STUDIES IN EXPERIMENTAL HYPERTENSION

by

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ABSTRACT

The effects of dietary and hormonal factors upon the blood pressure of male Wistar rats were investigated.

1. Desoxycorticosterone acetate was found to increase the blood pressure ~~only~~ in the presence of excess dietary salt.

2. Estrogen overdosage produced hypertension in rats. Castrate animals were more sensitive to the effects of estrogen. Estrogen overdosage aggravated experimental hypertension induced by nutritional choline deficiency.

3. A period of nutritional choline deficiency was followed by hypertension. Desoxycorticosterone accelerated the development of hypertension in choline deficient animals.

4. Hypertension developed in rats 2 months after a prolonged period of inanition.

5. Antihistamine was found to induce profound variations in the blood pressure of male rats.

6. Rats pre-treated with desoxycorticosterone acetate showed a greater pressor response to adrenaline than normal intact rats.

7. Desoxycorticosterone and antihistamine were found to

facilitate the occurrence of the Trueta shunt.

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ACKNOWLEDGEMENTS

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INTRODUCTION

A. Historical Review

Hypertension constitutes one of the most serious problems facing civilized man. Goldring and Chasis (25) in 1944 estimated that in the United States this condition accounts annually for more than one third of the total number of deaths.

Richard Bright (5) in 1827 pointed out that an enlarged heat and albuminous urine accompanied a diseased condition of the kidneys and since that day the kidney has been recognized as an important factor in the etiology of hypertension. It is now clear that organic renal lesions precede the onset of hypertension in a considerable number of cases, but there is a large group of cases where organic renal disease is not an obvious precursor of the hypertension. This group is comprised of the cases of so-called essential hypertension.

The work of Goldblatt et al (24) in 1934 marked an epoch in the experimental investigation of experimental hypertension. They showed that transient hypertension could be produced in dogs by partially constricting the renal artery. By moderately constricting both renal arteries, or by constricting one renal

artery and removing the contralateral kidney, they were able to produce chronic hypertension.

Goldblatt's work was well substantiated by other investigators (Wilson and Pickering (68), Wilson and Byrom (69), Verney and Vogt (65)) who found too that the ischemic kidney produced hypertension even when completely denervated. They concluded from these experiments that the hypertension was caused by the formation in the ischemic kidney of a pressor substance which escaped into the general circulation.

In 1946 Cruz - Coke (11) showed that lack of oxygen is of vital importance at certain stages in the formation of pressor substance. Anoxia presumably develops with decreased blood flow in the kidney.

At the present time hypertensive patients are classified into two main groups, namely; those in whom organic renal disease is recognized by all to be the cause of the hypertension (secondary hypertension) and those in whom no organic renal disease is apparent, and the cause of the hypertension is obscure (essential or primary hypertension). In secondary hypertension the cortical anoxia is caused from the outset by organic change but the etiology of the theoretical renal cortical anoxia of essential hypertension has remained unknown.

B. Theories on the Etiology of Hypertension

The number of cases of hypertension in man that can be attributed to a reduction in calibre of the renal arteries by mechanical obstruction (i.e. atheroma, thrombi) is small and as an etiological factor such obstruction can be discounted.

(1) Vascular Origin

Goldring and Chasis (25) consider that renal arteriolosclerosis with resultant renal cortical anoxia does not precede the development of essential hypertension, although it is a concomitant or consequence of hypertension. Castleman and Smithwick (6) in 1943 examined renal biopsy specimens from one hundred hypertensive patients, and concluded that the evidence of renal vascular disease in more than one half of the cases was inadequate to prove this to be the sole factor in producing high blood pressure.

Work done in this laboratory in 1948 by Logan (37) showed that there was no marked vascular degeneration in kidneys of rats hypertensive three to eight months. However, Moritz and Oldt (38) and Ellis (18) reported that post-mortem findings in cases of essential hypertension almost constantly revealed intra-renal vascular damage as well as widespread arteriolar

sclerosis. Child (8) suggested in 1938 that although the
initiating factor is unknown, induced arteriolar disease
might account for the maintenance of hypertension.

(2) Hormonal Origin.

The role of the adrenal cortex in the induc-
tion and maintenance of hypertension is, at present,
imperfectly understood. It's secretions however, are
essential to the experimental establishment and mainten-
ance of high blood pressure (4, 13, 23, 40).

In 1942 Selye (46) produced nephrosclerosis
and cardiac hypertrophy in chicks by overdosage with the
adrenal cortical hormone desoxycorticosterone. Renal
lesions included cloudy swelling of the tubules and hy-
pertrophy and hyperplasia of both parietal and visceral
layers of Bowman's capsule. The blood vessels appeared
intact and blood pressure changes were not significant.

Darrow and Miller (12) in 1942 observed that
DCA overdosage in rats produced necrosis of the cardiac
musculature and hypertrophy of the renal tubules.

Selye et al (47) in 1943 produced experimen-
tal malignant hypertension in rats receiving excess
dietary salt by administering to them large doses of
desoxycorticosterone. Later Selye (48) induced hyper-
tension with kidney disease by subjecting rats to

damaging agents such as prolonged exposure to cold.
Hypertrophy of the adrenal was a characteristic feature
of this treatment.

Corcoran (9) in 1948 pointed out the fact that
~~in~~ patients manifesting "Cushing's Syndrome" are generally
hypertensive and show functional levels of blood flow,
glomerular filtration, and tubular secretion attesting to a loss of
50% of the functional and presumably structural integrity
of the kidney.

Dougherty (14) observed that arteriosclerotic
lesions similar to those produced by administration of
large amounts of desoxycorticosterone acetate were observed
following daily treatment of mice with adrenotrophic horm-
one for a period of weeks.

The tendency of Addisonians to develop hyper-
tension after replacement therapy with desoxycorticosterone
acetate (DCA) has long been recognized (49). General
reports also indicate that the ACTH used for arthritic
therapy frequently produces hypertension. Nephritis and
hypertension is a common occurrence following treatment
of arthritis with cortisone (Knowlton et al, 36).

The precise nature of the part played by the ad-
renal gland, as previously mentioned, is not known. How-
ever, the evidence that has accumulated in recent years
indicates that it is undoubtedly involved in the chain of

events that terminates in hypertension.

(3) Nervous Origin.

The possibility that psychogenic renal vasoconstriction may be a factor in the etiology of human essential hypertension has been recognized by various workers, and a consideration of the psychological factors in essential hypertension is given by Weiss (67). Nevertheless there is considerable difference in opinion as to whether the nervous system is of etiological importance in this condition.

Garai (22) found that shipwrecked sailors who had suffered prolonged immersion tended to have a raised blood pressure and that they showed increased vasomotor reactions (as gauged by the cold pressor test). He suggested that the reflex constriction of the vessels of the kidney, known to be caused by exposure to cold, had played a part in producing hypertension. Medoff and Bongiovanni (39) and Farris, Yeakel and Medoff (19) found that they were able to produce hypertension in rats by stimulating repeatedly with intense noise. Heymans (33) and Grimson, Bouckaert and Heymans (29) record the production of sustained hypertension in dogs from which they had removed the moderator nerves and the entire sympathetic nervous system, with the exception of the ennervation of the kidneys and adrenals. Subsequent denervation of the kidney

resulted in restoration of normal blood pressure.

a) Renal Circulation.

Trueta, Barclay, Daniel, Franklin and Prichard
(31) in 1947 made an important contribution to the physio-
logy of the kidney and to the study of the nervous elem-
ent involved in essential hypertension. They discovered
that the blood reaching the kidney has two potential
routes through that organ and, according to the circum-
stances, it may pass almost exclusively by one or the other
of these routes, or in varying proportions through each of
them. The two routes diverge when the afferent arterioles
of the juxtamedullary glomeruli leave the interlobular
arteries. One route, the medullary, continues through the
juxtamedullary glomeruli, the efferent vessels of these
glomeruli and their derivative vasa recta, to the inter-
lobular veins. The other route, the cortical, continues
through the interlobular arteries, to the afferent arter-
ioles of the remaining glomeruli, these glomeruli them-
selves, their efferent vessels and the cortical inter-
tubular capillary network and finally through the veins
draining this network, into the interlobular veins. In
the normal kidney the medulla is poorly supplied with
blood and the cortical circulation predominates. However,
under certain conditions the medullary circulation pred-
ominates while circulation through the cortex all but
ceases.

The evidence is as follows:-

The outer layers of the cortex of the kidney can be blanched by stimulating the peripheral end of the cut splanchnic nerve, by stimulating the nerve plexus surrounding the renal artery, by injecting adrenaline, pituitrin or pitressin and reflexly, by stimulating the central end of the cut sciatic nerve, or placing a tourniquet round the thigh for some hours. Sectioning of the splanchnic nerve causes a flushing of the cortex and abolishes reflex effects.

It is difficult to evaluate the significance of this work. It is pertinent however that in the kidneys of elderly human subjects, and those suffering from hypertension, many of the juxtamedullary glomeruli were of a degenerate type. It seems as if one particular capillary channel in a glomerulus can become wider and wider -- owing, it is suggested, to the strain of repeated diversion of blood through this part of the kidney, until the glomerulus is no longer a functioning mechanism. A true short circuit of this kind is presumed to be virtually out of control, so that unless a person with widespread degeneration of this type had high blood pressure, he might have very little cortical circulation. It is suggested by Trueta et al. that this discovery points the way to a rational explanation of the way in which psychological factors contribute to the induction of essential

hypertension.

So far as experimental hypertension is concerned, it is suggested that cortical ischaemia in the intact animal, brought about by stimuli of intense reflex or emotional origin, or more easily in susceptible subjects, is equivalent to the Goldblatt clamp, and that conversely, the latter acts in virtue of the ischaemia which it supposedly induces in the cortex.

(4) The Nature of the Renal Pressor Mechanism.

Investigators seem to be agreed that hypertension of renal origin is due to some humoral pressor substance formed in the kidney, but it has not been definitely established where in the kidney this substance is produced. Opinion favors the renal cortex as the source of pressor substance.

Goormaghtigh (26, 27) has described granular, afibrillar cells in the walls of the arterioles of the renal cortex and in the juxtaglomerular apparatus, and as he found that these cells were larger and more numerous in experimental animals with renal ischaemia, he suggested they secreted and liberated a pressor substance. Goormaghtigh (27) also observed the enlargement of these cells in the fatal crush syndrome. Kaufmann (34) found hypertrophy of these cells in the kidneys of patients with hypertension. Friedman and Kaplan (21) believe, on the

other hand, that the pressor substance is formed in the cells of the proximal convoluted tubules.

It has long been known that a substance called renin, elaborated by the kidney, will cause a rise in blood pressure. This substance is apparently an enzyme that acts on a plasma globulin (α_2 globulin) to produce a pressor substance called hypertensin. The role renin plays in essential hypertension is not clear. Repeated injections of it elicit a progressively decreasing response (tachyphylaxis) and it cannot be regularly found in the blood of chronic hypertensives (45).

Wakerlin et al. (66) conclude that there is no correlation between the renal renin concentration and the level of experimental renal hypertension, either chronic or malignant. Work in recent years has indicated that other vasodepressor and vasoexcitor principles may be involved in hypertension but the nature of these principles and their mode of action is, as yet, obscure (32, 45, 53, 66, 76)

APPARATUS AND METHODS USED IN DETERMINING THE SYSTOLIC PRESSURE IN RATS.

