THE HORMONAL PRODUCTION

OF

CARDIOVASCULAR LESIONS

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INTRODUCTION

The pre-eminent role of hypertension and cardiovascular-renal disease in human pathology has resulted in intensive research into the underlying etiology. In spite of this fact the progress of elucidation has not been commensurate with the vigor and diligence with which the investigations have been conducted. This is, perhaps, largely due to the involvement of so many apparently unrelated factors. Notwithstanding the uniformity of the symptomatology and pathology evoked by different clinical and experimental conditions various groups of investigators have, according to their predilections, implicated the nervous system, the kidneys, dietary influences, primary disease of the blood vessels of unknown etiology and a host of other agencies.

The endocrine glands have been considered to be involved in many cases, but not until the impetus provided by the discovery and clarification of the syndrome which has come to be known as the "general adaptation syndrome" has it been possible to discern clearly the important role of the adrenal cortex. Although adrenalectomy has been found to abolish hypertension regardless of the method by which it was elicited in experimental animals and removal of parts of hyperactive adrenals has been of benefit in many clinical cases of hypertension, the adrenals have generally been relegated to an unimportant and subsidiary position in the maintenance of high blood pressure. Similarly, the occurrence of hypertrophic adrenal glands in patients with hypertension, nephrosclerosis or both has all too often been dismissed as an interesting but incidental observation.

In recent years endocrinologists have become interested in the general systemic effect of hormones rather than the specific effects on endocrine glands or the more obvious actions which they exert upon accessory structures as, for example, the effect of sex hormones on secondary sexual

characteristics. With the extraction of relatively pure hormonal mixtures and pure crystalline compounds from the glands having a steroid hormone secretion, this line of research has progressed apace.

A large number of pure hormones, both testoid and corticoid, have been found to produce an enlargement of the kidney. This has been termed the renotropic effect and is characterized by hypertrophy and hyperplasia of the proximal and distal convoluted tubules and, in the mouse, a hypertrophy of the cells in the parietal layer of Bowman's capsule. It has been shown that such kidneys are beneficially affected by the enlargement caused by testoids since the animal enjoys a greater measure of protection from kidney damaging agents. The work which is to be reported in the experimental section indicates that the kidney enlarging effect of the corticoids on the other hand is of a damaging nature. In chronically treated animals the increase in size is observed to be due to dilatation of the tubules by casts and consequent fluid and protein retention. To this action which, under certain experimental conditions is shared by crude anterior pituitary extracts, has been given the name "nephrosclerotic effect". It appears to be probable that, among the hormones with corticoid action, this effect is restricted to D.C.A. and closely related compounds which are not oxygenated at C^{11} since it is exhibited by progesterone and acetoxy-pregnenolone but not, at the dose levels tested, by whole adrenal cortical extract.

An attempt has been made to present a thorough review of the experimental methods whereby hypertension and nephrosclerosis may be induced in animals, and to indicate the important role of the adrenals in each of these. In the clinical sections an endeavor has been made to correlate the cardiovascular and renal lesions with pathologic alterations of the adrenals and pituitary gland.

In view of the enormous volume of literature dealing with patho-

logic involvement of the kidney in various clinical and experimental conditions, it has been necessary to restrict the survey to renal lesions which are primarily vascular and upon which the experimental section has a direct bearing. Thus no attempt has been made to discuss the various factors which may lead to renal hypertrophy unless there is some evidence of concomitant vascular damage. Conditions, either clinical or experimental, in which the lesions are confined to the tubular or non-vascular elements of the kidney have not been considered; consequently nephrosis and nephritis are dealt with only when there has been the connotation of nephrosclerosis.

PART I

THE NORMAL MORPHOLOGY OF THE RENAL AND CARDIOVASCULAR SYSTEMS

CHAPTER I

A. The Blood Vessels

The main blood vessels of the body may be divided into four categories. These are the arteries, arterioles, capillaries and veins. Some knowledge of the typical structure of each is necessary in order to understand the changes which take place in them under various pathologic conditions.

Arteries

The arterial wall is composed of three layers—the tunica intima, tunica media and tunica externa. The thinnest of these is the intimal coat which includes the endothelium, which is the lining common to all blood vessels, and the underlying inner elastic membrane which is usually present. The latter is separated from the former by a small amount of cellular and fibrous tissue. This subendothelial layer shows a varying development in different arteries being relatively thick in some and absent in others. The inner elastic membrane consists of a network of fine elastic fibers which in certain arteries, e.g. the aorta and large divisions thereof, are so close together as to form a fenestrated membrane.

The media consists of smooth muscle and elastic tissue the relative proportions of each being characteristic of the two main types of artery. The aorta and its larger branches in the region of the heart are known as elastic arteries owing to the predominance of the elastic component over the muscular; while the small and medium sized arteries, which are concerned mainly with the conveyance of blood to the various parts of the body, are termed muscular arteries because of the reverse situation. The muscle

fibers in the media are disposed in circularly and spirally arranged layers. Between these muscle bundles is interposed a network of elastic tissue and reticular fibers. Certain arteries possess an outer elastic membrane which separates the media and adventitia.

The adventitia is chiefly composed of a loose arrangement of collagenous fibers which blends peripherally with the connective tissue surrounding the vessel. Depending on the size of the artery this layer may be very thin or exceed the media in width. Nerves, lymphatics and small blood vessels (vasa vasorum) are found here.

Arterioles

The smallest arteries, which connect directly with the capillaries, are known as arterioles. Typically these consist of a simple endothelial tube surrounded by a discontinuous layer of smooth muscle fibers. The cytoplasmic limits of the endothelial cells are usually not visible, but the oval nuclei of the cells are conspicuous and are elongated parallel to the course of the vessel. In the larger arterioles the media is more robust and has a continuous layer of smooth muscle fibers surrounding it. An adventitia, which is absent in small arterioles, may be represented by a thin compressed layer of connective tissue.

Capillaries

These may be regarded as simple endothelial tubes the size of which, in different capillaries, may vary from 5-12 microns. The walls are composed of thin cells which contain an oval nucleus and a cytoplasm which, under certain conditions, is seen to be finely granular. A delicate network of interlacing reticular fibers surrounds the vessel wall, which may also support nerve cells, undifferentiated mesenchymal cells, histiocytes and peculiar branched cells of unknown function (Rouget cells).

Veins

These also consist of an intima, media and externa. The intima includes the endothelium, a scanty subendothelial layer of fibrous tissue and an inner elastic membrane. In certain veins the intima also includes scattered muscle fibers obliquely or longitudinally disposed. At some points the endothelium is thrown into paired ridges which have a central core of mesenchyme. These form the valves of the veins and are designed to prevent the backward flow of blood.

The media is subject to considerable variation. In general it consists of a thin layer of smooth muscle fibers circularly arranged, an elastic network and relatively abundant connective tissue.

The externa or adventitia is the most prominent layer of the veins. It is composed of interwoven bundles of connective tissue, elastic fibers and longitudinal bands of smooth muscle which are more abundant than in the externa of arteries. This muscular development reaches its peak in the renal and adrenal veins where it constitutes an almost complete layer of considerable thickness. A rich lymphatic supply and numerous vasa vasorum course through the adventitia.

B. The Heart

The mammalian heart is essentially a four chambered pump divided into right and left halves. The right half consists of an auricle which receives venous blood and a ventricle which forwards it to the lungs. The left heart is similarly constituted, the left auricle receiving blood from the lungs and the left ventricle which forces it into the systemic circulation. A system of valves at the juncture of the auricles and vessels and auricles and ventricles assures the correct direction of blood flow.

Embryologic and evolutionary evidence supports the view that the

heart is essentially a specially developed blood vessel. It consists of the same elements as the vessels namely an endothelial lining, collagenous and elastic fibers, muscle, nerve fibers, vasa vasorum and lymphatics. As a consequence of its specialized function it has developed a musculature which, in contrast to that found in the vessels, is of striated type.

The internal lining is a typical endothelium resting on a connective tissue bed which contains lymphatics, blood vessels and nerves. A specialized muscle tissue distinguished by abundant cytoplasm and peripheral distribution of myofibrils, the units of which are known as Purkinje fibers, is found here.

The muscle proper is known as the myocardium, and is pervaded throughout by a diffuse network of connective tissue fibers and cells. These serve for the attachment of valves and for the origin and insertion of muscle fibers. The vasa vasorum for this extensive area of muscle consist of the coronary arteries and veins. Lymphatic vessels are numerous and well developed in the myocardium. The muscle fibers are of striated type as in skeletal muscle, from which they differ, however, by branching repeatedly so as to form a syncitium. Transverse lines, of obscure function, termed intercalated discs traverse the cytoplasm of the cardiac muscle and serve to differentiate it from muscle of skeletal type, as also do the centrally disposed nuclei. Fine myofibrils course throughout the length of of the fibers parallel to their direction. The fibers themselves are circularly or spirally arranged.

The epicardium corresponds to the adventitial coat of the blood vessels and covers the external surface of the heart as a visceral coat. It consists of a thin sheet of mesothelial cells supported by a connective tissue framework.

The pericardium forms the parietal coat and consists of meso-

thelium backed by dense fibrous tissue, which encloses the heart as a serous sac. A subpericardial layer of lymphatic vessels is present.

The valves of the heart which separate the auricles from their corresponding ventricles on the one hand, and the auricles from the vessels which open into them on the other, are composed of connective tissue with a covering of endothelium on their inner surface. They serve to prevent blood from flowing backwards.

C. The Kidney

The mammalian kidneys are compound tubular glands with the main function of discharging from the body those substances which are of no further use and retaining those which are required. They also serve as organs of detoxification and metabolism and possibly as glands of internal secretion. The latter function will be discussed more fully in a forthcoming section.

The kidney may be divided into a cortex and medulla and consists of a series of renal lobes, pyramidal in shape, each of which has its base on the connective tissue capsule enclosing the gland and its apex in one of the minor calyces. The latter join together to form the major calyces which open into the renal pelvis, at the hilum of the gland, whence the urine is discharged. Each lobe may be subdivided into lobules the core of which consists of the rays and their continuations. The medullary rays consist of tubules which run out into the cortex of the gland. The structural unit of the kidney is the nephron which consists of the renal corpuscle and four tubular segments. Each of the tubular segments is characterized by a typical epithelium.

