STUDIES IN EXPERIMENTAL HYPERTENSION

by

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Approved
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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A Introduction

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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 induction and maintenance of hypertension is, at present, imperfectly understood. Its secretions however, are essential to the experimental establishment and maintenance 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 hypertrophy 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 experimental malignant hypertension in rats receiving excess dietary salt by administering to them large doses of desoxycorticosterone. Later Selye (48) induced hypertension 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 patients manifesting "Cushing's Syndrome" are generally hypertensive and show functional levels of blood flow, glomerular filtration, and tubular secretion 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 hormone for a period of weeks.

The tendency of Addisonians to develop hypertension 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 adrenal gland, as previously mentioned, is not known. However, 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 enervation 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 physiology of the kidney and to the study of the nervous element involved in essential hypertension. They discovered that the blood reaching the kidney has two potential routes through that organ and, according to the circumstances, 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 interlobular veins. The other route, the cortical, continues through the interlobular arteries, to the afferent arterioles of the remaining glomeruli, these glomeruli themselves, their efferent vessels and the cortical intertubular 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 predominates 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 ($\alpha_2$-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 anaesthetic 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 observation of the interdigital web. Note the pressure cuff wrapped about the thigh.
THE EFFECT OF DESOXYCORTICOSTERONE OVERDOSE 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 desoxycorticosterone 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.
The solid line represents the average systolic blood pressure changes of 6 rats, each receiving 1.0 mgm. injections 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 inclusive.
(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 X intramuscular 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 X 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 knowledge in medical fields that in women suffering from chronic nephritis re-occurrence of the grosser symptoms (extensive pitting edema, increase in blood pressure, re-appearance of albumin in the urine (?)) is associated with the onset of menis.

Selye (50) does not agree with the statements above and states that the claim that folliculoids increase the blood pressure in the rat has not been substantiated 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 peripheral discharge of acetylcholine occasioned by the folliculoids.

The controversial action of estrogen sponsored the following investigation of its 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 average of the readings made on each individual animal was considered to be the animal's normal systolic blood pressure.

Starting on day 0, each rat received subcutaneously 0.5 mgm. of diovocylin. (Ciba's brand, of estradiol 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 230 mm./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. 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 elevation 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.

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<th>Rat. No.</th>
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Table I.

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

(Normal heart weight of rats is 0.28% of body weight as determined by Best et al. (1))
The solid line represents the average increase in systolic 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 (↑).
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 systolic pressure changes of 3 castrate male rats, each receiving 0.5 mgm. of estradiol dipropionate subcutaneously 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 increase in the systolic blood pressure of three male Wistar rats. The castrate animals showed a sustained pressor response to similar treatment. No pressor response was evident in intact males each receiving 1 injection 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 subcutaneous injection of 0.5 mgm. of diovoclylin (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
Fig. 5

This graph represents the average change in the blood pressures of 4 hypertensive male rats following the subcutaneous administration of 0.5 mg/m 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 hypertension 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 hypertensive rats. This animal is also suffering hypertension secondary to renal lesions and aggravated by estrogen overdosage.
34.

Observed 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.

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<td>0.53</td>
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<tr>
<td>4</td>
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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. (*)

The gross appearance of these animals indicated a general physical degeneration. There was a marked decrease in weight, hemorrhage about the eye, scabby skin lesions, extensive edema (in 1 animal), and diuresis 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 estradiol dipropionate.

(5) Summary.

Four male Wistar rats with hypertension secondary 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 pressure.
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 its 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 4½ 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.

<table>
<thead>
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<th>Rat No.</th>
<th>Blod. Press.</th>
<th>HT.WT.</th>
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<td>8</td>
<td>220</td>
<td></td>
<td>0.41</td>
</tr>
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</table>

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))
The solid line shows the average changes in blood pressure 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 pressure of 4 male rats that each received 140 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 developed within 3 weeks in the mature animals. Best found that in weanlings hypertension did not generally develop for several months.

Such features (as seen by Best) as hyalinization 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 in 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 (\(\star\)) per day for 21 days. Starting on day 8 of the enforced fast 5 animals each received an intramuscular injection of 1.0 mgm. desoxycorticosterone 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.