A. Apparatus.

The blood pressures of the rats were measured indirectly by observing the pressure required on the thigh of the anaesthetized animal ~~necessary~~ to stop the blood flow in the capillaries of an interdigital web. The method is described by Griffith and Farris (28), and modifications found useful in this laboratory have been reported by Fitch (20) and Semple (52).

Photographs of the apparatus are shown in Plate I.

B. Methods.

a(Anaesthesia.

Fitch (20) and Semple (52) satisfactorily standardized the use of sodium pentothal as an anaesthetic so that little difficulty was encountered when applying the technique. The rats were anaesthetized by giving them intraperitoneal injections of a solution of sodium pentothal.

It was found that 0.35 ml. of a freshly prepared solution of 25 mgm. sodium pentothal dissolved in 1.0 ml. of distilled water injected intraperitoneally was sufficient to anaesthetize a rat weighing 150 gm. This

dose was increased 0.05 ml. for every increase in weight of 50 gm. The action of the anesthetic was more reliable when the animals were left without food for 2 hours before anaesthetization. It was also observed that if the initial injection did not produce a profound enough anaesthesia that an extra 0.1 ml. of pentothal could be administered with no apparent deleterious effect on the animal.

PLATE I.

The photograph on the right illustrates the apparatus used
in determining the systolic blood pressure of rats (see
text)

The photograph on the right is a vertical view of the
microscope stage showing the toes of the hind leg of an
anesthetized rat pinned out (with plasticene) for observat-
ion of the interdigital web. Note the pressure cuff
wrapped about the thigh.
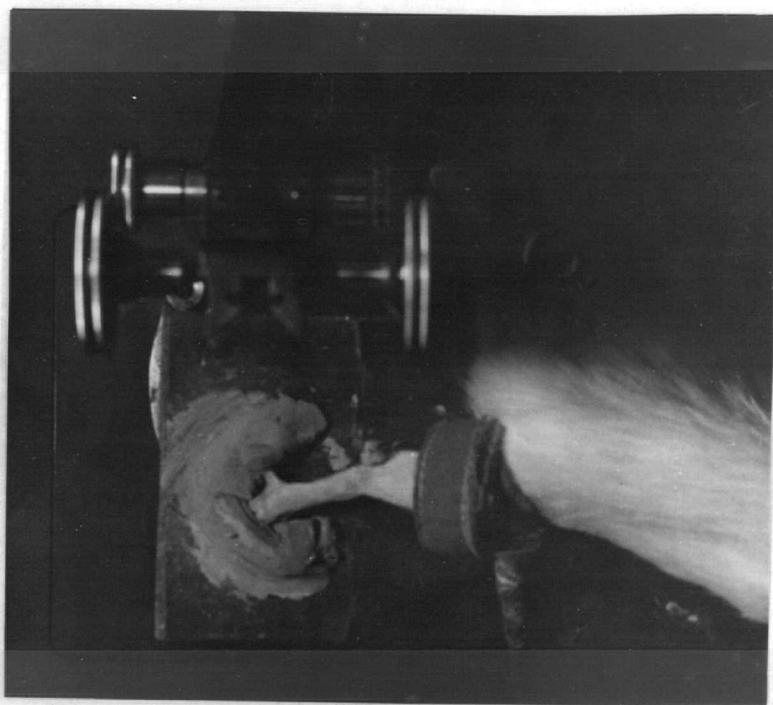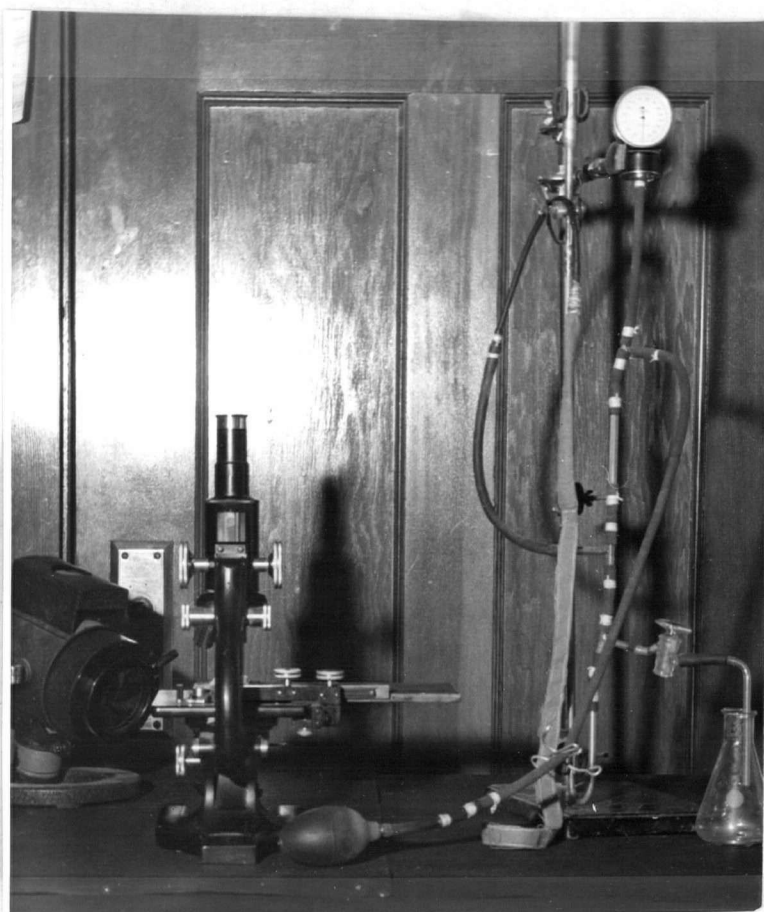
THE EFFECT OF DESOXYCORTICOSTERONE OVERDOSAGE ON THE BLOOD PRESSURE OF MALE WISTAR RATS

A. Introduction.

Semple (52) and Fitch (20) working in this laboratory found that one intramuscular injection of 1.0 mgm. of DCA sufficed to produce a transient hypertension in Wistar rats. The following investigation was undertaken in order to confirm their results and to note the effect of dietary salt supplements on the course of a hypertension thus induced.

(1) Methods.

Trial 1.

Eight male Wistar rats 5 to 7 months old, were each injected intramuscularly with 1.0 mgm. of desoxycorticosterone in oil. The systolic blood pressures of these animals and 8 control animals were determined daily for 10 days.

Trial 2.

Six male Wistar rats were each given daily for 6 days, intramuscular injections of 1.0 mgm. of desoxycorticosterone acetate in oil. Blood pressure determinations were made on each animal every day for 10 days and again on days 20 and 30.

Trial 3.

Eight male Wistar rats each received an intramuscular injection of 1.0 mgm. of desoxycortico-sterone every day for 14 days. Four days before the experimental treatment 2% salt was added to the drinking water of the animals and supplementary salt was given throughout the course of injections. The systolic pressures were determined throughout a period of 30 days.

(2) Results.

Trial 1.

The results are presented graphically in Fig. 1. No pertinent changes in blood pressure were observed with the exception of an initial drop in systolic pressure averaging 14 mm/Hg. Several repetitions of the above procedure produced negative results.

Trial 2.

The results are presented graphically in Fig. 2. It is notable that the systolic pressure reached an average value of 165 mm/Hg. in 12 days and had returned to a normal value in 16 days.

Trial 3.

The results are presented graphically in Fig. 2. The blood pressure of these animals was observed to rise steadily after the third injection of DCA to an average value of 174 mm./Hg. 3 days after the last

hormone injection. The average systolic value had
dropped to 174 mm./Hg. on the twentieth day and tended
to stabilize at this point.

Histological examination of the kidneys,
heart, liver, and adrenals of 3 of the above animals
by Logan (37) revealed no signs of pathological change.

Systolic Blood Pressure mm/Hg
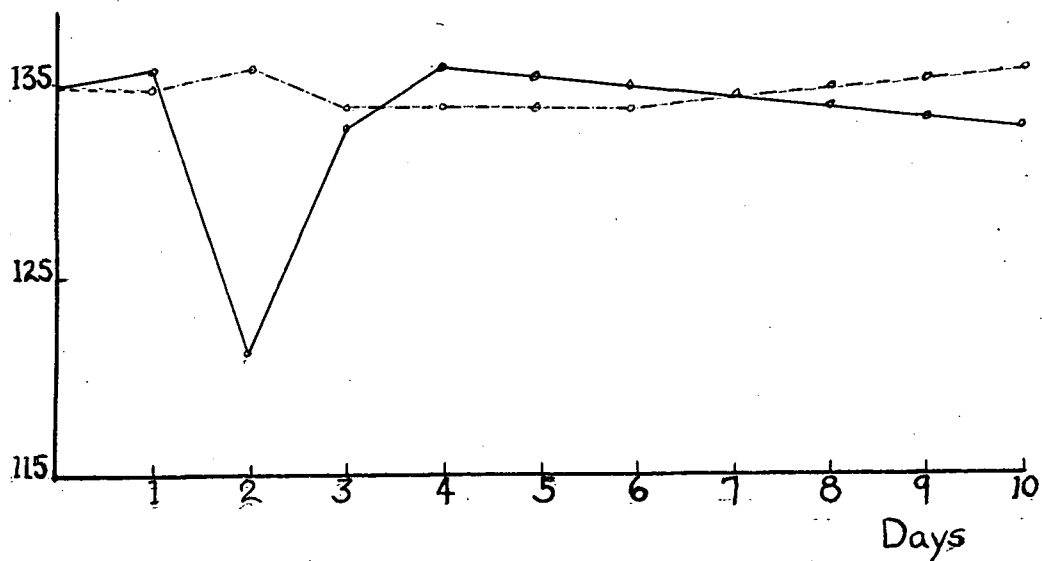
Fig. 1

The solid line represents the average systolic blood pressure variations in 8 male rats, each receiving 1.0 mgm. of DCA intramuscularly on day 0.