The renal corpuscle is composed of an interwoven tuft of capillaries, or glomerulus, surrounded by a double layer of flattened epithelial

cells which are separated from each other by the capsular space. The outer layer consitutes the wall of the renal corpuscle while the inner coat is reflected over the surface of the glomerulus. These are, respectively, the parietal and visceral layers of Bowman's capsule both of which rest on a delicate basement membrane.

The glomerulus is served by a relatively thick afferent and a somewhat thinner efferent arteriole. The former has an especially well developed system of elastic fibers in its wall which is thought to perform the dual function of protecting the glomerulus against sudden rises in blood pressure and helping to force blood past the extensive capillary bed into the efferent arteriole. Encasing the afferent arteriole at the point where it enters the glomerulus is a peculiar group of cells characterized by their oval vesicular nuclei and clearly defined cytoplasmic granules. These comprise the juxtaglomerular apparatus which has been thought to be the most probable site of renin formation although, as will be shown later, recent research seems to have invalidated this view.

Joined to the renal corpuscle by a short neck segment is the proximal convoluted tubule. These tubules form the bulk of the cortical portion of the kidney and are lined by a brush border which serves to distinguish them from the remaining segments of the tubule.

Connecting the proximal and distal portions of the convoluted tubule is the loop of Henle, which is divided into a thin or descending branch and a thick or ascending part. The former resemble capillaries, from which they may be differentiated by the more robust appearance of the epithelial cells which line them and the more numerous nuclei when seen in cross-section. The thick segments ascend in the medulla and medullary rays and come into close contact with the afferent arteriole of the glomerulus. The cells which constitute this part are more cuboidal in shape and more

numerous than those of the thin segment.

Opening into the thick segment and emptying into the collecting ducts is the distal portion of the convoluted tubule. The distal tubule is of lesser diameter and its cells are shorter than those of the proximal.

The collecting tubules, each of which serves more than one nephron, conduct the excretion to the pelvis whence it is discharged into the ureter.

Blood enters the kidney via the renal artery at the hilum. This vessel subdivides into several branches on the ventral surface of the pelvis, and continues as interlobar arteries in the renal columns between the cortex and medulla. These turn and, as arcuate arteries, run parallel to the surface of the kidney. These branch in turn to give off interlobular arteries which run perpendicular to the kidney surface through the convoluted part of the cortex, their terminal branches penetrating the capsule. From the interlobular arteries proceed still smaller branches each of which serves as an afferent arteriole to a single glomerulus and subdivides to form the network of glomerular capillaries which then reunite to form the vas efferens. This divides as a capillary plexus among the convoluted tubules and into the cortical rays. The blood is returned to interlobular veins, which run alongside the interlobular arteries, and thence to arcuate and finally to the interlobar veins. The blood then leaves the kidney via the renal vein at the hilum.

The kidney has a rich supply of nerves, mainly of unmyelinated type. These are derived from the coeliac plexus and from the tenth to twelfth thoracic nerves. It is thought that the kidney also receives parasympathetic innervation from branches of the vagus. Fine plexuses, which terminate in numerous endings in the vessel walls, are formed by the non-medullated fibers which follow the course of the blood vessels and end at

the glomeruli. Finer terminations from the same plexuses are said to end on the basement membrane of the tubules and between the epithelial cells which form their walls. Sensory myelinated fibers supply the capsule, the smooth muscle component of the renal pelvis and the adventitial coat of the renal vessels.

E X P E R I M E N T A L

PART II

The Experimental Production of Cardiovascular-Renal Lesions and Hypertension by Non-Hormonal Methods

CHAPTER II

Direct Interventions on the Kidneys

A. Arterial Constriction

In 1836 Richard Bright commented upon the association of kidney disease and elevated blood pressure (60). Although he lacked a method of estimating the actual pressure, he noted the combination of left ventricular hypertrophy and vascular lesions in the kidney and deduced that the former was due to an increased load thrown upon the heart as a result of raised systemic resistance to blood flow.

The attention thus drawn to the kidney as a possible causal agent of hypertension led to the discovery by Tigerstedt and Bergmann in 1898 (476) of a pressor substance in rabbit kidneys which, when injected intravenously, caused an elevation of blood pressure for as long as twenty minutes. This substance, which could be extracted only from kidneys, they called "renin". Of the kidney extracts made in an attempt to confirm this, some exerted pressor effects while others had a purely depressor action. The chief obstacle to progress was the fact that there was no method whereby a sustained hypertension could be produced in an experimental animal thus affording the opportunity of extracting kidneys that should, in theory, yield an increased amount of the pressor hormone.

The first step in the right direction was taken by Katzenstein in 1905 (246). He observed in acute experiments on dogs that a slight elevation in arterial pressure resulted from partial occlusion of the renal arteries. In 1927 Pedersen (355) described a method of producing chronic

hypertension in the rabbit which consisted of placing an aluminum band around the renal vein and preventing collateral circulation by placing a membrane around the kidney. This was confirmed in rabbits (37) and in dogs (313). The method was further developed by Loesch (282, 283), in 1933, who noted in chronic experiments on either intact or unilaterally nephrectomized dogs that a marked rise in systolic pressure resulted from short intermittent periods of occlusion of the renal arteries, veins and ureters. Pathologic changes strikingly similar to those accompanying malignant hypertension in man were observed in the kidneys of these animals at necropsy.

Final clarification of the problem was due to Goldblatt and his co-workers (157). They devised a silver clamp, by means of which the pressure on the renal artery could be altered and controlled, and carried out experiments on dogs. They found that constriction of one renal artery was followed by a moderate rise of blood pressure which, after a period of several weeks, gradually fell to normal. Severe constriction of both renal arteries resulted in a marked rise of systolic blood pressure accompanied by disturbances of renal function and uremia. Signs of decreased renal function were not observed. Similar results were obtained on the monkey (153). Bilateral renal ischemia was shown also to cause a persistent elevation of the diastolic pressure (153, 515). This was demonstrated to be due to a humoral substance elaborated by the kidney and not to the accumulation of nephrogenic toxins by showing that hypertension did not result from the simultaneous clamping of both arteries and veins (155), and did not occur in animals which were bilaterally nephrectomized (155) or in which a uretero-venous anastomosis had been effected (148). Kidneys of hypertensive animals proved to contain a greater quantity of pressor substance than did those from normal animals (166, 187, 188, 363). Re-establish-

ment of the circulation to a previously ischemic kidney also was shown to cause a rise in the arterial pressure (463). This proved to be due to the formation of a vasoconstricting substance "hypertensin" or "angiotonin" from the interaction of renin with blood globulins (522). It could be detected in blood from the renal vein (221).

Attempts were then made to discover the cells in the kidney responsible for this hormone. The presence of epithelioid afibrillary cells in the renal arteriolae, which were said to undergo hypertrophy and hyperplasia in the kidney of the rabbit during ischemic hypertension, was reported (162). Accumulations of these cells are prominent in the walls of the afferent glomerular arterioles where they constitute the juxtaglomerular apparatus (161). Early investigations pointed to these as being responsible for renin formation. It was found that renin was absent from the aglomerular kidneys of the midshipman fish (Porichthys notatus) and abundant in the glomerular kidneys of the carp (Cyprinus carpio) and the catfish (Ameiurus nebulosus) (143). However, it was later found to be impossible to isolate renin from the glomerular kidneys of the sole, cod, (145) or shark (35). The inability to obtain renin from the snake and toad seems to indicate that poikilothermic animals do not form renin (35). Finally, renin has been demonstrated to be present in the mesonephric or metanephric kidneys of the hog fetus, neither of which possesses specialized juxtaglomerular cells, and to increase in abundance with progressive tubular hyperplasia and decrease in proportion to tubular degeneration (244). In a later study it was shown that the injection of sodium tartrate into rabbits caused a selective degeneration of the proximal convoluted tubules and it was not possible to extract renin from such kidneys (144). The authors concluded that renin was either produced or stored in the proximal convoluted tubules.

Apparently an immune response, perhaps through the formation of antihormones, results from the injection of heterologous renin (483). Other investigators have extracted from the kidney substances which depress the blood pressure in hypertensive animals and man (173, 348, 349).

It has been suggested that possibly the hypertension which is caused by renal ischemia might be due to an increased sensitivity of peripheral blood vessels to neurogenic vasoconstrictor influences (207). However, it has been shown that hypertension due to renal ischemia is not abolished by denervation of the kidney (87, 341), by section of the anterior spinal nerve roots from the sixth thoracic to the second lumbar inclusive (158), by subdiaphragmatic splanchnicectomy and removal of the celiac and upper lumbar ganglia (49), by excision of the thoracic portion of the splanchnic nerves and removal of the lower four sympathetic ganglia (156), or by excision of the entire sympathetic chain in the abdomen and chest including denervation of the heart (210, 138, 480). Finally, hypertension results if a clamped and ischemic kidney is removed from its normal position and grafted into the neck or inguinal region (221, 49, 151).

The hypertensive response to renal ischemia is, however, dependent upon the integrity of the hypophysis and adrenal glands. Following hypophysectomy the blood pressure of hypertensive animals drops markedly (14, 336, 337, 350, 351) although not always to pre-operative levels unless the hypertension is of less than one month's duration. Complete removal of the posterior lobe with development of diabetes insipidus is without effect on the hypertension, as is the administration of sufficient pitressin to relieve the diabetic symptoms of hypophysectomized rats (337). The blood pressure of completely hypophysectomized rats is restored to pre-operative levels by the administration of purified adrenocorticotropic

hormone, while lactogenic hormone is without effect (14). Houssay (220) has reported that hypophysectomized dogs react normally to the injection of renin. It would seem that the hypophysis does not play a direct role in the maintenance of hypertension, but exerts its action through the adrenal glands.

