. Hg and of control rats was 64.63 mm. Hg. There is no significant difference between the blood pressure levels of B and C rats after giving hexamethonium \(0.40 < P < 0.50\). The fall of blood pressure in the hypertensives was 73.77 mm. Hg and
in the controls 57.47 mm. Hg. The difference in the extent to which the blood pressures fall after hexamethonium is significant (0.001 < P < 0.01). Among the controls, the higher the initial blood pressure the greater was the blood pressure fall after hexamethonium. The regression line in controls of blood pressure fall on initial blood pressure was highly significant (P < 0.001). Similarly, the corresponding regression line in the hypertensives was significant (0.01 < P < 0.05). The corresponding regression line of controls and hypertensives taken together was highly significant (P < 0.001).

When norepinephrine was administered after hexamethonium, the mean rise of blood pressure in the hypertensives was 80.1 mm. Hg and in the normotensives was 68.7 mm. Hg. The difference is significant (0.001 < P < 0.01).

Discussion

In our early attempts to establish a satisfactory kymographic technique, the blood pressure of hypertensive rats often fell after surgery, and some control rats showed rises of blood pressure. Later, an improved technique greatly lessened this difficulty, but its occurrence was fortunate in that it provides us with results on rats bred for hypertension and on control rats over a wide range of initial blood pressures. Insertion of a cannula into a carotid artery is undesirable, being commonly associated with a rise of blood pressure.

The pressor agents studied were norepinephrine, epinephrine, synthetic and biologically prepared angiotensin, vasopressin, and s-methyl iso-thiourea. It was apparent in hypertensives that the responses to epinephrine, angiotensin, vasopressin and s-methyl iso-thiourea were inversely related to the initial level of the blood pressure prior to the injection.

In controls, a corresponding relationship between initial blood pressure level and pressor response occurred when the pressor drugs were angiotensin (synthetic and biological) and vasopressin. A quantitatively unimportant but similar trend was seen with s-methyl iso-thiourea and results were not significant (0.1 < P < 0.2). The slope of the regression line for C rats was almost horizontal with epinephrine.

When norepinephrine is given, however, the response does not appear to be influenced by the initial level of the blood pressure in either the B or C rats; nor is there any significant overall difference between the blood pressure rises of B and C rats.

The results render generalization regarding the relationship between the initial level of the blood pressure and the response to pressor agents inapplicable in that the relationship not only varies from one pressor agent to another, but depends also upon the factors which have determined the initial blood pressure level. Thus to some drugs, for example vasopressin, B rats with under-average blood pressures for the B rat colony have, as an average, larger responses than C rats with over-average pressures. By contrast, this difference between B and C rats exhibiting similar initial blood pressures is not normally observed when the pressor drug is norepinephrine.

Yet after large doses of hexamethonium have been administered, the response of B rats to norepinephrine is larger than that of C rats. Furthermore, after hexamethonium is given, the magnitude of responses of both B and C rats is related to the level of the blood pressure in the sense that higher initial blood pressures (after hexamethonium) are associated with smaller responses.

It is of interest that the average level of the blood pressure after a large dose of hexamethonium, "the hexamethonium floor," is approximately the same in the inherited hypertensive rats and in the controls. A corresponding result was reported by Laverty and Smirk.24 This suggests that increase in the "neurogenically maintained fraction" of the blood pressure 24, 25 is responsible for the increase above normal of the blood pressure in the B rats. This "neurogenically maintained fraction," however, is not the expression of conscious nervousness in that it persists under general anesthesia.
Summary

The establishment, by selective breeding, of a colony of rats with a high incidence of spontaneous hypertension has been confirmed by a kymographic technique with femoral artery cannulation. The reaction of rats to several pressor drugs has been altered by selective breeding. In both control and inherited hypertensive rats, the initial level of the blood pressure prior to administration of the drug influences the magnitude of the responses to several pressor drugs but not to norepinephrine. If hypertensives are compared only with other hypertensives and controls with other controls, it is clear that high preinjection pressures have an inhibiting effect on the pressor responses to biologically and synthetically prepared angiotensin, to vasopressin, and possibly lessen also the responses to s-methyl iso-thiourea. When under experimental conditions the blood pressures of rats with inherited hypertension have fallen into the upper range of control rat blood pressures, the responses to epinephrine, vasopressin, s-methyl iso-thiourea and biological angiotensin are greater in the hypertensives than in the controls. The difference in the case of synthetic angiotensin is not statistically significant. In the case of norepinephrine, the responses are equal. Hexamethonium reduced the blood pressures of inherited hypertensive and control rats to the same level.

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References

19. Mendelowitz, M., and Naffchi, N.: Work of...


Observations on the Responses of Rats with Spontaneous Hypertension and Control Rats to Pressor Drugs and to Hexamethonium

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