The broken line represents the average systolic blood pressure changes in 8 control animals receiving no treatment.
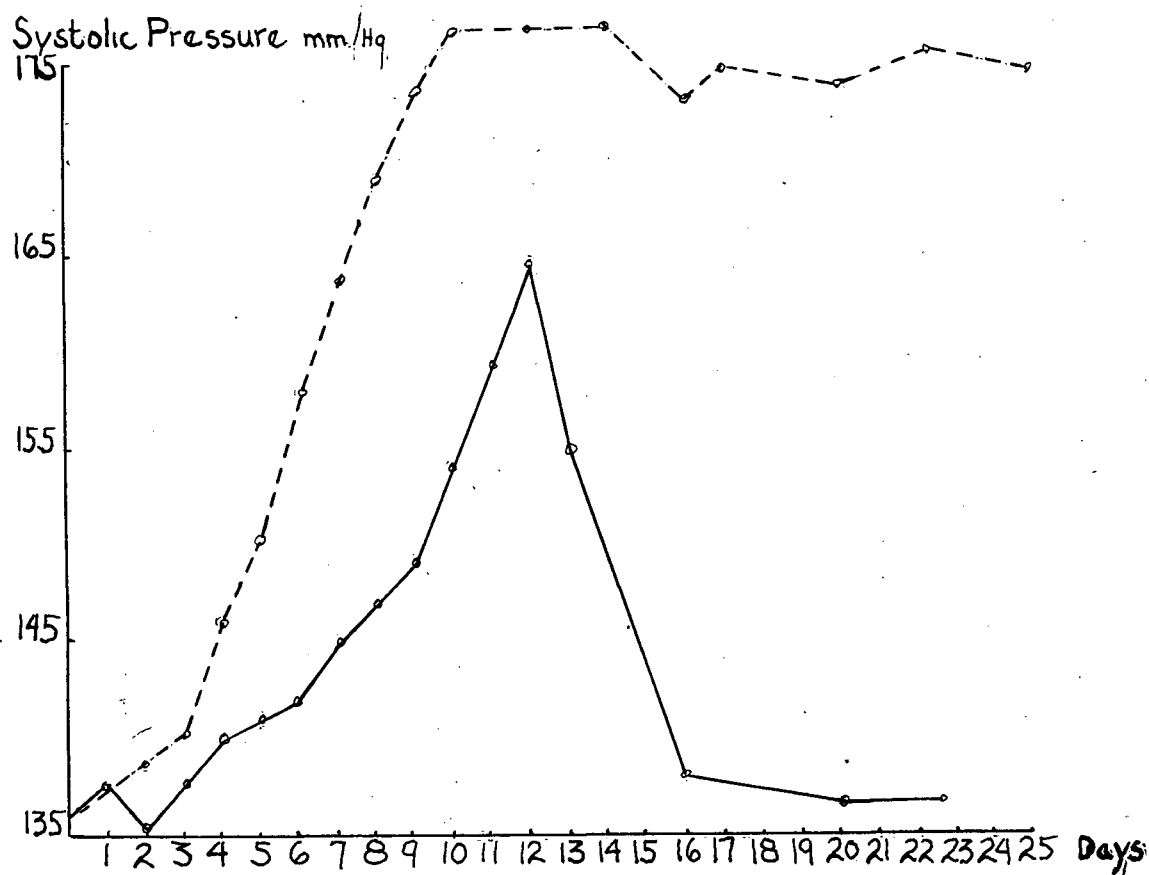
Fig. 2

The solid line represents the average systolic blood
pressure changes of 6 rats, each receiving 1.0 mgm. inj-
ections of DCA daily from day 0 to 5 inclusive.

The broken line represents the average systolic pressure
change in 8 male rats receiving excess dietary salt and
1.0 mgm. injections daily of DCA from days 0 to 13 inclus-
ive.

(3) Discussion.

Semple (52) and Fitch (20) found that one injection of 1.0 mgm. of DCA produced a transient hypertension lasting from 7 to 8 days. Despite the fact that the results of this investigation are contradictory to the results obtained by Fitch and Semple, it does not tend to invalidate their work in this author's mind.

It was puzzling to find that Rixon (61) simultaneously found that female Wistar rats (some of which were littermates to the males used in this investigation) developed a severe and chronic hypertension when injected intramuscularly with 1.0 mgm. of DCA. Rixon, on repeating the procedure at a later date, obtained no response. It is not likely that errors in blood pressure determinations were involved, as the pressure values taken by each investigator closely agreed when they were made on the same animals.

(4) Conclusions.

Chronic overdosage with desoxycorticosterone will produce hypertension in rats when excess salt is added to the diet.

(5) Summary.

Male Wistar rats were divided into three experimental groups.

The animals of the first group each received
1 intramuscular injection of 1.0 mgm. of DCA. They
showed no apparent pressor response over a 10 day period.

Those of the second group each received 1 in-
tramuscular injection of 1.0 mgm. of DCA daily for 6
days. There was a moderate transient pressor response
observed.

The animals of the third group, whose drinking
water contained 2% salt, each received 1 intramuscular
injection of 1.0 mgm. of DCA daily for 14 days. The
systolic pressure of these animals reached hypertensive
levels that were sustained without further treatment.

THE EFFECT OF ESTROGEN OVERDOSAGE ON THE BLOOD PRESSURE
OF INTACT MALE AND CASTRATE MALE RATS.

A. Introduction.

The effect of estrogens in mammals has been
a subject of considerable debate.

It is claimed (30) that in rats, hypertrophy
of the kidneys, an elevation in blood pressure and salt
and water retention follow the daily injection of large
doses of estrogen. The salt and water retention is
probably due to the adrenal corticomimetic action of
this hormone (64). Estrogens have also been claimed to
produce hydro-ureters and hydronephrosis (30) and are
apparently involved in producing the common phenomenon
of pre-menstrual edema (62). It is also common know-
ledge in medical fields that in women suffering from
chronic nephritis re-occurrence of the grosser symptons
(extensive pitting edema, increase in blood pressure,
re-appearance of albumin in the urine (?)) is associated
with the onset of mensis.

Selye (50) does not agree with the statements
above and states that the claim that folliculoids in-
crease the blood pressure in the rat has not been sub-
stantiated and that women with menopausal hypertension
often show a decrease in blood pressure. Folliculoids

exert a vasodilator effect which is readily verifiable
by direct inspection (e.g., in the rabbit ear). The
vessels of the nasal mucosa, and those of the accessory
sex organs are particularly sensitive to this effect.
It has been assumed that the action is due to a periph-
eral discharge of acetylcholine occasioned by the foll-
iculoids.

The controversial action of estrogen sponsored
the following investigation of it's effect on the blood
pressure of rats.

(1) Apparatus and Methods.

Apparatus and methods used for blood pressure
determination as previously described.

Trial 1.

Five pressure determinations were made over
a 7 day period on each of 6 male Wistar rats and the av-
erage of the readings made on each individual animal was
considered to be the animal's normal systolic blood press-
ure.

Starting on day 0, each rat received subcut-
aneously 0.5 mgm. of diovocylin. (Ciba's brand, of est-
radiol dipropionate) dissolved in 1.0 ml. of oil. The
injections were repeated daily, for 5 days. The systolic
pressure of each animal was determined on days 3, 6, 8,

13, 20, and 30.

Trial 2.

Five male Wistar rats castrated eight weeks previously were treated identically as those in Trial 1.

Trial 3.

a). Four male rats were (given each) one injection of 0.5 mgm. of estradiol in oil (diovocylin). Their individual systolic pressures were determined daily for the first five days then on days 7, 10 and 14.

b). Six male rats, 3 castrates and 3 intact animals, were each given two subcutaneous injections of ⌀0.5 mgm. diovocylin, one injection on each of two consecutive days.

(2) Results.

Trial 1.

One day after the third injection of estrogen (day 3) it was found that there had been an average increase in blood pressure of 26 mm./Hg. Determinations made one day after the last injection of estrogen revealed the average blood pressure of the six rats to be 225 mm./Hg. Two days later (day 8) the average systolic pressure was observed to have fallen back to a value of approximately 190 mm./Hg. Subsequent determinations showed that the systolic pressure rose steadily until day 20, where it tended to stabilize at a value of 230mm./Hg. (see Fig. 3)

Trial 2.

The effects of estrogen on the blood pressure of the castrate animals were found to be very similar to effects it produced in intact males. However, it is evident from the graph that the pressor response occurs more rapidly in the gonadectomized animal, although the elevation in pressure is no greater in the castrate than the intact animal (see Fig.3)

Trial 3.

a). As shown in Fig. 4, the administration of 0.5 mgm. of estrogen to 4 male rats produced no marked change in blood pressure. There was a slight indication of a transitory fall in systolic pressure.

b). The administration of 1.0 mgm. of estrogen (0.5 mgm. on 2 consecutive days) produced, as indicated in Fig. 4, a definite pressor response.

The intact males showed an initial drop in pressure averaging 8 mm./Hg. The smallest decrease was 4 mm/Hg., the greatest 14 mm/Hg. Immediately following this slight depression the pressures rose by the end of day 2 to an average value of 25 mm/Hg. above normal. The pressures dropped steadily after the second day and were found to be at normal levels by day 14.

The graph (Fig. 4) of the pressor response to 1.0 mgm. of estrogen in castrate males is incomplete, as in 2 of the 3 experimental animals a sustained pressor

response was obtained. *which* The elevated pressure of the

third animal dropped to normal levels in 14 days.

It is notable that in the castrate animals no

initial fall in pressure was detected. The systolic

pressures of the 2 animals showing the sustained elevat-

ion were found to be 165 and 190 mm/Hg. at the end of

14 days.

Further Note:

An error in the anaesthetization of two rats

(not included in the previous discussion) that had each

received three injections of 1.0 mgm. estrogen through

three days resulted in their death. Immediate autopsy

of these animals revealed a marked hyperemia of the liver,

and hemorrhagic adrenals and kidneys. The right ureter

of one of these animals was markedly enlarged.

TABLE I.

	Rat. No.	Bld. Press.	HT.WT. % Body Wt.
INTACT			
	1	226	0.44
	2	240	0.52
	3	232	0.44
	4	216	0.35
	5	210	0.39
	6	228	0.42
CASTRATES			
	1	215	0.34
	2	248	0.56
	3	220	0.39
	4	225	0.48
	5	236	0.5

Table I.

The above data represents the heart weight expressed
as % body weight of intact and castrate male rats made hyper-
tensive by estrogen overdosage.

(Normal heart weight of rats is 0.28% of body weight
as determined by Best et al. (1))

Systolic Blood Pressure mm/Hg
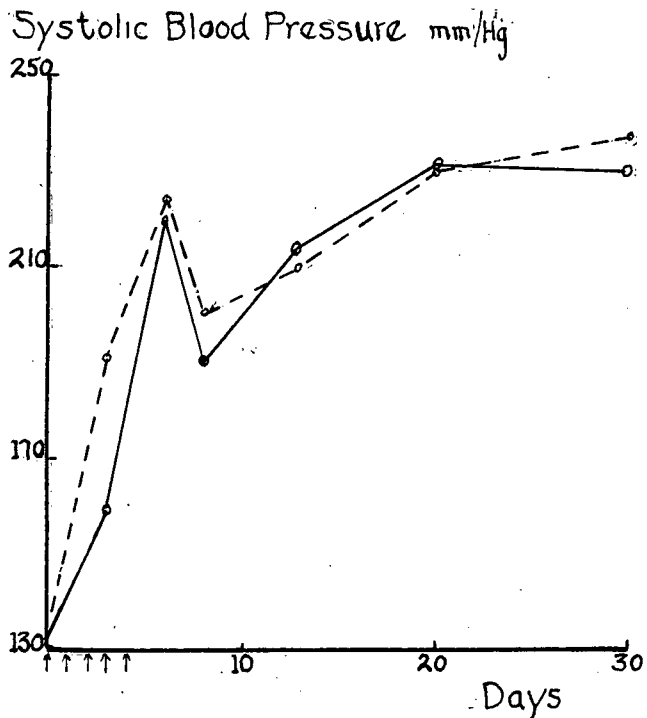
Fig. 3

The solid line represents the average increase in syst-
olic blood pressure of 6 male rats, each injected with
0.5 mgm. estradiol dipropionate at times indicated by
the arrows (↑).

The broken line represents the average increase in blood
pressure of 5 male castrate rats injected with 0.5 mgm.
estradiol dipropionate at times indicated by the arrows
(↑).