The adrenal medulla does not influence the blood pressure response to arterial clamps, for it has been shown that the extirpation of one adrenal and the medulla of the remaining one does not abolish the response (157). During the course of hypertension there is no evidence of increased epinephrine secretion (388). Bilateral adrenalectomy, however, inhibits the elevation of blood pressure or causes it to decline if it is established (49, 89, 154, 343). Supportive therapy in the form of sodium salts does not re-establish the hypertension, but substitution therapy in the form of adrenal cortical extracts will do so (154, 343). Others have pointed to the fact that previously adrenalectomized or hypophysectomized dogs will develop hypertension if the renal arteries are subsequently occluded, but the hypertension is not as severe nor is it maintained (122, 351, 387).

The amount of renin is not reduced in the kidney of the adrenalectomized animal, indeed it may even be raised (141, 142, 502), but the responsiveness of the animal to injected renin is diminished (141, 142, 220, 502). The response is restored to normal by cortical extracts (141, 142). Castration of either sex (502) or total thyroidectomy (152) does not affect the course of hypertension.

Drury (112) has introduced a modification of the method. A loose ligature is placed about the renal artery of a rabbit thus causing, during the growth of the animal, a progressive constriction to which the kidney becomes adapted. Once the rabbit is fully grown the other kidney is removed and the hypertrophy of the ligated kidney which would normally

result is prevented by its reduced blood supply. The blood pressure is not measured, but the increased ratio of ventricular weight to body weight is used as the criterion of hypertension. However, in view of the cachexia which develops as a result of the onset of renal insufficiency, this ratio is apt to be misleading.

It is interesting to note that sodium chloride is the most effective dietary agent in producing an aggravation of symptoms. The administration of ten grams of NaCl per day for two days caused increased hypertension, water retention and edema. A similar but lesser effect was observed during a high protein (meat) diet or following the administration of urea, while large doses of potassium acetate were without effect (480). The effectiveness of meat protein could not be confirmed (356). It seems likely that both the total amount of protein and the degree of renal ischemia would influence the response to ingested materials. Schroeder and Adams (403) report that a single injection of tyrosinase into rats rendered hypertensive by renal clamps reduced the pressure to normal levels for as long as two weeks.

Widespread vascular lesions accompany the raised blood pressure, but generally are not found in the kidney to which the clamp is applied. Collins (87) observed some cardiac hypertrophy but no renal lesions in dogs that had clamps applied to both renal arteries. Loesch (283) described the kidneys as showing fragmentation of glomerular nuclei while other glomeruli were hyalinized or showed adherence of the layers of Bowman's capsule with consequent obliteration of the capsular space, in intact dogs in which one renal artery and vein had been periodically constricted. There were also a few hyalin cylinders in the tubules and some round cell infiltration. In unilaterally nephrectomized dogs the afferent arterioles showed thickening of the walls, the tubules showed a greater number of hyalin casts, the

heart was greatly hypertrophic and there was also brain and lung edema. In rabbits similarly treated, hyaline and fibrinoid degeneration and necrosis of arterioles in the kidney, intestines, stomach, liver, adrenals, heart and eye may be observed (508). These lesions are related to the intensity of hypertension, but not to the duration. In rats and dogs the medium and small arteries of the kidney show hyaline and fibrinoid swelling of the vessel wall involving all coats. The walls may be completely necrosed and contain fibrin and erythrocytes. The lumen is narrowed by intimal swelling and there may be fragmentation of the internal elastic membrane. The adventitia often is involved in an inflammatory reaction. Lesions resembling periarteritis nodosa are not uncommon (506). These findings have been amply confirmed (360, 405, 504, 505). The clamped kidney does not develop these pathologic vascular changes, apparently because it is protected against the high blood pressure (398, 504, 505, 506, 508). In intact dogs hypertension, which is established by unilateral constriction of the renal artery, may be abolished by removal of the clamped kidney. Although in about two-thirds of such cases there remains a residual hypertension which is proportional to the extent of lesions in the other kidney (505).

It is curious to note that such extensive lesions may be present without markedly affecting the renal function. Using animals with renal arterial clamps Page (341) was unable to observe any alteration in renal efficiency. Wood and Cash (515) report that in animals with bilateral arterial clamps the most severe renal insufficiency may not be accompanied by hypertension and vice versa. In such animals the non-protein nitrogen and phenolsulphonphthalein renal function tests may be entirely normal (87, 506). Indeed the onset of renal insufficiency usually results in a decline of blood pressure (221). These findings have been confirmed by

Corcoran and Page (90) who have shown that marked hypertension may exist without there being any constant or persistent changes in the renal clearance of diodrast, phenol red, inulin or urea, and without significant abnormalities in the ability of the tubules to carry out the normal functions of excretion and resorption. This they consider to indicate that a marked ischemia of renal tissue does not exist. Page (346) suggests that hypertension may be due to the intrarenal reduction in pulse pressure rather than ischemia.

B. Perinephritis

If the kidney of a dog, cat or rabbit is enclosed in a cellophane or silk membrane a mild and transient hypertension develops in a few weeks. If both kidneys are so treated, or if one kidney is wrapped and the other removed, a marked and persistent rise of blood pressure results (295, 344). This has been confirmed by several investigators (90, 95, 205, 248, 402, 405, 446). It does not result from renal constriction by the material which encloses the kidney for this is loosely applied, but is due to the proliferative granulomatous response which the offending membrane elicits. The kidney comes to be enclosed in a fibrous hull which compresses it and thereby induces ischemia. The blood pressure returns to normal if the hull is removed but is not prevented by renal denervation (344). This is to be regarded as a modification of the Goldblatt method since the response is caused by renal ischemia. The effectiveness of this method seems to be influenced greatly by the type of material which is used to enclose the kidneys, and is enhanced by the application of collodion to the surface of the wrapping employed (205).

Dietary factors influence the response to a considerable extent. It has been reported that a unilaterally nephrectomized dog with a cast upon its only kidney developed a marked rise in blood pressure, accompanied by bilateral retinal detachment and cerebral symptoms, within twenty-four hours, when a diet of meat was substituted for the usual regimen of dog biscuits. This was reversed when the usual diet replaced that of meat (295). As is the case with the Goldblatt technique the method is most effective when both kidneys are treated. It has been shown that if only one is wrapped the hypertension drops to normal following its extirpation (344). Gaudino (147) has recently demonstrated that this post-operative drop is only transient and is followed by a slow and late rise which may

reach levels exceeding those attained prior to renal ablation. He has further shown that the re-establishment of hypertension is independent of the duration and severity of that which existed before removal of the damaged kidney and bears no relation to the existence of pathologic lesions in the remaining kidney. The hypertension is associated with a rise of renin activator in the blood and is not abolished by renal denervation, however it is prevented by adrenalectomy and restored by the administration of adrenal cortical extract and sodium chloride (147, 344).

The vascular lesions do not differ from those described in the last section and similarly they appear to be correlated with the degree and severity of the induced hypertension, since they do not occur in the absence of cardiac hypertrophy and elevated blood pressure (405). The renal lesions which develop after unilateral wrapping are confined to the contralateral kidney and consist of muscular hypertrophy of the media followed by hyaline degeneration and necrosis of the arteriolar walls, accompanied by glomerular hyalinization and tubular atrophy (405). In both rats and dogs periarteritis nodosa is a conspicuous feature at necropsy (446). The most obvious difference between the animals which do and those which do not develop this lesion is the higher mean blood pressure and the greater frequency of suppurative reaction about the kidneys of the former.

C. Subtotal Nephrectomy

The first experiments which indicated that subtotal nephrectomy could cause hypertension were those of Pässler and Heinecke (352). They removed about 75% of the total kidney mass from dogs and observed that a marked rise in blood pressure and cardiac hypertrophy resulted, provided that the animals did not become cachectic subsequent to the operation. The degree of hypertension they thought to be roughly proportional to the degree of kidney insufficiency. Their findings have been confirmed in the dog (197, 269, 301) and the rat (36, 81, 82, 83, 95, 105, 110, 516). Wood and Cash (515) do not believe that hypertension is proportional to the degree of renal insufficiency.

The most successful experiments along this line were those of Chanutin and his associates (81, 82, 83). They have shown that if one kidney is subjected to polar ligation and excision of two-thirds of its bulk and the other one is removed, there occurs a marked hypertension accompanied by cardiac hypertrophy and moderate to severe lesions in the remaining kidney fragment. Chronic renal insufficiency with albuminuria, polyuria and nitrogen retention ultimately supervenes (82). The rapidity of onset and severity of lesions is considerably accelerated in rats if they are given a high meat (liver or muscle) diet, especially if this constitutes 80% or more of the food intake. Casein is not as effective in this respect (83).

Peculiarly it has not been possible to demonstrate the existence of a pressor substance either in the remaining portion of kidney, or in the blood or urine of such animals. Indeed extracts of such kidneys contain less pressor substance than those prepared from normal kidney tissue (36, 110). This is in contrast to the increased concentration of pressor sub-

stances within kidneys that have been subjected to arterial ligation. The existence of hypertension in spite of this suggests the possibility of some extrarenal pressor substance which accumulates in the absence of a sufficient amount of functional renal tissue. Confirmatory evidence is presented by the finding that parabiotic rats, from which three of the four kidneys have been removed, often develop hypertension although there is no damage to the remaining kidney (236).

Adrenalectomy (105) or complete destruction of the central nervous system (110) abolishes the hypertension produced by this method. Hypertensive animals are found to have a higher adrenal weight than do controls (105).

The lesions in the vascular system are similar to those found in animals suffering from hypertension caused by renal ischemia. In the kidney obliteration of the capsular space has been described and also hypertrophy of the walls in the smaller arteries and arterioles with deposition of fat within the media (301, 516).

D. Ureteral Ligation

Rautenberg (376) appears to have been the first to obtain a rise in blood pressure by ligation of the ureters. He induced hypertension in rabbits by occluding the ureter to one kidney and then removing the other one. From the serum of animals rendered hypertensive by this method he extracted a substance which, because of its mydriatic action on the pupil of a frog's eye, he believed to be similar to adrenalin. Hypertension following the blocking of one or both ureters has been reported in the dog (106, 189, 197, 198), and the rat (402, 403). The increase in blood pressure is more severe in bilaterally operated animals than in those in which only one ureter has been ligated, but does not occur in bilaterally or unilaterally nephrectomized animals (197, 198), or those in which a ureterovenous anastomosis has been established (106, 148). Rats which have developed spontaneous bilateral hydronephrosis display a marked rise in arterial pressure which may or may not be present in those suffering from the unilateral anomaly (503).