(\(\star\))...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.**

<table>
<thead>
<tr>
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<tr>
<td></td>
<td></td>
<td>% Body Wt.</td>
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<tr>
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<td>0.53</td>
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<td>8</td>
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</table>

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.

Discussion.

It is pertinent in this experiment that both the undernourished animals receiving desoxycorticosterone 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 pathology 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.
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 disbalance of this mechanism might account for either hypotension or hypertension.

Histamine is a very potent material producing marked pharmacologic effects. Upon intravenous injection 0.1γ suffices to produce a marked fall in blood pressure in ether-anaesthetized cats.1γ produces severe hypotension even in humans. It is not therefore, extravagant to postulate that this substance may function in normal animals as a factor involved in a system that controls vascular activity; nor is it too imaginative 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 antihistaminic 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 antistin 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 antistin dissolved in 1 ml. of physiological normal saline. The systolic pressure of each rat was determined 1½ hours after the antistin 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, using 0.5 mgm. of pyribenzamine dissolved in 1.0 ml. of physiological saline, in place of antistin.

c) Procedure a was repeated on 2 male Wistar rats with the antistin injected subcutaneously, instead of intraperitoneally.

**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 antistin dissolved in physiologically normal saline.

Blood pressure determinations were made on each animal 5 minutes after receiving the antistin, 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 antistin 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 antistin. Pressure determinations were made on each of the 3 rats 2, 10, 24, 32 and 48 hours after they received the antistin.

**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 pressure was 55 mm./Hg. (135-190 mm./Hg.). It was found that with further injections of antistine, blood pressure 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 significant 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 appreciably from those obtained in part a.

**Trial 2. (results)**

a) It was observed (see Fig 7) that one intraperitoneal injection of 1.0 mgm. antistine apparently produced its 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 intramuscular 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 treatment 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).
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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) consistently 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 antihistamic 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 pressor 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)
Fig. 8

The curve represents the average change in systolic pressure of 4 male rats over a 2 hour period immediately following the intraperitoneal administration of 1.0 mgm. of antistine.
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 trial 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.
4. The drop that precedes the elevation of blood pressure, when 1.0 mgm. antistine is administered to rats, and the 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.

5. The elevation in blood pressure induced by antistine is presumably due to the loss of histamine. If this is true, the loss of a vasodepressor material from the blood is as pertinent to the initiation of hypertension as the increase in circulating vaso-excitator material.

6. 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 performed for academic interest only, led to the following investigations. During the laboratory exercise designed 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 response 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 possibility 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 terminals. When this stimulus had been obtained the secondary coil was left intact throughout all the experiments.

Observations were made by exteriorizing the left kidney of all animals and applying the stimulating 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 second apart. The animals were anaesthetized with nembutal.

Trail 1.

a) Five intact male rats were treated as above and observed for signs of blanching in the surface of the kidney. These animals were considered as controls.

b) Five male rats that had each received 0.5 mgm. desoxycorticosterone 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 vasaecular 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, developed 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 overdosage could be antagonized by co-incident administration of histamine.

It is generally accepted that histamine will antagonize the action of adrenaline. It was felt that since DCA appeared to have antihistaminc 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 a period 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.
The blank bar represents the average increase in blood pressure of 6 intact male rats following the subcutaneous 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 weight 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 its etiology). 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 substance has been claimed in recent years by several investigators (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 stimulation 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 maintain the balance of electrolytes in the blood. It affects the retention of sodium and the excretion of potassium (35). Kendall (35) has shown that adrenalectomized rats can be maintained indefinitely under laboratory 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 simultaneously overdosed with DCA it would appear that the hormone, 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 excess of hormone causes a metabolic mechanism to convert it to another hormone of similar structure but with different 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 hypertension (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 animal and the DCA increased the pressor response to adrenaline.
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 desoxycorticosterone 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 dipropionate 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 castrate 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 dipropionate 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 secondary 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 desoxycorticosterone 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.

9. Nine male Wistar rats were placed on a sub-minimal 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 intraperitoneally.

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 blanching was evident. In those animals receiving no previous treatment no renal cortical blanching was evident.
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