Change in Systolic Pressure mm/Hg

Days
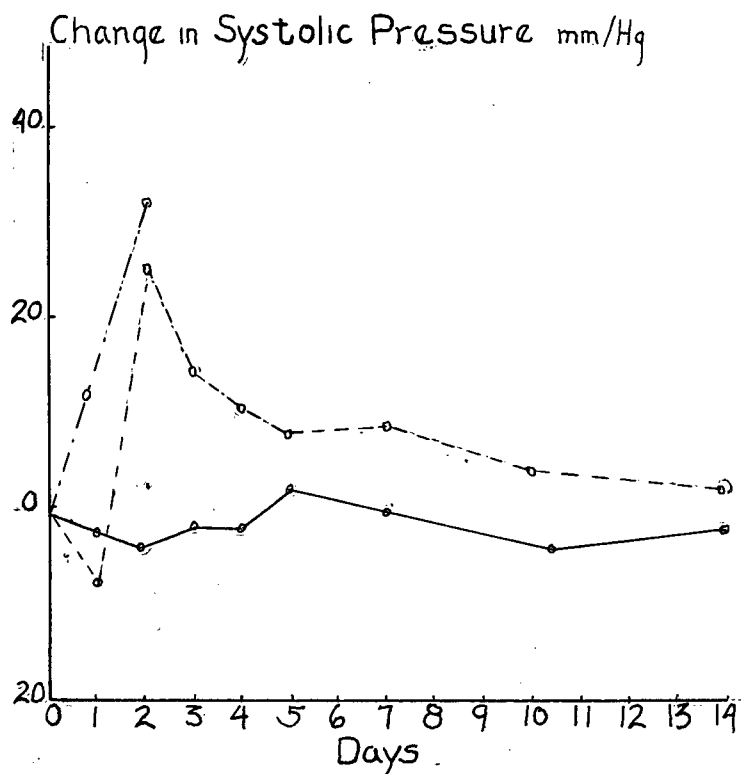
Fig. 4

The solid line represents the average systolic pressure
changes occurring in 4 male rats after 1 subcutaneous
injection of 0.5 mgm. of estradiol dipropionate on day 0.

The broken line represents the average pressure change
in 3 male rats, each receiving a subcutaneous injection
of 0.5 mgm. of estradiol dipropionate on days 0 and 1.

The broken and dotted line represents the average sys-
tolic pressure changes of 3 castrate male rats, each
receiving 0.5 mgm. of estradiol dipropionate subcutan-
eously on days 0 and 1.

Retraction of the testes occurred in all animals that received 2.5 mgm. of estrogen (in 0.5 mgm. doses) and autopsy revealed the livers to be abnormally small.

(3) Discussion.

The results of these experiments indicate that estradiol dipropionate has sustained pressor effect in male Wistar rats. The initial decrease in blood pressure found to occur after administration of this hormone is not marked enough to be considered significant. Further investigation of this depressor effect would be of interest.

(4) Conclusions.

1) Sustained hypertension can be initiated in intact male and castrate male Wistar rats by estradiol dipropionate overdosage.

2) Castration of the male rat sensitizes the animal to the pressor effects of this hormone.

3) Estradiol overdosage causes a decrease in the size of the liver.

(5) Summary.

The administration of 0.5 mgm. estradiol dipropionate daily for 5 days to each of 6 intact and 6 castrate male rats produced an average increase in their

systolic blood pressures of 100 mm./Hg. The castrate
animals were found to be more sensitive to the pressor
effects of estrogen than were the intact males.

The induced hypertension was sustained and 16
days after treatment there was no sign of the induced
condition abating. The heart weight made 40 days after
treatment indicated that the hypertension was chronic.

The administration of 0.5 mgm. of estradiol
dipropionate daily for 2 days produced a transient in-
crease in the systolic blood pressure of three male
Wistar rats. The castrate animals showed a sustained
pressor response to similar treatment. No pressor resp-
onse was evident in intact males each receiving 1 inject-
ion of 0.5 mgm. of estradiol dipropionate.

THE EFFECT OF ESTROGEN UPON EXPERIMENTAL HYPERTENSION IN MALE WISTAR RATS.

(1) Statement.

This investigation was carried out as an extension of the previous study of estrogen.

(2) Methods.

Four male Wistar rats in which hypertension had been previously induced by renal lesions resulting from nutritional choline deficiency (see choline deficiency and hypertension) were given ~~one~~ subcutaneous injection of 0.5 mgm. of diovocylin (Ciba's brand of estradiol dipropionate) daily for 4 days.

The average systolic blood pressure of these animals had been established previously at 222 mm/Hg. The range of these elevated pressures was from 218 - 226 mm/Hg.

The blood pressures following the initial injection of estradiol were determined daily for 6 days and again on the eighth, tenth and twentieth days.

(3) Results.

The systolic pressures of all 4 animals was

Systolic Blood Pressure mm/Hg
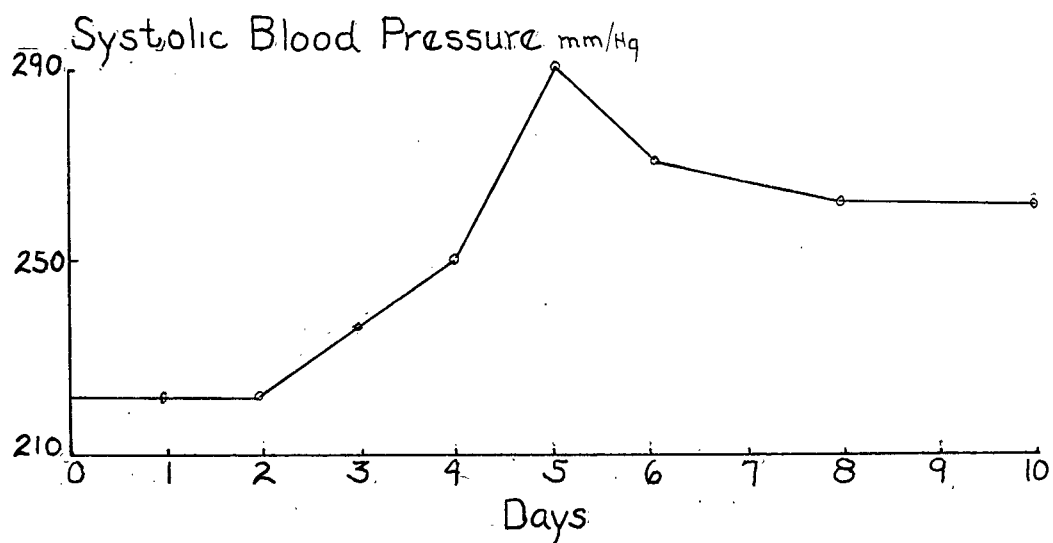
Days

Fig. 5

This graph represents the average change in the blood
pressures of 4 hypertensive male rats following the
subcutaneous administration of 0.5 mgm. of estradiol
dipropionate to each daily from days 1 to 4 inclusive.

PLATE II.

The picture on the right shows a typical skin lesion
that occurs in hypertensive rats. (The area around the
lesion has been shaved). This animal suffered hyperten-
sion induced by renal lesions and aggravated by estrogen
overdosage (The rat was anesthetized for the photo).

The picture on the right of the anesthetized animal shows
a typical haemorrhage about the eye that occurs in hyper-
tensive rats. This animal is also suffering hypertension
secondary to renal lesions and aggravated by estrogen over-
dosage.
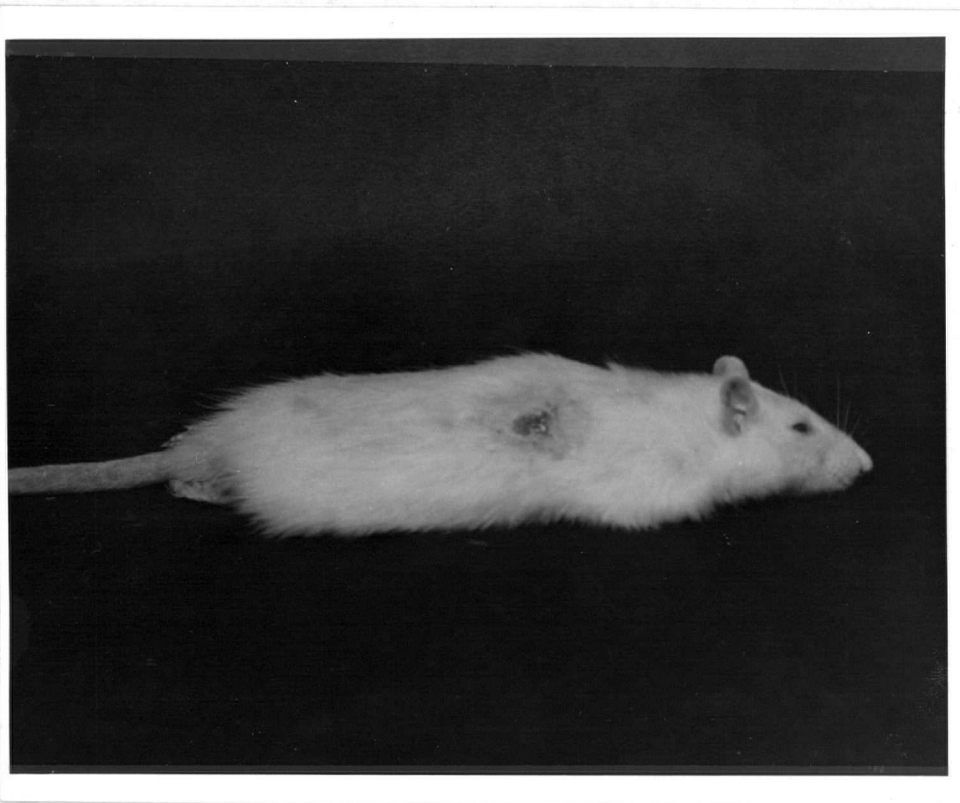
o/bserved to rise from an average value of 222 mm/Hg. to
an average value of 290 mm/Hg. (see Fig. 5) on the fifth
day. (The pressures ranged from 280 - 300 mm/Hg.)

The systolic pressures dropped from day 5 to
day 8 to an average value of 262 mm/Hg. Observations
made on day 20 revealed no change in the latter value
(262 mm/Hg.). Heart weights of these animals are given
in Table II.

TABLE II.

Rat. No.	Bld. Press.	HT.WT. % Body Wt.
1	290	0.61
2	240	0.48
3	265	0.53
4	250	0.5

Table II.

The data given above shows the heart weight expressed as
% body weight, of 4 hypertensive animals whose condition
was aggravated by estrogen overdosage. (*)

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The gross appearance of these animals indicat-
ed a general physical degeneration. There was a marked
decrease in weight, hemorrhage about the eye, scabby
skin lesions, extensive edema (in 1 animal), and diu-
resis and anorexia. (See Plate II)

(4) Conclusions.

1) Hypertension secondary to renal lesions is agg-

*....(The heart weight of normal rats is 0.28% as is shown by
Best et al (1))

ravated in male Wistar rats by overdosage with es-
tradiol dipropionate.

(5) Summary.

Four male Wistar rats with hypertension sec-
ondary to renal lesions induced by nutritional choline
deficiency were injected subcutaneously with 0.5 mgm.
estradiol dipropionate daily for 4 days and were found
to respond with a sustained increase in systolic press-
ure.

THE EFFECT OF DCA ON THE DEVELOPMENT OF HYPERTENSION SECONDARY TO RENAL DAMAGE INDUCED BY CHOLINE AVITAMINOSIS.

A. Introduction.

Best and Hartroft reported in 1949 (1) that weanling rats that were fed a diet low in choline for 6 days then placed on a normal food mixture for the remaining experimental period of 4 to 7 months, tended to develop a moderate or severe degree of hypertension during the period of observation. The hypertension was thought to be due to the renal lesions produced by such treatment. In view of these results it was decided to note the pressure changes occurring in mature rats and the effect that desoxycorticosterone acetate might have in animals whose renal tissue had been reduced in such a manner.