Renal arterial lesions have not been described in this condition although arteriosclerosis of the aorta has been observed to occur in rabbits with one kidney removed and the ureter from the other occluded (376). The hypertensive state is not abolished by the denervation of both kidneys (437).

Hypertension does not result when the urine is deviated into the blood stream, and if this is done only on one side the animal remains normal indefinitely. It does not seem likely therefore that the rise in blood pressure is due to the accumulation of nephrotoxins or vasoconstricting substances. Possibly it is a compensatory process designed to allow normal filtration against abnormally high blood pressure, but the mechanism is obscure.

CHAPTER III

Allergy and Anaphylaxis

A. Glomerulonephritis

The earliest stages of acute diffuse glomerulonephritis are characterized by swelling and proliferation of the cells composing the walls of the glomerular capillaries accompanied by exudation into the capsular space. In the terminal stages the glomeruli may be hyalinized or show complete fibrosis, and at this period the tubules may also exhibit swelling, degeneration and cast formation. Inasmuch as this process may be quite severe and is always bilateral the renal tissue must suffer from ischemia, and in this respect the hypertension which occurs is somewhat reminiscent of the experimental types which have been discussed.

Lindemann(281) was the first to demonstrate that the serum of guinea pigs which had previously been injected with a mash of rabbit kidneys was toxic for the rabbit. He noted that rabbits when so treated develop albuminuria and uremia, but detected no pathologic changes in the kidneys. This line of investigation was continued by others, among them Bierry (44) who prepared an anti-dog kidney serum from the rabbit and also found that the nucleoalbumins of donor blood were effective in this respect. The first evidence that glomerulonephritis resulted from this type of treatment was presented by Masugi and his co-workers (303, 304, 305), and has been verified by others (24, 201, 442, 444, 457, 493). The pathologic changes which have been observed following such treatment consist of thickening of the glomerular capillary walls followed by hyalinization; degeneration of the renal tubules with cast formation; hypertrophy of the smaller arteries in the kidney with perivascular infiltration of lymphocytes, mononuclears and eosinphils; and acute focal necrosis of

the myocardium with reduplication of the internal elastic membrane in the coronary arteries. Hypertension (24, 442) and cardiac hypertrophy may also occur. Such toxins are not strictly organ specific for it has been observed that anti-brain or anti-liver serum may also exhibit an anti-kidney action (441).

In the rat the occurrence of renal lesions following the injection of antiserum is almost completely prevented by a low protein - high carbohydrate diet (124, 443). They are prevented also by the injection of a saline extract of rat kidney if this is administered prior to the antiserum (441). Most observations would tend to support the theory of an antibody-antigen reaction, but Weiss (493), who noted that the lesions developed after a single injection of nephrotoxin, did not consider it to be an allergic manifestation.

Longcope (288) reported that the repeated administration of horse serum or egg white to guinea pigs, rabbits, cats or dogs led to what he considered to be nephritis, accompanied, especially in rabbits, by diffuse chronic myocarditis and mild cirrhosis of the liver. The action of horse serum, which will be discussed more fully in the next section, has been confirmed by others (2, 335).

B. Periarteritis Nodosa

Reference has been made to the occurrence of this lesion in animals which have been rendered hypertensive by various methods. The malady has a predilection for small and medium arteries of muscular type and consists of inflammation and necrosis of the media, and later intima, accompanied by exudation and hyalinization. There is a characteristic extensive leucocytic infiltration of the adventitia and surrounding tissues, and the lesion may be found in any orgran of the body. It may be especially well seen in the mesenteric artery and its branches where, in its most advanced form, multiple nodular thickenings coursing the length of the vessel are present. In man the organs most commonly involved are, in the order of decreasing frequency, the kidney, heart, liver, gastrointestinal tract, mesenteric artery, muscles, pancreas, peripheral nerves and the central nervous system (23, 175). In other species the distribution may vary.

Kussmaul and Maier (264) who first described the disease in man noted its association with Bright's disease, but thought that it might be caused by trichiniasis. Since then it has been ascribed to streptococcic infection (256, 315); to an allergic reaction (255, 315, 381, 382, 383, 513); to rheumatic fever (79, 140, 254, 450); to virus infection (186, 199), and to an unknown etiologic factor accompanying a variety of infections (135, 140). The frequent association of periarteritis with nephrosclerosis, hypertension or both receives considerable attention in the literature (33, 95, 264, 408, 450, 489, 513).

Von Haun (199) believed the disease to be due to a transmissible infectious agent and to prove the point he injected the blood from a proven case of periarteritis nodosa into guinea pigs. After a period of incubation he injected either blood or an organ emulsion from these animals

into a second series of guinea pigs and these developed an inflammatory lesion of the arteries which he considered to be periarteritis.

Harris and Friedrichs (186) repeated the experiment but used rabbits as test objects and again, in the second generation of donor animals, inflammatory lesions resembling those of periarteritis were observed. Further, they found that the organism was able to pass through a Berkfeld N filter. Unfortunately both of these experiments were poorly controlled and neither Carling and Hicks (79) nor Franz (135), who by means of inoculations from five proven cases into guinea pigs failed to transmit the lesions, were able to confirm them.

Klinge (255) appears to have been the first to show that repeated injections of horse serum into rabbits induced changes similar to those of periarteritis. The observations were extended by Metz (315) who showed that in rabbits the lesions could be produced either by horse serum or by injections of streptococci, but that the individual constitution of the animal was the most important factor. Clark and Kaplan (84), Rich (381, 382) and Rich and Gregory (383) have observed periarteritis nodosa both in patients who have demonstrated anaphylactic symptoms to foreign serum or sulfanilamides, and in rabbits that have been rendered hypersensitive to horse serum. This they attribute to an allergic reaction. However, the patients which they report upon were admitted to the hospital with every indication of severe illness before receiving serum therapy and there is no proof that the lesions observed at necropsy did not antedate serum treatment. In the case of the rabbits which developed periarteritis as a consequence of serum injections no control animals were used, which makes it difficult to evaluate the findings (383). Rabbits are notoriously unsuited to this type of experimentation because of their susceptibility to spontaneous vascular lesions (48, 113, 292). This must be borne in mind when

estimating the importance of experimental damage to the vascular system from any intervention when only rabbits have been used. The spontaneous occurrence of periarteritis nodosa has also been observed in old rats (300, 501) pigs (237) and deer (329). Others repeating the experiments of Rich have been unable to confirm the finding of periarteritis (133).

Considering experimentally produced glomerulonephritis and periarteritis nodosa together it may be said that while it has been possible to induce lesions resembling glomerulonephritis of man in experimental animals, the etiologic agent is not clear and there is no proof that the pathogenesis of the two is identical. In periarteritis nodosa it does not seem likely that an anaphylactoid response is the causal agent because the lesion can be produced in rabbits either by a single injection of horse serum or by the daily injections of large quantities in the absence of any anaphylactic phenomena (176). It is possible that serum constitutes a non-specific damaging agent and that hyperactivity of the adrenal cortex is responsible for the lesions. This view is supported by the observation that administration of desoxycorticosterone acetate causes the development of large macroscopic nodules throughout the body (430) while the lesions observed after horse serum treatment are microscopic.

CHAPTER IV

Neurogenic Hypertension

A. Nerve Section

A marked rise of blood pressure has been noted by Heymans (209, 207, 208) and others following bilateral denervation of the carotid sinus and section of the aortic depressor nerve. It is thought that this procedure permits the vasoconstrictor and caridio-accelerator centers to exert their maximum effects unchecked by moderating influences. A hypertension persisting for as long as three years (332) at a level of up to 300 mm. Hg. (208) has been induced in dogs by this method. Others have maintained that in either rabbits or dogs the hypertension is only transient and fluctuating (168). The blood pressure rise is not prevented by denervation of the kidneys (119), but is prevented by excision of the sympathetic paravertebral chains from the stellate ganglion down to the pelvic ganglion (208). Fontaine and Mandel (132) found that in dogs rendered hypertensive by this means the removal of one adrenal was without effect, but that unilateral ablation and complete denervation of the other was followed by a marked drop which returned to hypertensive levels in about two weeks. Complete bilateral adrenalectomy abolishes the hypertension (274). Elaut (118) claimed to have observed hypertrophy of the media of small arteries and of the juxtaglomerular apparatus in the kidneys of such animals but the majority of investigators have not been able to confirm this (48, 212).

The idea that certain forms of human hypertension might be due to an interference with the carotid sinus and depressor reflexes arose from the demonstration that high blood pressure could be experimentally produced by denervation of the carotid sinus and arch of the aorta. A comparison of

the chief features exhibited by patients suffering from the common forms of persistent hypertension (chronic nephritis and essential hypertension) with those exhibited by the animal with this form of experimental hypertension reveal striking differences that leave no doubt as to the essentially different origin of human and experimental hypertension. Thus tachycardia is invariable in the experimental and exceptional in human hypertension; compression of the carotid artery below the sinus gives no response in the animal and a definite response in man; sensory stimuli produce a fall of blood pressure in the animal and a rise in man; in sleep the pressure falls to normal in the animal and remains elevated in man; and lastly, characteristic higtological changes in the arterioles are absent in the experimental and usually present in the human form (358a).

B. Increased Intracranial Pressure

Dixon and Heller (109) found that persistent hypertension could be induced in dogs by the injection of a kaolin suspension into the Cisterna magna. This has been confirmed in dogs (48, 137, 181, 235, 357) and rats (169, 170) but not in cats (280). The exact mechanism of action is not well understood. Perhaps it is due to stimulation of the vasopressor centers as a result of cerebral anemia and anoxia, because of deficient lymphatic drainage (169). There is no increase in blood volume (170).

Various methods have been adopted in an attempt to inhibit or abolish this type of hypertension, with varying degrees of success. Freeman and Jeffers (137), who employed an intracisternal injection of physiological saline, removed parts of the sympathetic nervous system and found that removal of the entire sympathetic chain from the fifth thoracic to the fifth lumbar was without effect. However, removal of the upper thoracic T1 - T6 and lower thoracic T 9 - T 13 together was followed by a

decrease in blood pressure. Unfortunately only a few dogs were used and inasmuch as this type of hypertension is characterized by wide fluctuations and spontaneous remissions (109, 170, 235) definite conclusions are not warranted. The hypertension is abolished by bilateral adrenalectomy, but not by adrenal denervation (137, 481) in dogs; however, the hypertension returns if adrenal cortical extract and sodium chloride are administered (235). Griffith and Roberts (170) claim that adrenalectomized rats develop hypertension if the kaolin is injected after adrenalectomy, but this has not been confirmed.

Vogt (481) detected a pressor substance which was not adrenalin but may have been angiotonin in the blood of hypertensive dogs. This could not be detected in the blood of similarly treated adrenalectomized animals and these never developed hypertension. The presence of a pressor substance in the blood was noted also by Pick (357).

Arterial or arteriolar lesions in the kidney or elsewhere have not been found, even in animals which have been hypertensive for a period of years (109, 181). This is probably due to the tendency of the blood pressure to fluctuate widely and to drop to normal levels for long periods of time.

It is doubtful that cerebral anoxia plays more than a subsidiary role in human essential or malignant hypertension. In contrasting fourteen cases of chronic hypertension with ten of low or normal pressure Bordley and Baker (55) recognized an association of persistent hypertension and arteriosclerosis of the cerebral vessels. They suggested that arteriosclerosis of the vessels in the medulla oblongata might be the essential factor in chronic hypertension, but realized that this might be an effect rather than the cause. Ruckert and Deilmann (392) examined the medulla oblongata from 49 cases of hypertension and reported complete absence of

vascular lesions in 33, stenosis of arterioles in 6, and atherosclerosis of the basal cerebral arteries while the small and medium arteries were normal in 10. They concluded that arteriosclerosis is a result of persistent hypertension and not the cause.

CHAPTER V

The Effect of Dietary Factors

A. Proteins and Amino-Acids

The fact that a high-protein diet often tends to aggravate experimentally induced hypertension has been discussed. There exists some evidence that high-protein diets *per se* may cause hypertension and renal vascular lesions.

It is well known that renal hypertrophy is stimulated by high-protein diets (293a, 294, 509, 293); this is dependant to some extent on the type of protein used and the total protein intake. When casein is employed the resulting hypertrophy is proportional to the total consumption (294). This effect is diminished if the same proportion of vitamin B (yeast extract) is present in both the high protein and basal diets (293). Gelatin (509), egg albumin and blood albumin (293a) are more effective than casein in producing renal hypertrophy. High-protein diets may inhibit the body growth of rats (445), and this undoubtedly enhances the apparent renal hypertrophy when the kidney weights are expressed as percentages of the body weight.

Ignatowski (229) fed rabbits on a high-protein diet and observed lesions in the aorta and fatty infiltration of the kidneys and liver. Newburgh and Marsh (328) thought that the toxic action of proteins was due to the amino-acid constituents and reported that aspartic acid, histidin, tyrosine, tryptophane and cystine were nephrotoxic for the dog and rabbit.

It was also found that in rats a high casein diet caused tubular degeneration and some glomerular hyalinization, and that these changes developed more rapidly in unilaterally nephrectomized rats (317). Animals on an 85% casein diet excreted more protein in the urine and showed a higher

incidence of urinary casts than normals (318). Unfortunately these diets were so low in vitamins and other essential constituents that the renal lesions cannot be ascribed to any single dietary factor. However, others confirmed these observations and found that older animals were more susceptible to the lesions than young ones, and that individual variations in response were marked (233). The kidneys of rabbits fed a high-protein diet have been claimed to exhibit enlargement of the glomeruli, shrinkage of the convoluted tubules and overgrowth of interstitial connective tissue (231).

The importance of the type of protein used was emphasized by Newburgh and his co-workers (326) who found that beef liver produced greater renal damage than any pure protein, animal or vegetable tissue employed. A diet containing as little as 40% liver he found to be nephropathic for the rat, while a diet containing 75% produced a granular kidney in less than a year. It was also found that sodium nucleate alone was extremely toxic and it was suggested that water-soluble nitrogenous extractives of proteins were nephrotoxic (327). It seems just as likely, however, that the effect was due to the extra burden involved in the excretion of nitrogen metabolites *per se*. Moise and Smith (319) also noted similar renal lesions after a high-meat diet in rats, but found that the blood pressure was unaffected. Blatherwick *et al* (50) found that high-protein diets caused severe nephrosclerosis in unilaterally nephrectomized rats. Nuzum observed that such diets induced renal lesions and hypertension in rabbits (333). It has been shown that the renal arterioles undergo hypertrophy and hyperplasia (333) and the glomeruli become hyalinized on high-protein diets (311). A diet with excess of defatted casein has been found to evoke arteriosclerotic changes in rabbits (312). On the other hand, Campbell (77) who fed a high-protein diet in which the other essential dietary constituents were adequately represented, could not detect renal lesions in rats that had

been on a 33% protein diet for 150 days.

It appears that while renal lesions of various kinds may be produced by dietary excess of protein, these cannot be ascribed to an increased or decreased intake of any single nutritional entity. In general the diets have not been well balanced in vitamins and minerals and the lesions, other than those in rabbits, have been observed mainly in old rats which also suffer from spontaneous renal injury.

Experiments have shown that adrenal enlargement occurs in both rabbits and rats as a consequence of the administration of diets high in protein (229, 465). Tepperman, Engel and Long (465) found that diets high in meat or casein caused a 40-50% increase in the size of the adrenals of rats. These glands showed every evidence of hyperactivity. In view of the fact that the adrenal compound desoxycorticosterone is capable of eliciting identical lesions to those described in high-protein diets as will be shown in the experimental section, it appears to be likely that adrenal hyperactivity is an important factor in the production of renal lesions due to protein excess.

B. Cholesterol

Ignatowski (228, 229) noted that rabbits fed a high-protein diet consisting of meat, milk and eggs developed fatty plaques in the aorta and fatty infiltration of the liver and kidneys. This was accompanied by marked adrenal enlargement. It developed that these lesions were due to the cholesterol content of the diet (15, 16) and could be produced in guinea-pigs by the same method (29). Duff (113) has reviewed the literature and does not consider that the lesions are comparable to those seen in human arteriosclerosis. The lesions are only reproducible in guinea-pigs and rabbits and are confined to the aorta and its larger branches. The cerebral and retinal vessels, so commonly affected in the human disease, are never involved and the renal vessels only occasionally.

A high-protein diet containing soybean flour diminishes both the incidence and severity of cholesterol atherosclerosis, while a high-protein diet containing defatted casein aggravates the condition (312). Indeed, rabbits maintained on a high-protein diet containing defatted casein often develop lesions indistinguishable from those produced by a high-cholesterol diet. The degree and extent of the lesions cannot be attributed to hypertension which is only occasionally manifested by the animals.

In view of the pronounced adrenal enlargement which the cholesterol animals display, it is possible that these glands are involved in the production of the disease. Cholesterol and high-protein diets containing defatted casein both produce similar lesions but only in the rabbit or guinea-pig. It is possible that these substances constitute non-specific damaging agents for herbivorus animals, and such agents are known to cause vascular lesions (417). However, the peculiar distribution of the lesions and the absence of hypertension militates against this view.

C. Vitamin D.

Appelrot (22) and others (207, 102, 182, 183, 184) have found that the chronic administration of Vitamin D per os leads to the development of a hypertensive state in dogs. The blood pressure returns to normal upon discontinuation of the treatment. While in the state of hypervitaminosis the animals are more sensitive to injections of adrenalin, which causes marked elevation of the blood pressure in quantities which ordinarily would be ineffective (163, 182). It is claimed that the arterioles of the spleen and intestine and especially those of the kidney show evidence of hypertrophy (22, 182, 183, 184, 451) leading ultimately to atrophy and necrosis at the higher dose levels (183, 184). Photographic evidence of these alterations has not been presented although pictures have shown calcification of the aorta and other vessels. Similar lesions have been found in rats, rabbits and mice.

The lesions appear to be a consequence of disturbances in calcium and phosphorus metabolism inasmuch as they are considerably aggravated by diets high in sodium phosphate (373, 164) or calcium carbonate (114, 373). Tissue analysis of dogs treated with Vitamin D indicates that concentrations of calcium and phosphorus are greatest in the kidney, and this is the organ which is most affected by the treatment (337). It appears that the calcification of the kidney is a consequence of hypercalcemia since the renal accumulations are greatest in the animals showing the greatest urinary excretion of calcium. Actually calcification of the renal arterioles and arteries is a more prominent feature than the medial hypertrophy (45, 216).

Spies and Glover (451) found that rabbits treated with irradiated ergosterol developed marked nephropathic changes. These consisted of sclerosis and hyalinization of the renal arteries and arterioles leading

occasionally to obliteration of the lumen, accompanied by sclerosis of the glomeruli and tubular basement membranes and extensive sub-endothelial hyalin deposition.

Ham (178) has reported hypertension, calcification of the renal tubules, glomeruli and arterioles—there was also hyalinization and fibrosis of glomeruli and arterioles and marked periarteritis nodosa of the intestinal vessels—as a result of a single massive dose of irradiated ergosterol or a diet rich in calcium, phosphorus and phosphoric acid, in the rat. Photographs, or details as to the size, sex, and number of animals used and the dosage employed were not presented, and this renders evaluation of the results most difficult.

Briskin et al (61) on the other hand found that toxic doses of vitamin D_2, D_3, or Ertron sufficient to cause marked weight loss, invariably led to hypotension in rats. The same authors were unable to produce hypertension in either dogs or humans by the administration of various forms of vitamin D.

The pathologic action of hypervitaminosis D is apparently related to the hypercalcemic action and thus resembles the effect of overdosage with parathyroid hormone. It is not obviously related to any common form of hypertensive disease in man. In discussing the effect of vitamin D overdosage in rabbits Spies and Glover (451) stated that "The composite histological changes in the kidneys of the animals were strikingly different from any known pathological process occurring in man".