(1) Methods.

Eight mature male albino rats of the Wistar strain were fed a diet (low in choline and it's precursors) identical to that used by Best and Hartroft (1) (61) for 5 days and were then returned to normal stock diet. On the sixth day 4 of the 8 rats were given intramuscular injections of 1.0 mgm. each of

desoxycorticosterone acetate in oil. This was repeated on days 7 and 8. The remaining 4 animals received no further treatment.

(2) Results.

The results are represented graphically in Fig. 6.

The animals receiving the 3 injections of DCA showed an immediate increase in systolic pressure. The increase was not marked during the first $4\frac{1}{2}$ days, but had risen sharply by the sixth day and continued to rise until day 10 to an average value of 222 mm/Hg. The average systolic pressure of these animals 40 days later was 226 mm/Hg.

The animals that were subjected to 5 days of a choline deficient diet only, showed little or no increase in systolic blood pressure after 9 days on a normal diet. The pressure showed a slight increase on day 12 and was found on day 20 to be at an average value of 226 mm/Hg. On day 25 the pressure had declined to a value of 212 mm/Hg. and 40 days later was found to be at a value of 222 mm/Hg.

Heart weights are presented in Table III.

TABLE III.

Rat No.	Bld. Press.	HT.WT. % Body Wt.
1	232	0.45
2	218	0.39
3	220	0.40
4	240	0.53
5	216	0.35
6	228	0.38
7	222	0.33
8	220	0.41

Table III.

The above data represents the heart weights expressed as % of body weight for male rats 45 days after terminating 5 days on choline deficient diet.

Rats 1 to 4 received DCA the first 3 days after terminating the nutritional deficiency.

(The heart weight of normal rats is 0.28% as is shown by Best et al (1))   (of body weight)

Systolic Blood Pressure   mm/Hg.
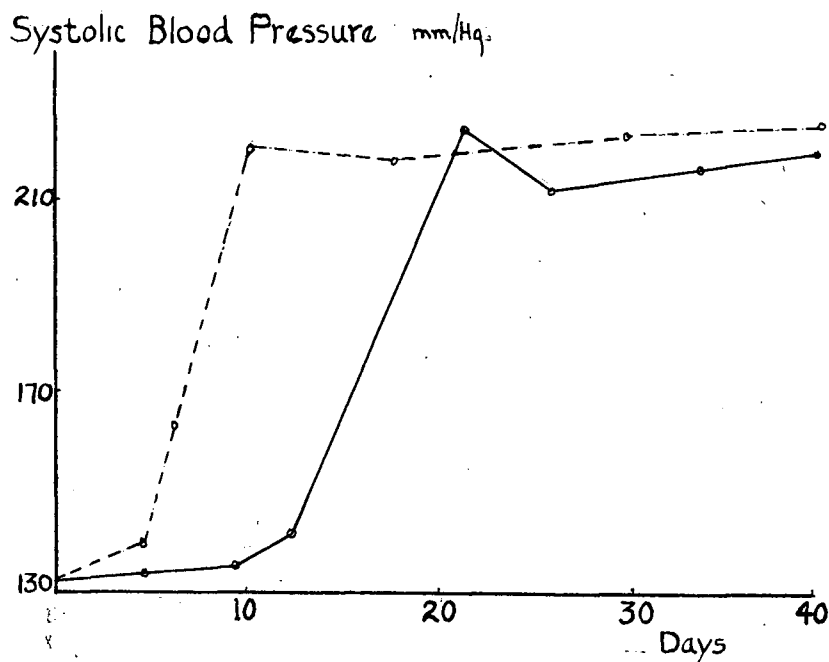
Fig. 6

The solid line shows the average changes in blood press-
ure occurring when 4 male rats were returned to a normal
diet (on day 0) after 5 days on a choline deficient diet.

The broken line represents the average increase in press-
ure of 4 male rats that each received 1.0 mgm. a day of
DCA for 3 days following their return from a choline
deficient to a normal diet.

(3) Discussion.

Best and Hartroft claim (1) that they cannot
consistently produce renal lesions by feeding mature
rats a choline deficient diet. The rats used in this
investigation were of the same strain as those used by
Best et al., the diet was prepared according to their
formula and the animals were maintained on the deficient
diet for similar, or shorter periods of time. It was
found both by Rixon (61) and me that choline deficiency
produced renal lesions in all the animals histologically
examined. The renal pathology is shown in Plates II and
III.

Hypertension was invariably produced and dev-
eloped within 3 weeks in the mature animals. Best found
that in weanlings hypertension did not generally devel-
op for several months.

Such features (as seen by Best) as hyalinizat-
ion of the glomerular loops and thickening of Bowman's
capsule are, in the opinion of Best (1), most likely the
result of high levels of intravascular pressure, and
parenchymal loss is probably attributable to the acute
dietary deficiency. However, a clear picture of the
pathogenesis of these renal lesions has not been given.

The influence of DCA in accelerating the

development of hypertension is not known. Dean and Oleson (15) have shown that there is hypertrophy of the adrenal cortex in weanling rats which exhibit the syndrome of hemorrhagic kidney. Best (1) suggests that this hypertrophy may contribute in some manner to the development of hypertension. Adrenal hypertrophy may, in this case, occur as a direct response to the stress.

(4) Conclusions.

1) A period of choline deficiency, followed by a normal diet, will produce hypertension in male Wistar rats within 3 weeks.

2) The administration of desoxycorticosterone will accelerate the production of hypertension in rats that have survived a period of choline deficiency.

(5) Summary.

Eight male Wistar rats were maintained 5 days on a choline deficient diet. The animals were returned to a normal diet and 4 of the 8 rats were given DCA injections intramuscularly. The animals receiving the DCA developed hypertension in 1/3 to 1/2 the time required for the control animals to develop the syndrome.

THE EFFECT OF STARVATION ON THE BLOOD PRESSURE OF WISTAR RATS.

A. Introduction.

Biskind and Shelesnyak (2) Biskind and Biskind (3), Singher et al (55) Shipley and Gyorgy (54) claim to have shown that vitamin B complex factors are necessary for the inactivation of estrogen and that the site of this catabolic process is in the liver. There is considerable evidence to indicate that progesterone and desoxycorticosterone are also inactivated in the liver through similar catabolic processes (43).

The conclusions drawn on the relationship between estrogen metabolism and B complex factors has been questioned by Drill and Pfeiffer (44). They point out that in the foregoing work paired inanition controls were not used and that when paired inanition controls (animals which were receiving the same amount of food but receiving the B vitamin) were used in their work, the controls showed the same response to estrogen as did the experimental animals. The authors conclude therefore that the effect of B complex deficiency is the result of concomitant inanition. With this is mind it was decided upon to observe the blood pressure effects produced by administration of DCA to rats in a

state of general inanition.

(1) Methods.

Nine male Wistar rats, 7 to 10 months old, were given no food (water ad lib.) for three days. Following this they were placed on a diet consisting of 7.0 gms. of fox chow each (*) per day for 21 days. Starting on day 8 of the enforced fast 5 animals each received an intramuscular injection of 1.0 mgm. desoxycortico-sterone acetate daily for 5 days. (The remaining 4 animals were considered controls.) The course of injections were repeated over a period of 5 days beginning on the day the animals were returned to a normal diet (days 25 to 30).

Attempts to make systolic pressure determinations during the period of starvation were discouraged by the distressing effects the anaesthetic had on the undernourished animals. The systolic pressures were read on days 31, 33, 36, and 40.

(*)....The normal weight of fox chow consumed by one rat in a day is approximately 20 gms.

(2) Results.

Ten days after the last injection of DCA the blood pressures of the animals receiving the DCA were still normal and no change in systolic pressure was

evident in the paired inanition controls. At this time
the results of the experiment were considered negative
and no further determinations were made for a period of
approximately 60 days, during which time the animals
were maintained under normal conditions.

It was surprising to the author to find that
on re-checking these animals after the 60 day period,
the blood pressures of both the experimental animals and
the controls had reached hypertensive levels. The data
is presented in the table below. It is to be noted that
the heart weights verify these findings.

TABLE IV.

Rat No.	Bld.Press.	Ht.Wt. % Body Wt.
1	230	0.53
2	210	0.42
3	165	0.35
4	220	0.51
5	210	0.40
6	218	0.39
7	165	0.30
8	215	0.4

Table IV.

In the above data the heart weights are expressed as %
body weight. The animals were found to be hypertensive
2 months after being subject to 3 weeks of a subminimal
diet. Blood pressures were determined 2 days before the
animals were sacrificed.

(*)
        -- -- -- --

*...(the heart weight of normal rats is 0.28% of body weight
   as shown by Best et al (1))

At the time of writing histological sections
of the organs have not been completed. However, there
is gross evidence of fatty infiltration in the liver,
accompanied by hemorrhagic lesions and small areas of
focal necrosis. There is also gross evidence of renal
lesions and possibly enlargement of the adrenal gland.

(3) Discussion.

It is pertinent in this experiment that both
the undernourished animals receiving desoxycorticoster-
one acetate and the paired inanition controls developed
hypertension. Thus the exogenous cortical hormone was
not apparently responsible for the pressure changes.
It is also of interest to note that Rixon (61) found no
such pressure changes in female Wistar rats starved to
a lesser degree and for a shorter period of time.

The factors involved in the production of
this syndrome are not known to the author. It would
appear reasonable to assume that the condition resulted
from irreversible pathological changes, resulting from
a general avitaminosis. In the light of recent findings
of Best and Hartroft (1) and the apparent gross path-
ology of the liver and kidneys of these animals, it
appears that the changes may be due to renal lesions

produced by a choline deficiency incurred during inanition.

(4) Conclusions.

1) A prolonged period of inanition will produce hypertension in male Wistar rats.

2) Desoxycorticosterone does not markedly influence the development or intensity of the hypertension thus produced.

(5) Summary.

Nine male Wistar rats were placed on a subminimal diet for 30 days. Five animals received intramuscular injections of DCA for 5 days during the period of inanition and for 5 days immediately following it. Four animals received no hormonal treatment. Both the control and experimental animals were found to be hypertensive 60 days after their return from a subminimal to a normal diet.

THE EFFECTS OF ANTIHISTAMINES ON THE BLOOD PRESSURE

OF MALE WISTAR RATS.

A. Introduction.

Observations on parabiotic twins led Grollman
(30) in 1946 to the conclusion that the role of the
kidney in hypertension is not one of actively secreting
a pressor substance, but rather one of failing to form
an antipressor substance. In 1947 Shorr, Zweifach
and Furchgolt (56) (57) (58) reported observation of
an apparent renal pressor-depressor system (see - nature
of pressor mechanism). They postulated that a disbal-
ance of this mechanism might account for either hypo-
tension or hypertension.

Histamine is a very potent material producing
marked pharmacologic effects. Upon intravenous in-
jection 0.1γ suffices to produce a marked fall in blood
pressure in ether-anaesthetized cats. 1γ produces sev-
ere hypotension even in humans. It is not therefore,
extravagant to postulate that this substance may func-
tion in normal animals as a factor involved in a system
that controls vascular activity; nor is it too imagin-
ative to assume that the loss of histamine from the
circulating blood may allow vasoconstriction to occur
with a subsequent increase in blood pressure.

It is also notable that histamine has been used successfully to cause peripheral vasodilatation in the treatment of certain vascular diseases (70).