CHAPTER VI

The Role of the Kidney in Hypertensive Disease

Pertinent statistics vary, but in general it is agreed that about 23% of all deaths of persons over 50 is attributable to to hypertension or its consequences (123). These diseases are, hence, even more common causes of death than cancer and it is natural that a good deal of attention has been paid to their etiology and pathogenesis. The work of Goldblatt has led clinicians to implicate the kidney as the primary factor in the malady, but much evidence supports the view that the renal changes are secondary to the hypertension.

Classification of the hypertensive diseases is extremely difficult and there is none which would meet with unanimous approval. The most recent, however, is that of Page and Corcoran (347) which lists the types as renal (where the lesions may be vascular, parenchymatous, perinephric, or ureteral), cerebral, cardiovascular, endocrine and unknown. The last named includes "at least 90 to 95%" of all cases of hypertension, and is divided into essential and malignant forms, the latter differing from the former only in its severity and greater rapidity of progression. Nephrosclerosis they consider to be the terminal stage of hypertension when the kidney is primarily involved. It is not considered as a disease entity any more than is the cerebral vascular sclerosis which also occurs in hypertension.

An alternative classification of Bright's disease (nephrosclerosis) differentiates between types in which renal lesions are the cause and those in which they are the consequence of hypertension (253, 449).

It was natural, following the observations that hypertensive substances could be detected in the kidneys of animals with experimental hypertension, to seek for such in the blood of human hypertensives. Many attempts to demonstrate a greater amount of pressor substances in the blood

of patients suffering from different types of hypertension than in normal patients have failed (272, 358, 359). More recently, however, Page (345) (quoted by 360) has reported that patients suffering from benign, malignant or nephritic hypertension show increased quantities of pressor substance in the peripheral blood. Until the question is settled final decision must be held in abeyance. Wollheim (514) has reported the presence of a thermolabile depressant in the urine of the horse and man which is absent from that of hypertensives and concludes that hypertension is due to a deficient production of this substance.

In spite of the fact that essential hypertension has been regarded as a disease in which there is no evidence of renal lesions, this classification does not stand up to critical examination. Fishberg (129) reports that in 77 cases of essential hypertension coming to autopsy arteriosclerosis of the smaller arterioles of the spleen, cerebrum and pancreas was present in a large number of cases, and invariably present in the renal arterioles. Similar findings have been made by others (102, 406, 407). The fact that chronic hypertension is always associated with renal arteriolar disease, regardless of the etiology, has frequently been commented up (320, 439, 504, 120, 247, 80, 58). It is obvious, of course, that hypertension may be fatal before renal damage occurs.

Proponents of the ischemic theory of hypertension have tended to support the contention that the disease arises as a consequence of renal arteriolar hypertrophy with resulting diminution of the lumina thus, in effect, reproducing the end-result of the Goldblatt clamp. If this be accepted as the true explanation then we must abandon the primacy of renal ischemia and accept the primacy of renal arteriolar disease of unknown etiology. The evidence which the renal ischemia school of thought ad-

vances in support of its hypothesis consists chiefly of hypertensive cases in which there has been observed a co-existing unilateral renal disease.

Saphir and Ballinger (398) have reported two cases of unilateral renal arterial stenosis in which the contralateral kidney was nephrosclerotic while the stenosed organ was free from lesions. Platt (361) remarks upon a similar condition prevailing in a patient in which one kidney was hypoplastic. Others have observed that hypertension, when it co-exists with unilateral pyelonephritis, is often cured by removal of the offending kidney (57, 252, 507). Farrel (125) noted the abatement of hypertension in a patient following the excision of an intramural kidney which had become involved in a surgical scar. Conversely it has been reported that the removal of a pyelonephritic kidney failed to cure the patient's hypertension although tests revealed the remaining kidney to be neither diseased nor ischemic (494). Smith (447) has reviewed the entire literature on the subject up until 1943 and finds that of the 76 patients with hypertension who were subjected to unilateral nephrectomy because of supposed renal disease only 7 were favorably affected. In summarizing the reported literature concerning the incidence of hypertension in patients with demonstrated unilateral renal disease he finds that if all cases be considered, and there were 2203 of them, the incidence is 26.5%. This is of the order of magnitude accepted by most medical statisticians as designating the incidence of the disease in the normal adult population.

In discussing the reported cases where gross obstruction of the renal artery could account for the development of hypertension Smith finds ten cases and accepts four of them. In the other six, two were not benefitted by nephrectomy and in four there was no evidence that the hypertension did not antedate the obstruction (447). Thus from the thousands of cases of hypertension with associated renal disease there are only

eleven which favor the argument that unilateral arterial disease or compression of the kidney is the causative factor. In an independent investigation Pearman (354) has reported that in 500 patients with pyelonephritis only 9% were hypertensive while in an equal number of patients with gallbladder disease the incidence was 7%.

Prinzmetal (365) and others have commented upon the fact that bilateral infarction of the renal arteries by thrombus formation may lead to hypertension. This is not unexpected, but even here it has not always been shown that the hypertension did not exist before infarction. Thrombus formation is well known to be a sign of vascular damage and to occur at the site of pathologic alterations in the vessel wall. The fact that renal involvement in hypertension, when it occurs, is bilateral is generally accepted (129, 243, 404, 447). It appears then to be fairly well established that hypertension is the cause—and not a result of renal arteriolar lesions. This is supported by the fact that biopsy specimens from patients who are victims of a disabling but not yet fatal hypertension show in 28% "no or insignificant vascular disease and (in) an additional 25% only mild changes" (80). Functional studies in early hypertensive patients indicate that the pattern of renal blood flow and function are inconsistent with the presence of significant vascular disease (347).

In view of the failure of extensive sympathectomy to influence the hypertension following various types of renal intervention it was not to be expected that the operation would be of benefit to human hypertensives. Prinzmetal (366) drew attention to the fact that anaesthetization of the vasomotor nerves to the arms produces the same degree of increased blood flow in normal patients as in hypertensives, thus proving that the vascular hypertonus is independent of vasomotor nerves. He concluded that there was an intrinsic vascular hypertonus, and this observation has been

confirmed by others. Allen and Adson (9) employed extensive sympathectomy with a view to decreasing the arteriolar tone of a large part of the vascular system by interrupting the vasomotor pathways, and increasing the blood flow of the kidney. They felt that results were encouraging, but the blood pressure did not always return to normal. Others have used the method and have removed varying amounts of sympathetic nervous tissue (93, 448, 172, 171, 396, 462, 28). The most extensive operations are those of Smithwick (448) who, in a two-stage transdiaphragmatic operation, removes the entire great splanchnic nerves with their aortic branches, and the sympathetic ganglions, the 9th-12th dorsal ganglions, the first and sometimes the second lumbar ganglion, and Grimson (171) who performs a total thoracic and lumbar sympathectomy together with a celiac ganglionectomy. In general clinical and symptomatic improvement have been much more frequently reported than blood pressure lowering. Failure to effect a drop in blood pressure in a large proportion of patients following a more or less complete sympathectomy is the rule rather than the exception (9, 93, 396, 172). If the follow-up period is long enough there is observed a tendency for the hypertension to recur and attain its former level (172). In forty patients with various types of hypertension who submitted to section of the splanchnic nerves and removal of three pairs of lower thoracic ganglions, Rytand and Holman (396) observed brilliant results only in one, while six felt better even though the hypertension remained.

Takats et al (462) report on thirty patients with benign or malignant nephrosclerosis who underwent sympathectomy. They believe that malignant hypertension is a contraindication to the operation, and are of the opinion that adrenal denervation is responsible for much of the improvement which occurs in some cases.

An analysis of the literature indicates that the operation is suc-

cessful only when the sympathectomy is more or less complete, and then only if the hypertension is of recent development so that arterial lesions are mild. Even then it does not result in constantly normal blood pressures (28). The operation does not abolish the vascular hypertonus which is primarily responsible for the hypertension (366). This, together with the failure to prove directly the secretion of pressor substances by the kidney through detecting them in the blood of hypertensive animals or patients (358, 245, 364, 342, 88) indicates that possibly the primary cause of hypertension is extrarenal.

PART III

Hypertension and Cardiovascular-Renal Lesions as a Consequence of Endocrine Dysfunction or Hormone Administration.

CHAPTER VII

The Role of the Pancreas

Diabetes mellitus, or pancreatic diabetes, is now clearly established as a disease due to the deficient production of the internal secretion of the pancreas (insulin). Since the discovery of insulin by Banting and Best (30) and its extensive use in the therapy of diabetes, arteriosclerosis has replaced coma as the chief cause of death (239). The most evident symptoms of the disease in man are hyperglycemia, glycosuria, ketosis, acidosis, polydipsia, polyuria, polyphagia and often hypertension (510). The vascular lesions are mainly intimal in distribution and atherosclerotic in type. Pancreatic arteriosclerosis is never marked and the kidneys are not severely affected (389). The pathologic process is most marked in those muscular arteries which are under the greatest physical stress, and for this reason the coronary arteries are especially prone to involvement.

It has been suggested that a disordered lipoid metabolism is the precipitating cause of the vascular lesions (389). Aschoff (25) thought that hypercholesterolemia was responsible for the vascular lesions and Rabinowitch (372) considered this disturbance to be aggravated by a high fat diet. Hypertension does not have the close relationship to arteriosclerosis in diabetics that it has in non-diabetics. Joslin (240) (quoted by Shields Warren 487), found no hypertension in over half of a series of 482 diabetic patients followed for a period of ten years. This may, perhaps be due to the

relatively low frequency of severe sclerosis in the renal vessels of diabetic patients (487). It is well known that the characteristic vascular lesions of diabetics occur in patients without hypertension (75).

In 1930 Houssay and Biasotti (219) demonstrated that the diabetes of depancreatized dogs was rendered less severe, and the survival time increased, by hypophysectomy. It has since been shown that this is entirely due to removal of the anterior lobe. Long and Lukens (287) found that the pancreatic diabetes of the cat was similarly affected by hypophysectomy. This evidence pointed to the possible participation of the anterior lobe of the pituitary in diabetes and led to a search for the responsible hormone. Shortly afterwards, investigators found that the injection of a saline extract of anterior pituitary gland produced glycosuria in the rabbit (34). Young (518) found that the injection of anterior lobe material led to the production of permanent diabetes in the dog and this was subsequently confirmed (42, 43, 78). The injection of these "diabetogenic" extracts led to the appearance of hydropic degeneration in the islands of Langerhans and the insulin content of the pancreas was found to be low (43, 78) or absent (42).

The discovery of extracts of the adrenal cortex which were able to correct the abnormal carbohydrate metabolism of either adrenalectomized animals or patients with Addison's disease, taken together with the well known stimulating action of pituitary extracts on the adrenal glands, indicated that possibly the effects of removal or injection of pituitary material might be ascribed to the inactivation or activation respectively, of the adrenal glands.

Long (286) observed that a depancreatized dog could be maintained without hormonal supportive measures for five weeks if adrenalectomized. Such an animal with intact adrenals would scarcely have survived a week

and their relative independance of hypertension, places them in a category with experimental arteriosclerosis caused by cholesterol overdosage. Emphasizing the close relationship which exists between arteriosclerosis and cholesterol is the observation of Rabinowitch (372a) who noted that in a series of 1,400 diabetic patients the plasma cholesterol values of those with arteriosclerosis were significantly greater than those without, regardless of whether or not insulin therapy was employed.

Severe hypertension is commonly accompanied by retinitis. This manifestation is usually present in the malignant phase of essential hypertension in man and also in animals suffering from experimental renal hypertension. In either event it is more closely associated with the severity of the disease than the duration.

In chronic diabetes, thrombosis is one of the most frequently encountered vascular manifestations. The lower extremities and the heart are the sites of predilection. In the former situation the condition of diabetic gangrene occurs in the tissues normally served by the thrombosed vessel, and in the latter event the usual sequel is death from coronary thrombosis. The most prominent renal manifestation of long standing diabetes is chronic vascular nephritis, and this is most encountered in hypertensive diabetics. It must be re-emphasized, however, that the renal lesions in this condition are very different from those so characteristic of essential hypertension.

Rabinowitch (372a) points out that diseases of the heart, arteries and kidneys is the chief cause of death among diabetics today. This is, perhaps, largely due to the fact that modern therapy of the disease permits of survival to the age when arteriosclerosis develops. Since diabetes is essentially a disease of middle age, diabetics as a group are older than the general population (372a).

Rabinowitch (372a) found that a high carbohydrate-low calorie diet

without insulin. This was confirmed in the cat with the additional observation that denervation or enucleation of the adrenals was without effect on the course of pancreatic diabetes (287). The same was found to hold true for the dog, and in both cats and dogs the latent diabetes was stimulated to normal severity by treatment with adrenal cortical extract (291). The extract had similar effects on either hypophysectomized-depancreatized or adrenalectomized-depancreatized animals (291). Long (284) believes that adrenal decortication and hypophysectomy alter the response to pancreatectomy by interfering with the same metabolic mechanism. Neither the Houssay dog nor the adrenalectomized-depancreatized animal is to be regarded as normal since both hover between fatal levels of hypoglycemia and hyperglycemia. If a high-carbohydrate diet is used hyperglycemic crisis may ensue while if a low-carbohydrate diet is given hypoglycemic convulsions supervene. The lack of adrenal cortical hormone also modifies the severity of diabetes in humans (51). The adrenal compound 17-hydroxy-11-dehydrocorticosterone and other related hormones have been shown to be diabetogenic for the partially pancreatectomized rat (230).

The inclusion of the adrenals and hypophysis among the factors influencing the diabetic state has led to the division of diabetes mellitus into pancreatic diabetes, adrenal diabetes and pituitary diabetes. The latter two types are characterized by relative resistance to insulin therapy. The fault is not primarily due to pancreatic deficiency in these cases, but to excessive production of carbohydrates from protein precursors as a result of pituitary or adrenal hyperactivity. However, the load thus thrown upon the pancreas may prove to cause, secondarily, an exhaustion atrophy of the gland.

The unusual distribution of the vascular lesions in pancreatic diabetes, together with the association of disturbances in lipoid metabolism,

and their relative independance of hypertension, places them in a category with experimental arteriosclerosis caused by cholesterol overdosage. Emphasizing the close relationship which exists between arteriosclerosis and cholesterol is the observation of Rabinowitch (372a) who noted that in a series of 1,400 diabetic patients the plasma cholesterol values of those with arteriosclerosis were significantly greater than those without, regardless of whether or not insulin therapy was employed.

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Rabinowitch (372a) found that a high carbohydrate-low calorie diet

prevented the premature development of arteriosclerotic changes in about 72% of fifty cases of diabetes of more than five years duration. With more conventional diets the incidence of arteriosclerosis would have been about 75% in this length of time. He has found that many cases of diabetes may be adequately controlled on such high carbohydrate-low calorie diets alone, thus eliminating the necessity of insulin therapy. The diet causes nitrogen retention and a prompt and sustained fall in the level of plasma cholesterol. Much of the value of this treatment is attributed to its protein sparing action. In this connection it may be pertinent to re-emphasize that, just as in clinical cases of diabetes, the vascular lesions induced in the experimental animal by treatment with either desoxycorticosterone acetate or crude anterior pituitary extracts are inhibited by high carbohydrate diets (40). Conversely, there is evidence to indicate that high protein diets aggravate the severity of the vascular lesions induced in the experimental animal by treatment with hormones.

CHAPTER VIII

The Role of the Ovary

During the transition between the reproductive life and the menopause in women there occurs a period known as the climacteric. Sometimes the change is symptom-free, but often there are a number of diversified complaints of varying intensity which may persist for years. Among these are the normal regressive changes in the primary and secondary sexual characteristics and a variety of nonsexual disturbances which may precede, accompany or follow them. It is the latter with which the endocrinologist is mainly concerned.

The circulatory disturbances consist of the hot flush, alterations in cardiac rhythm and blood pressure and the vasalgias. The hot flush is the most constant and characteristic change. It consists of periodic seizures during which the patient experiences a sudden wave of heat to the head, neck and upper thorax and the face becomes intensely flushed. Later there is profuse sweating, pallor and shivering. Such manifestations may be accompanied by nausea, vomiting, weakness, vertigo and a feeling of anguish. Abnormalities in cardiac rhythm may express themselves as simple paroxysmal tachycardia and bradycardia without apparent anatomic basis, or there may be other vasomotor symptoms. Marked instability and variability of the blood pressure is frequently encountered. This may change from time to time and is characterized by being influenced by muscular effort, emotion or digestion changes. This differentiates the hypertension from that due to cardiovascular-renal disease. The vasalgias, which are apparently due to vascular spasms elicited by stimuli affecting the vasomotor mechanism of the blood vessels, consist of paroxysmal attacks of pain along the arteries and veins.

The rise of blood pressure occurring during the change of life

has been termed "climacteric hypertension" or "menopausal hypertension". Some clinicians do not regard this as a clinical entity but merely the expression of a latent abnormal vascular disturbance. They point to the masculine habitus, tendency towards obesity, excessive hirsutism and the occurrence of the manifestations during the fourth and fifth decade of life which is characteristic of hypertensive vascular disease in general, and therefore doubt the specificity of hypertension in the menopausal state. Other investigators, however, regard it as a specific disease and it is from this point of view that it will be discussed.

Withdrawal of the normal ovarian secretions incident ot the natural or artificial menopause is followed by cytologic alterations in the anterior lobe accompanied by a rise in gonadotropic hormone content (512, 202) and the appearance of increased amounts of gonadotropin in the body fluids (131, 484). This forms the basis for the view that hyperactivity of the pituitary, secondary to ovarian hypofunction, plays an important part in the symptomatology of the climacteric (6). It also provides the rationale for the therapeutic use of estrogens and androgens in suppressing the abnormal manifestations of the climacteric, since the latter suppress hypophyseal activity while the former both suppress the excessive pituitary activity and restore the deficiencies of estrogenic hormones in the blood.

Sevringhaus (436) reported therapeutic benefit by simple psychotherapeutic measures and small doses of folliculin in a series of 32 menopausal cases, ten of which suffered from hypertension. Albright (5) found that hot flushes and excessive gonadotropic hormone were both prevented by administration of estrin, although he doubted that the flushes were due to a deficiency of estrogen production. Similar observations on the efficacy of the administration of the natural hormones, estrone or estradiol, or the artificial estrogen stilbestrol, in inhibiting the untoward manifestations

of the climacteric (including hypertension) were made by others (94, 400, 401, 437, 223). The usual dosage is that which produces a normal estrogenic vaginal smear, although Shorr (437) has stated that: "Wide variations in the subjective and biological response to estrogens make attempts to standardize dosage futile."

Estrogenic treatment of climacteric symptoms has not escaped adverse criticism. Ayman (27) reports that the administration of estrone or estradiol, in large doses for a period of three months, had no effect whatever on the hypertension. Similar observations have been made by others (454, 306). Stolkind (454) finds estrogenic treatment to be useless and prefers psychotherapy. Dunn (115) finds estrogens much inferior to sterile saline injections, and Hoffman (215) is in entire agreement. Pratt and Thomas (362) made a very well controlled study of various treatments in a series of 100 patients with menopausal disturbances. They used bromide mixture, phenobarbital, estradiol, lactose, emmenin, and plain peanut oil. These were given various code numbers which were periodically changed by one of them without informing the other. This was done in such a manner that the one who administered the treatment was unaware of the drug used. They found that regardless of the form of therapy the majority of patients were relieved or improved. Indeed the most striking results (85% of the patients improved) were obtained with plain peanut oil. In evaluating estrogenic treatment it should be emphasized that the miraculous results now claimed for the potent ovarian extracts or crystalline hormones were formerly claimed for extracts which now are known to have been devoid of hormonal content.