With the information above in mind, it was decided to investigate the pressor changes that might occur in rats after the administration of some of the commercial antihistamic compounds.

(1) Apparatus and Methods.

The apparatus and methods used in determining blood pressures have been previously described in this paper (see - apparatus and methods-Introduction)

Trial 1.

a) The normal pressures of white male Wistar rats numbered 1 to 10 were determined daily over a 4 day period. The average value of the 4 readings taken on each rat was accepted as the approximate normal systolic pressure of the animal.

On day 0, rats 1 to 5 received intraperitoneal injections of 1 cc. physiological saline and were thus considered as controls. Rats 6 to 10 received intraperitoneal injections of 1.0 mgm. of the antihistamine, antistine (Ciba's brand of phenylbenzylaminomethyl-imidazoline hydrochloride). This procedure was repeated every second day (The antistine solution was freshly

prepared before each injection) until 5 injections had
been given each animal.

b) The procedure followed was identical to that of part
a above, with the exception that 0.2 mgm. injections of
antistine were given rather than 1.0 mgm.

Trail 2.

a) The normal systolic pressure of 5 male Wistar rats
was determined as in Trial 1. Each animal was then
given one injection intraperitoneally of 1.0 mgm. of
antistine dissolved in 1 ml. of physiological normal
saline. The systolic pressure of each rat was determ-
ined $1\frac{1}{2}$ hours after the antistine injection and then on
days 3, 4, 7, 12, 14, 16, 18, and 20 after the initial
injection.

b) Procedure a above was repeated on 3 male rats, us-
ing 0.5 mgm. of pyribenzamine dissolved in 1.0 ml. of
physiological saline, in place of antistine.

c) Procedure a was repeated on 2 male Wistar rats with
the antistine injected subcutaneously, instead of intra-
peritoneally.

Trial 3.

Four male Wistar rats were anaesthetized and their
normal systolic pressure determined. Each rat then

received an intraperitoneal injection of 1.0 mgm. of antistine dissolved in physiologically normal saline.

Blood pressure determinations were made on each animal 5 minutes after receiving the antistine, again at 10 minutes, and thereafter every 10 minutes throughout the period of an hour. A final reading was made at the end of the second hour.

Trial 4.

a) The normal pressure of 3 rats were determined. The animals then received one intramuscular injection each of 0.1 mgm. of antistine dissolved in 0.1 ml. of water. Pressure determinations were made 2, 18, 34, and 50 hours after the initial injection. A final reading was made on each animal 7 days later.

b) Procedure a was repeated using intramuscular injections of 0.01 mgm. of antistine. Pressure determinations were made on each of the 3 rats 2, 10, 24, 32 and 48 hours after they received the antistine.

Trial 5.

The normal blood pressure of 6 students (5 males and 1 female) between the ages of 22 and 30 years was established for each individual by taking five pressure determinations at 2 hour intervals throughout a day in which they remained relatively quiet and spent most of

their time sitting at a desk. On a day that their
activities were similar to those previously described,
each student was given orally one tablet of 100 mgm.
antistine at 9 AM, at which time their blood pressure
was again recorded. Blood pressure values for each
student were determined 2, 6, 8, 27, and 43 hours after
administration of the antistine.

(2) Results.

Trial 1 (results)

The results (as represented graphically in
Fig. 7) show that after the injection of 1.0 mgm. of
antistine, the blood pressures of the experimental
animals had risen in 24 hours to an average value of
220 mm./Hg. from an average value of 132 mm./Hg. The
greatest increase in pressure was 100 mm./Hg. shown in
an animal whose normal pressure was 140 mm./Hg. and
whose pressure reached a value of 240 mm./Hg. at the end
of the first 24 hours. The smallest increase in press-
ure was 55 mm./Hg. (135-190 mm./Hg.). It was found
that with further injections of antistine, blood press-
ure variations decrease and the pressures tended to
stabilize at an average value of approximately 200 mm/Hg.
(see Fig. 7)

Forty-eight hours after the last injection of
antistine the average systolic pressure dropped from a

value of 200 mm./Hg. to 185 mm./Hg. and rose slowly

throughout a period of 6 days to stabilize itself at an

average value of 200 mm./Hg. The highest individual

value was 220 and the lowest 188 mm./Hg.

It was also found that control animals injected

several times with 1.0 ml. of saline in place of 1.0

ml. of a 1.0 mgm. solution of antistine, showed no sig-

nificant change in blood pressure over a period of 20

days. The greatest average variation in the systolic

pressures of these animals was 6 mm./Hg. The greatest

individual variation was 10 mm./Hg., which occurred

twice in one animal and once in another over a period of

 20 days.

b)   It was found that repeating procedure a but

modifying the individual doses of antistine to 0.2 mgm.

produced pressure variations which did not differ app-

reciably from those obtained in part a.

Trial 2. (results)

a)   It was observed (see Fig 7) that one intra-

peritoneal injection of 1.0 mgm. antistine apparently

produced it's maximum pressure response in Wistar rats

1½ to 2 hours after injection, at which time the average

systolic pressure of the 5 experimental animals was

225 mm./Hg. The pressures ranged from 210 - 250 mm./Hg.

Over a period of 7 days the blood pressure dropped with

decreasing rapidity to a value of 175 mm./Hg. and rose

slowly again during the next 7 days to an average value of 190 mm./Hg. at which point they tended to stabilize. The pressures of the animals at the end of 20 days ranged from values of 180 - 220 mm./Hg. with the greatest number of values concentrated between values of 185 - 195 mm./Hg.

It is pertinent that one injection of 1.0 mgm. antistine will apparently produce an irreversible hypertension in male Wistar rats (see also Trial 3 results).

b)   It was found that antihistaminic substance pyribenzamine produces blood pressure changes identical to those produced by antistine.

c)   Antistine injected subcutaneously is as effective in raising the blood pressure as it is after intraperitoneal administration.

Trial 3 (results)

Observations showed (see Fig 8) that immediately following an intraperitoneal injection of 1.0 mgm. antistine the blood pressure of a male Wistar rat falls to a value markedly below normal and then proceeds to increase over a 2 hour period to acute hypertensive levels. The blood pressures of these experimental animals fell to an average value of 90 mm./Hg. in 10 minutes after which time they rose steadily for 2 hours

to an average value of 215 mm./Hg. The lowest pressure recorded was 80 mm./Hg. and the highest 235 mm./Hg. The normal values were all 133 mm./Hg   .

As a partial confirmation of Trial 2, part a, the blood pressures of these animals were read after 23 days and found to be still at hypertensive levels.

Trial 4.(results)

a)   An intramuscular injection of 0.1 mgm. of antistine caused an average elevation of systolic blood pressure in male Wistar rats of 29 mm./Hg. The systolic pressure then dropped slowly but steadily over a period of 48 hours to a value of 14 mm./Hg. above the average normal pressure. Pressure determinations made one week later revealed that the systolic pressure of one of the animals had returned to normal, one remained 10 points above normal, and the third was apparently hypertensive. (systolic pressure - 170 mm./Hg.) (see Fig.9)

b)   It was observed that 2 hours after an intra-muscular injection of 0.01 mgm. antistine there was an average decrease in blood pressure of 14 mm./Hg. The systolic pressures rose slowly and 24 hours after treat-ment they had reached an average value 6 mm./Hg. above normal. At the end of 40 hours the systolic pressures of the 3 animals had returned to normal (See Fig. 9).

TABLE V.

Rat No.	Bld. Press.	Ht. Wt. % Body Wt.
6	220	0.40
7	210	0.36
8	205	0.36
9	195	0.37
10	185	0.35
11	200	0.36
12	190	0.39

Table V.

The data above represents the heart weights expressed as % of body weight of some of the experimental animals treated with antihistamine.

(The heart weight of normal rats is 0.28% of body weight as shown by Best et al (1))

Trail 5. (results)

The oral administration of 100 mgm. antistine apparently caused a decrease in blood pressure of 6 humans averaging 15 mm./Hg. The drop in pressure was evident at the end of three hours after which time it rose steadily and was found to be normal 26 hours after the drug was administered (See Fig. 9)

It is remarkable that a seventh student (not included in the above trial) consistantly showed an increase in blood pressure of 20 mm./Hg. after taking 100 mgm. antistine orally.

(3) Discussion.

The pressor effects of antihistamine are most simply explained as occurring through the loss of the vasodepressor, histamine. The exact nature of anti-histamic action is not known, although it is known that certain of these substances antagonize the action of other vasodepressors such as acetylcholine (42). Response to antihistamines varies with the species, however it is not generally accepted that it will elicit press-or response. Drug manufacturers claim that with a few exceptions, blood pressure changes have not been evident in individuals who regularly use antihistaminic preparations.
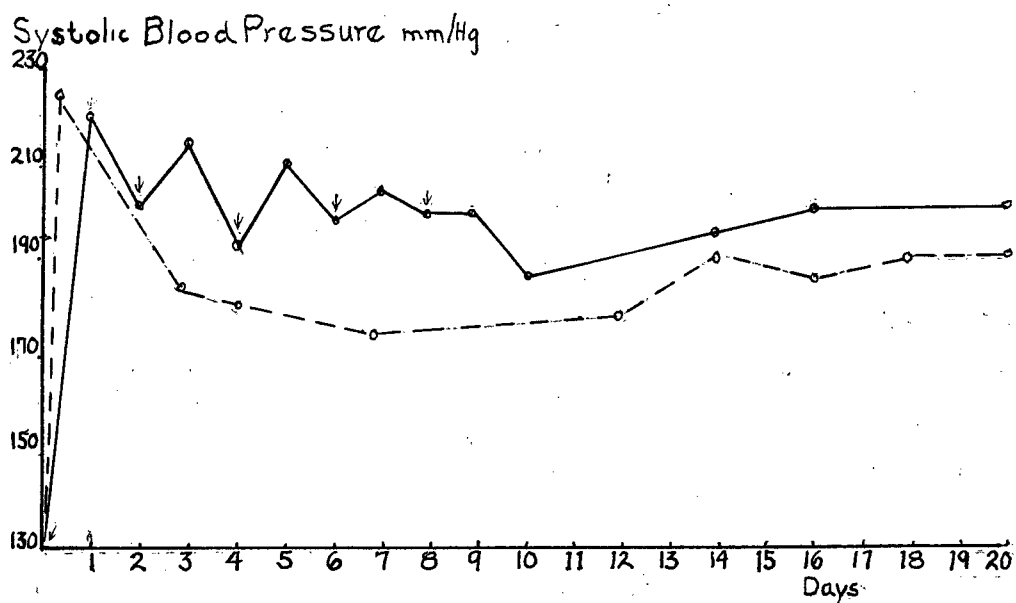
Fig. 7

The solid line represents the average systolic pressure
changes of 5 male rats injected intraperitoneally with
1.0 mgm. of antistine at time signified by the arrows
(↓). (See trial 1a)

The broken line represents the average systolic pressure
changes of 4 male rats receiving one intraperitoneal
injection of 1.0 mgm. of antistine on day 0.(see trial
2a)

Systolic Blood Pressure mm/Hg
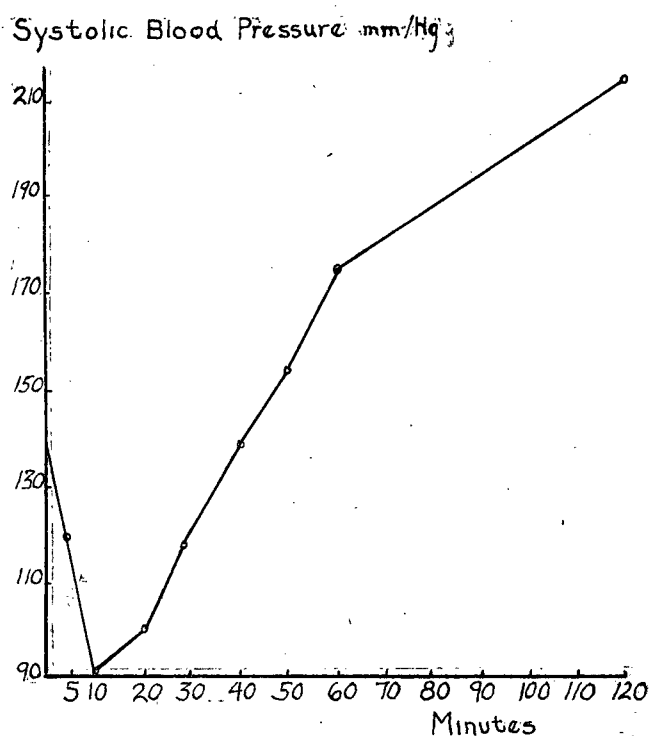
Fig. 8

The curve represents the average change in systolic press-
ure of 4 male rats over a 2 hour period immediately foll-
owing the intraperitoneal administration of 1.0 mgm. of
antistine.

Change in Systolic Blood Pressure mm/Hg

Hours
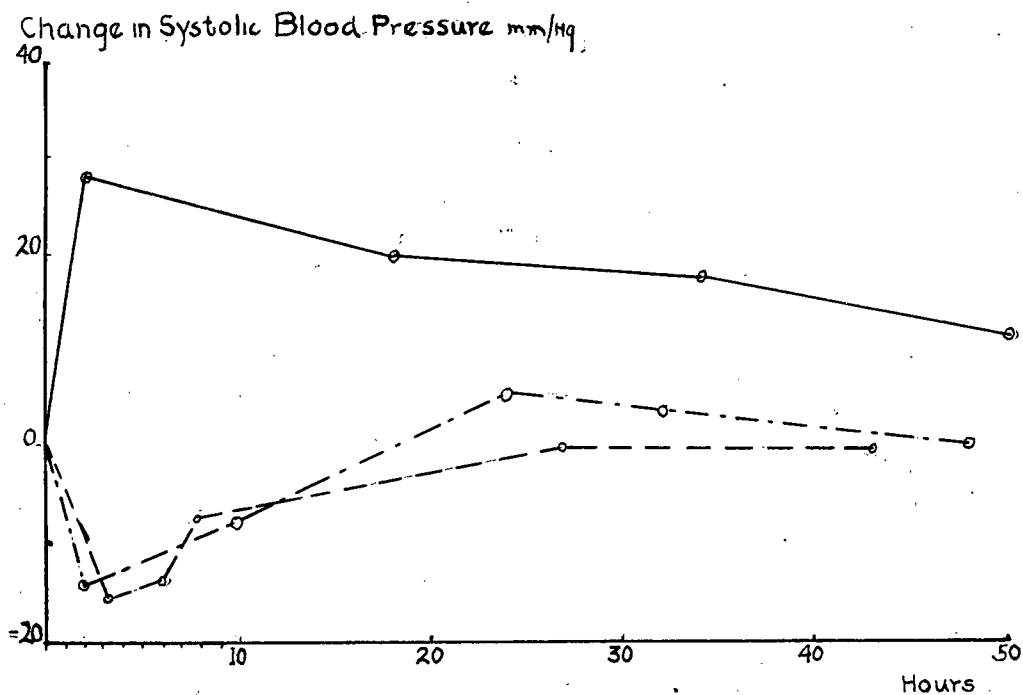
Fig. 9

The solid line represents the average change in systolic pressure of 3 male rats receiving 0.1 mgm. of antistine intramuscularly (see trial 4a).

The broken line represents the average pressure changes in 3 rats receiving one intramuscular injection of 0.1 mgm. of antistine (see trail 4b).

The curve consisting of a broken and dotted line represents the average pressure change in 6 humans after oral administration of 100 mgm. of antistine. (see trial 5)

If this compound imitates the action of certain adrenal cortical factors it could possibly cause functional changes in the organ (cortex) and work in an insidious and detrimental fashion. It appears that the physiological response to this compound should be further investigated.

Recently, antihistamines have been used in the treatment of chronic nephritis because the disease exhibits characteristics typical of an allergy (41). Histological sections of the kidney of animals used in this investigation have not yet been expertly examined. However, from the general results thus far obtained, the use of antihistamines in the treatment of nephritis is contra-indicated.

(4) Conclusions.

1. A single intraperitoneal injection of 1.0 mgm. of antistine or pyribenzamine will produce chronic hypertension in white male Wistar rats.

2. Repeated injections of 1.0 mgm. antistine do not appear to markedly augment the changes induced by a single injection of the same amount.

3. The administration of (small) amounts of antistine to both rats and humans causes a slight drop in the systolic blood pressure.

<u>4</u>. The drop that precedes the elevation of blood
pressure, when 1.0 mgm. antistine is administered
to rats, and the^Non-sustained hypotension that occurs
after administration of very small amounts to
both rats and humans appears to be due to the
intrinsic action of antistine as a vaso-depressor.

<u>5</u>. The elevation in blood pressure induced by an-
tistine is presumably due to the loss of histamine.
If this is true, the loss of a vasodepressor mat-
erial from the blood is as pertinent to the init-
iation of hypertension as the increase in circul-
ating vaso-excitor material.

<u>6</u>. Indiscriminate use of antihistaminic compounds
may be exceedingly dangerous.

(5) Summary. (as stated in Conclusions)

THE FACILITATION OF THE TRUETA SHUNT BY DESOXY-
CORTICOSTERONE ACETATE AND BY ANTIHISTAMINE

A. Introduction.

The results of an experiment originally per-
formed for academic interest only, led to the following
investigations. During the laboratory exercise des-
igned to illustrate the Trueta shunt (see Nervous Factors
in Hypertension) it was found that faradic stimulus of
very low intensity applied to the splanchnic nerve
plexus surrounding the renal artery produced a complete
blanching of the kidney of one experimental animal,
while a stimulus of the same intensity elicited no res-
ponse from other animals (rats). The rat showing a
marked response was an animal that had been treated a
few days previously with desoxycorticosterone (for an
experiment that could not be completed). Speculation
over the possiblity that the hormone might have some
influence on the induction of the renal shunt of Trueta
led to further investigation.

(1) Apparatus and Methods.

The faradic stimulus was applied with a silver
tipped electrode connected to a Harvard inductorium

which was in turn connected (to give a continuous shock)
to one 1½ volt dry cell.

The stimulus used was one that would just
elicit sensation when the thumb and index finger were
moistened with saline and applied to the secondary term-
inals. When this stimulus had been obtained the sec-
ondary coil was left intact throughout all the exper-
iments.

Observations were made by exteriorizing the
left kidney of all animals and applying the stimulat-
ing electrode to the renal artery about 1/8 of an inch
from the kidney. In each case 3 stimuli were given of
approximately one second duration and spaced one sec-
ond apart. The animals were anaesthetized with
nembutal.

Trail 1.

a) Five intact male rats were treated as above and ob-
served for signs of blanching in the surface of the kid-
ney. These animals were considered as controls.

b) Five male rats that had each received 0.5 mgm. des-
oxycorticosterone intramuscularly each day for 4 days
preceding the experiment were stimulated and observed
for renal pallor.

c) Five male rats were treated as above 3 hours after

they had each received 1 intraperitoneal injection of 0.5 mgm. of antistine dissolved in 0.5 ml. of physiological normal saline.

(2) Results.

Trial 1.

a) In no case was **renal blanching obvious** in the intact male rats after stimulation of the splanchnic plexus.

b) and c)

In every case where the animals had received desoxy-corticosterone acetate or antistine, marked blanching of the surface of the kidney was evident after stimulation.

(3) Discussion.

The above experiment has been through necessity, crudely performed, and is by no means conclusive. However, it does appear that on the basis of these results, further investigation into the matter would be of great interest. Trueta (63) states that there is marked individual variation in the ease with which one can normally obtain this shunt. If the adrenal cortical hormones are involved in such a manner it would possibly elucidate the relationship that apparently exists between hypertension and the adrenal cortical hormones.

(4) Conclusions.

Adrenal cortical activity may be associated with the mechanism controlling the "Trueta Shunt".

(5) Summary.

Animals treated with desoxycorticosterone acetate or with antihistamine (antistine) appeared to be more responsive to a stimulus eliciting the renal vasacular shunt (of Trueta) than animals receiving neither of these substances.

THE EFFECT OF DESOXYCORTICOSTERONE ACETATE ADMINISTRATION
ON THE PRESSOR RESPONSE TO ADRENALINE IN THE RAT.

A. Introduction.

Adrenalectomy decreases the size of the heart
and causes a fall in blood pressure. It also sensitizes
animals to the hypotensive action of various drugs (51)
and particularly to histamine (51a).

It has also been observed by Ellinger (16)(17)
that mice irradiated with lethal doses of X-rays, dev-
eloped characteristic pathological conditions, including
fatty degeneration of the liver. These changes, it was
determined, were the result of the elaboration of total
body tissue breakdown products, the most important of
which was histamine, or a histamine-like substance.

The daily administration of DCA exerted a
protective action and brought about a decrease in the
mortality rate. Fitch (20) and Semple (52) working in
this laboratory, reported that the effects of DCA over-
dosage could be antagonized by co-incident administrat-
ion of histamine.

It is generally accepted that histamine will
antagonize the action of adrenaline. It was felt that
since DCA appeared to have antihistamic properties that

it might also augment the vascular response to pressor agents such as adrenaline. It was also considered that since adrenaline will elicit the "Trueta Shunt" that investigations along these lines might aid in throwing some light upon the factors influencing renal vascular activity.

(1) Methods.

Eight male Wistar rats were each given one intramuscular injection of 1.0 mgm. DCA daily for 4 days. One day after the first dose of DCA each of the 8 rats was anaesthetized and the blood pressure changes determined over aperiod of five minutes immediately following subcutaneous administration of 0.01 mgm. of adrenaline per kilogram of body weight. Pressor changes subsequent to adrenaline administration were also observed on 6 control rats (not receiving DCA). The observations were repeated 4 and 6 days after the initial injection of DCA.

(2) Results.

The results are shown graphically in Fig. 9. It is to be noted that the animals receiving the DCA showed a greater response to adrenaline than did those receiving no DCA.

(3) Discussion.

Increase in Systolic Pressure mm/Hg

Days
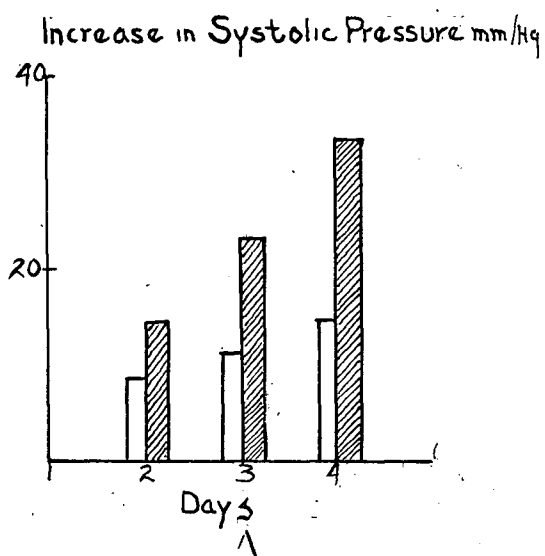
Fig. 10

The blank bar represents the average increase in blood
pressure of 6 intact male rats following the subcutan-
eous injection of adrenaline.

The lined bar represents the average increase in pressure
following the subcutaneous injection of adrenaline to male
rats pre-treated with intramuscular injections of DCA.

The time duration of the pressor response was very short-lived and in most cases the animals' systolic pressure rose and dropped to normal levels within 5 minutes. The animals could not be observed for periods over 5 minutes after adrenaline administration, as it tended to bring them out of the anaesthetic.

A very interesting side effect was observed to occur. Four of the animals receiving the DCA and adrenaline became chronically hypertensive. The systolic pressures ranged from values of 165 to 190 mm./Hg. The heart weights taken 45 days after the initiation of this hypertension verify these findings (See Table V). No incidence of hypertension occurred in the 6 control animals and previous work (Effects of DCA on Systolic Pressure of Rats) shows that DCA given in the amounts used in this investigation will not initiate a sustained hypertension.

(4) Conclusions.

Desoxycorticosterone acetate administration to male Wistar rats appears to increase the animals' pressor response to adrenaline.

(5) Summary.

The increase in systolic blood pressure following adrenaline administration was found to be greater

in male Wistar rats receiving DCA than it was in rats not pre-treated with DCA.

SYNTHESIS

It is interesting to note from this work and
from the work of others previously mentioned that liver
damage appears more or less as a constant feature in the
initial stages of hypertension (regardless of it's et-
iology). The exact nature of the role played by the
liver in the "detoxification" of the steroid hormones is
obscure but it is generally accepted that it is the site
of steroid catabolism (43).

Several workers have shown that estrogen,
desoxycorticosterone and progesterone are less active
when given via the liver and more active in the animal
after hepatectomy. It has also been shown that dietary
factors influence steroid metabolism and that the action
of these hormones is enhanced by general inanition and
by certain avitaminoses.

It has been observed that estrogen will cause
a reduction in the size of the liver (see Est. and Blood
Pressure), and that DCA will cause degenerative changes
(60) in the liver such as fatty infiltration, hyperemia,
focal necrosis, and hemorrhagic lesions.

Demonstration of a hepatic vasodepressor subs-
tance has been claimed in recent years by several inves-
tigators (7, 10, 56, 57, 58, 59, 72).

In view of the foregoing information, the following chain of events could conceivably occur:-

1) A nutritional deficiency renders the liver incapable of metabolising certain steroid hormones.

2) Normal concentrations of these steroids under these circumstances become toxic to the liver (and possibly the kidney) and initiate damage.

3) The damage could constitute a stress that occasions further steroid secretion from the adrenal cortex and aggravates the damage (vicious cycle).

4) The damaged liver becomes incapable of elaborating vasodepressor material and subsequent vasoconstriction and hypertension occurs, and/or the failure of the liver to "detoxify" steroid hormones (particularly corticoids) allows them to reach nephro-toxic levels. It would be of interest to know whether or not hypertension is preceded by liver damage or liver dysfunction.

There seems to be little doubt that the inherent action of estrogen is one of lowering the blood pressure (via vasodilatation) (50). However, the secondary pressor effect appears to be due to the corticomimetic action of this compound (64) (30).

The remarkable feature of this hormone is that

it has, in this investigation shown itself to be more
active in raising the blood pressure than has DCA, and
that such pressor effects are not dependent on the salt
intake of the experimental animal. If it causes stim-
ulation of the entire adrenal cortex and·the secretion
of several cortical factors, it may prove true that one
of these factors has a much greater pressor activity
than has desoxycorticosterone. In this regard, it is
interesting to note that Selye and others have given no
adequate account of why salt is such an important factor
in the production of nephrosclerosis and hypertension
through DCA overdosage. An explanation of the influence
of salt is suggested below.

The action of desoxycorticosterone is to main-
tain the balance of electrolytes in the blood. It
affects the retention of sodium and the excretion of
potassium (35). Kendall (35) has shown that adrenalec-
tomized rats can be maintained indefinitely under labor-
atory conditions when large salt supplements are added
to their diet. It is logical to assume therefore, that
the desoxycorticosterone requirements of the organism
decrease with an increase in salt intake. If an animal
is given large amounts of sodium chloride and simultan-
eously overdosed with DCA it would appear that the horm-
one, unless metabolized to some other compound, would
induce sodium retention and that the sodium levels in

the blood would rise rapidly and violently disturb water
and electrolyte balance. The effect upon the organism
would be extremely detrimental if not fatal (35). This
latter syndrome does not occur probably because the ex-
cess of hormone causes a metabolic mechanism to convert
it to another hormone of similar structure but with diff-
erent activity.

It is the feeling of this author that DCA is
not in itself responsible for the pressor changes that
are attributed to it and that another cortical factor
is involved.

It has previously been suggested that vascular
reactivity may be involved in the etiology of hyperten-
sion (see - Facilitation of Trueta Shunt, The Influence
of DCA on Pressor Response to Adrenaline).

Briefly stated, the theory suggests that a
lack of a vasodepressor material (such as histamine) in
the blood augments vascular activity and facilitates
vasoconstriction, and that cortical hormones antagonize
in some manner the vasodepressor action. It was observed
in the course of these investigations, renal cortical
blanching (vasoconstriction) was more easily stimulated
after the administration of DCA to the experimental anim-
al and the DCA increased the pressor response to adrenal-
ine.

There may be more than a casual relationship between these phenomena and the Trueta shunt. If vasoconstriction was augmented by either DCA or a lack of histamine (or similar substance) it would be expected that vasoconstriction in the cortex of the kidney would occur more easily and more frequently, thus producing renal ischemia and consequent renal damage.

Renin can be detected in the blood during the initial stages of hypertension, but cannot be detected during the later phases of hypertension. It has been claimed that pressor agents other than renin can be demonstrated in the blood of chronic hypertensives, but the claims are not well substantiated and not at all convincing. It appears as though renin functions primarily to raise the blood pressure to the levels required to ensure adequate renal circulation only for the time it takes for another pressure increasing mechanism (adrenal cortex responding to stress?) to become functional.

SUMMARY

1.   Male Wistar rats were divided into 3 experimental groups.

a)   The 8 animals of the first group each received 1 intramuscular injection of 1.0 mgm. of desoxycortico-sterone acetate. Blood pressure determinations made over a 10 day period revealed no pertinent pressor changes.

b)   The 6 animals of the second group each received 1 intramuscular injection of 1.0 mgm. desoxycorticosterone acetate daily for 6 days. A transient increase in the systolic pressure of each rat was observed. The highest pressure level was 165 mm./Hg. and occurred in 12 days. All pressures had returned to normal by day 16.

c.)   The 8 animals of the third group whose diet contained supplementary salt, were each injected intramuscularly with 1.0 mgm. of desoxycorticosterone daily for 14 days. The systolic pressure of the animals reached an average value of 177 mm./Hg. in 17 days, dropped to an average value of 170 mm./Hg. on the twentieth day and tended to remain at this point indefinitely.

2. a)   The administration of 0.5 mgm. of estradiol dipro-pionate daily for 5 days to each of 6 intact and 6 castrate male Wistar rats produced an average increase

in the systolic blood pressure of 100 mm./Hg. The cas-
trate animals were found to be more sensitive to the
pressor effects of estrogen than were the intact males.
The induced hypertension was sustained without further
treatment.

b)   The administration of 0.5 mgm. of estradiol dipro-
pionate daily for 2 days, produced a transient rise in
the systolic blood pressure of 3 intact male rats.
Castrate male rats treated similarly showed a sustained
pressor response.

c)   One injection of 0.5 mgm. of estradiol dipropionate
to each of 4 intact male Wistar rats appeared to produce
a slight transient decrease in blood pressure.

3.
        Four male Wistar rats with hypertension second-
ary to renal lesions induced by a nutritional choline
deficiency were injected subcutaneously with 0.5 mgm. of
estradiol dipropionate daily for 4 days and were found
to respond with a sustained increase in systolic blood
pressure.

4.
        Eight male Wistar rats were maintained 5 days
on a choline deficient diet. The animals were returned
to a normal diet and 4 of the 8 rats were each given 1
injection daily, for 3 days, of 1.0 mgm. of desoxycortico-
sterone acetate. The animals receiving the hormone

developed hypertension in 1/2 to 1/3 the time required for the control animals to develop the syndrome.

5. Nine male Wistar rats were placed on a subminimal diet for 30 days. Five animals received intramuscular injections daily of 1.0 mgm. desoxycorticosterone acetate for 5 days during the period of inanition and for 5 days immediately following it. Four animals received no hormonal treatment. Both the starved animals receiving desoxycorticosterone acetate and the starved controls were found to be hypertensive (0 days after their return from the subminimal to the normal diet). The hormone apparently had no effect. The blood pressure change was believed to be the result of the renal lesions that were found to be present.

6. a) Five rats each receiving 1 injection of 1.0 mgm. of the antihistamine, antistine, every second day until 5 injections had been given each animal, showed an immediate increase in systolic pressure to an average value of 220 mm./Hg. that was little affected by further antihistamine administration. The blood pressure change was sustained indefinitely with no further treatment.

b) One intraperitoneal injection of 1.0 mgm. of antistine was given each of 5 male Wistar rats. It was observed that the maximum pressure response occurred 1½ to 2 hours after injection, at which time the average systolic

pressure of the 5 animals was 225 mm./Hg. Within a period of 20 days the average systolic pressure decreased to 175 mm./Hg. and rose again to an average value of 190 mm./Hg. where it remained. Thus chronic hypertension was produced by 1 injection of 1.0 mgm. antistine.

c.) The blood pressure changes in 4 Wistar rats that occurred immediately following antistine injection were observed periodically throughout 2 hours. It was found that following these injections of antistine the blood pressure dropped immediately to abnormally low levels and then increased to hypertensive levels within 2 hours.

d) An intramuscular injection of 0.1 mgm. of antistine to each of 3 rats caused an average elevation in systolic blood pressure of 20 mm./Hg. The pressures returned to normal values within 48 hours. An intramuscular injection of 0.01 mgm. of antistine to each of 3 male Wistar rats caused a temporary decrease in blood pressure of 14 mm./Hg. The systolic pressures were found to be normal after 40 hours.

e) The oral administration of 100 mgm. antistine to 6 humans caused an average decrease in blood pressure of 15 mm./Hg. The blood pressure of the subjects was normal 26 hours after the drug was administered.

f) Pyribenzamine was found to produce the same effects

as antistine. These compounds were also found to be as
active when given subcutaneously as when given intra-
peritoneally.

7.   Fifteen male Wistar rats were divided into 3
groups. One group acted as controls, the second received
intramuscular injections of desoxycorticosterone acetate
and the third received an intraperitoneal injection of
antihistamine.

The nerves surrounding the renal artery of
every animal were stimulated with a weak faradic current
and the exteriorized kidney observed for blanching.

It was found that in both the animals that
received desoxycorticosterone acetate, and the animals
that received antihistamine marked renal cortical blan-
ching was evident. In those animals receiving no prev-
ious treatment no renal cortical blanching was evident.

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