Striking improvements in the symptoms of the climacteric have been claimed for androgenic hormones alone (262, 397) or in combination with artificial or natural folliculoids (438, 263). The specificity of androgenic treatment is also open to criticism. Thyroid hormone (121) and iodine

(266) have been found by some investigators to abolish the climacteric hypertension. Excellent results (470) and failure (454) have been reported in attempts to lower the hypertension by repeated small venesection. Of interest are the observations of Hannan (185) and Myers and King (324) who have found that the injection of small quantities (10 minims of a 1:1000 solution of adrenalin chloride) of adrenalin provoke typical flush responses in menopausal women who are subject to spontaneous flushes, but do not do so in those who are not predisposed. They attribute this to increased tonus of the sympathetic nervous system. To eliminate the possibility of pain or hypertension influencing the result they injected pituitrin to the same patients at other times and found it to be ineffective.

It is obvious that the climacteric may induce a profound and widespread disturbance in both the endocrine and nervous systems. In the former category there may be symptoms suggestive of ovarian, thyroid, adrenal or hypophyseal dysfunction or any combination of these. Treatment, therefore, is largely empiric and symptomatic and this accounts for the fact that so many diverse forms of therapy have proved to be of benefit. Any form of endocrine therapy which promotes restoration of the status quo ante, whether it be estrogenic, androgenic, thyroid or hypophyseal, is likely to exert a beneficial effect. The same may be said for psychotherapeusis in the form of simple reassurance or sedation.

Relief of the hypertension and other symptoms of Cushing's syndrome has also been claimed for estrogenic hormones (116, 375, 150). Albright, Parson and Bloomberg (8), however, have not been able to confirm this. It has been contended that estrogenic treatment inhibits the pituitary hypersecretion which causes the disease. In view of the important role of the adrenal glands in this condition, and the ability of the estrogens to induce marked adrenal cortical hyperactivity through stimulating the excess production of adreno-

corticotropin, this form of therapy does not appear to be the method of choice.

CHAPTER IX

The Role of the Thyroid Gland

Pathologic manifestations may arise as a consequence of either hypofunction or hyperfunction of the the thyroid. Either condition may be due to a primary abnormality in thyroid function or to secondary hypo- or hyperactivity of the hypophysis. Both states lead to widespread disturbances in metabolism, the nervous system and the cardiovascular system. Space limits a review to the last named manifestation, although this appears to be the result of metabolic upset and not directly to the absence or superabundance of thyroid hormone *per se*.

The characteristic, full-blown, thyreoprivic state in the adult human is that of myxedema. Such patients display puffiness of the face and eyelids, swelling of the tongue and larynx, a low basal metabolism and mental sluggishness. They may also suffer from hypertension (471). Those patients which come to autopsy are usually found to have an enlarged heart (276). The cardiac enlargement is due to a combination of diminished cardiac tonus and myxedematous infiltration of the myocardium, and it returns to normal size following adequate thyroid administration (276). The hypertension, which is accompanied by a drop in both the pulse pressure and minute volume of the heart, is more difficult to understand. It may be due to the hypercholesterolemia which is always prominent in myxedematous patients (225). Cameron (74) points out that there is good reason to believe that the thyroid has no specific effect upon vascular tension, but through its influence upon nutrition it tends to normalize either hypo- or hypertension. Certainly the administration of thyroid to either hypertensive (471) or hypotensive (32) patients with decreased thyroid function leads to restitution of normal blood pressure.

In hyperthyroidism on the other hand there is an increased

B.M.R. (basal metabolic rate), palpitation, tachycardia, loss of weight, dyspnea, muscular weakness and a number of other signs, including pressure symptoms in about one-quarter of the cases (471). However, Cameron (74) states that: " The concensus of recent opinion seems to be that hyperthyroidism per se has no toxic influence on the heart. The heart suffers from its own accelerated metabolism and the load thrown upon it by the increased general metabolism". There has been an increasing tendency to ascribe the hypertension observed in hyperthyroid conditions in both man and animals to the adrenal glands (149, 180).

It is well known that thyroid feeding or treatment with thyroxin increases the size of the adrenal cortex (271, 203, 204, 206, 76), kidneys (76, 206, 203, 259, 271) and heart (271, 203, 206, 76). The kidney enlargement is not accompanied by pathologic changes and therefore it cannot be said that thyroxin or thyroid substance is nephrotoxic. However, Selye (434) has recently shown that thyroxin synergises either the renotropic or nephrosclerotic action of other hormones when they are administered simultaneously.

It has been claimed that hypertension is equally pronounced in patients with toxic nodular (cardiotoxic) goiter or toxic diffuse goiter. The average age of the patients with the former disease, however, is higher and this tends to weight the incidence of hypertension in their favor (69). Noteworthy is the fact that in patients with thyrotoxicosis and hypertension, there often occurs a sharp and marked rise in both systolic and diastolic pressure when the thyrotoxicosis is controlled, and that if thyrotoxicosis develops in a patient who already suffers from hypertension there is a definite drop in the diastolic pressure (69).

Hyperthyroidism does not cause a true hypertension, since while the systolic blood pressure is increased the diastolic pressure remains

constant or drops. Much of the increased blood pressure observed in abnormal thyroid conditions undoubtedly is due to a pre-existing hypertensive state, inasmuch as both essential hypertension and thyroid disease tend to develop at the same period of life. If such cases are eliminated then the hypertension in the remaining hypo- or hyperthyroid patients may very well be ascribed to abnormal metabolism and the participation of other endocrine glands, especially the adrenals and pituitary, in the disease.

CHAPTER X

The Role of the Pituitary Gland

1. The Posterior Lobe

A. Clinical

The vascular disturbance which has most commonly been associated with altered function of the posterior lobe of the hypophysis is that which is found in the so-called "toxemias of pregnancy". The classification of the condition is still in a state of flux, but in general two main groups may be distinguished:

1. Diseases not peculiar to pregnancy (hypertensive disease, hypertensive cardiovascular disease and renal disease).
2. Diseases peculiar to the gravid state (preeclampsia and eclampsia).

This classification has been adopted by the American Committee on Maternal Welfare (quoted by Dieckmann 107). The term "toxemia" will be restricted to the second group in the present instance.

Preeclampsia and eclampsia may be defined as the appearance in the second half of pregnancy (usually in the last trimester) of an abnormal elevation of the blood pressure above the pregravid level, or an increase above the prepregnant level of albumin in the urine in the absence of pyuria and hematuria, with diminution of these abnormalities before or soon after delivery. The preeclamptic condition may be divided into two stages, mild and severe. Mild preeclampsia is the term applied to that condition which may arise during pregnancy, almost always in the twenty-fourth week, characterized by a moderate rise in systolic blood pressure to about 140 to 160 mm. Hg., and a diastolic blood pressure of 90 to 100 mm. Hg. The urine contains less than 0.6 gms.% of albumin and the edema is usually slight and, rarely, may be absent. There are usually no changes in the retinal arteries.

Severe preeclampsia is characterized by greater elevations in both systolic and diastolic pressure and albuminuria of more than 0.6 gms%. The edema is usually severe and hypertensive changes in the retinal arteries are common. Eclampsia is probably the same disease as severe preeclampsia, but, in addition, it is accompanied by convulsions. The lesions observed in preeclampsia and eclampsia differ only in severity.

Renal lesions are the most common finding in the eclamptic state. These consist of diffuse glomerular lesions, ischemic in type, due to thickening of the basement membrane of the glomerular capillaries. The tubules and arteries are usually not involved. Often there are also irregular areas of hemorrhage in the liver accompanied by degeneration and necrosis of the liver cords and thrombosis of the smaller vessels. The lungs are often congested and edematous. The heart shows petechial hemorrhages and focal necrosis of the myocardium in 40 to 60% of the cases. Edema and congestion are prominent in the brain. Degenerative changes occur in the placenta, and in other organs capillary hemorrhages and thrombosis is the common feature. The brief summary of the classification and pathology herewith presented is dealt with in greater detail in the excellent monographs of Dieckmann (107) and Crabtree (91).

Hofbauer (214) first implicated the posterior lobe of the pituitary in the conditions of preeclampsia and eclampsia. He thought it probable that the eclamptic convulsions were due to cerebral anemia caused by the vasoconstrictor action of the pituitary adrenal system. This is an extremely attractive hypothesis for it would explain the edema, the hypertension and the vascular abnormalities. Unfortunately it has not been proven.

The greatest stimulus to the association of the pituitary with eclampsia was the work of Anselmino and Hoffmann (17, 18, 19, 20, 21).

From the blood of twenty-four eclamptic patients they obtained by ultrafiltration a substance which, when injected into rabbits, inhibited water diuresis. They found this substance to be pharmacologically, chemically and physically similar to the pressor hormone "vasopressin", of the posterior lobe. They also detected a pressor substance in the blood ef eclamptic patients whose systolic blood pressure was greater than 180 mm. Hg. Injected into rabbits this led to water retention, hypertension, capillary spasm, coma, fits and lung edema. These substances were not present in the blood of normal pregnant or non-pregnant patients. Since these observations were made there has appeared a series of papers indicating that the ultrafiltration of plasma is too uncertain a method for quantitative determination and that the antidiuretic principle of the posterior pituitary is not present in the plasma in the quantities indicated by Anselmino and Hoffmann. Using similar or improved methods of ultrafiltration and by means of tests on various animals Levitt (278) Hurwitz and Bullock (224), Theobald (467), Wesselow and Griffiths (496), and Byrom and Wilson (73) have failed to detect the presence of antidiuretic or pressor hormone in the blood of hypertensive or eclamptic patients. Teel and Reid (464) have reported the presence of a substance in urine concentrates from preeclamptic and eclamptic patients, or that of normal patients from whom water has been withheld, which exerts an antidiuretic effect when injected into rats. They consider this substance to be similar to pituitrin which it resembles in physical and chemical behaviour. It has been shown that injections of vasopressin exert a marked pressor effect in preeclamptic patients, while normal patients, pregnant or non-pregnant, are relatively resistant (108, 477). The results are not sufficiently constant to justify the use of this reaction as a diagnostic test for preeclamptic toxemias (477).

Ham (179) has recently demonstrated the presence of an antidiu-

retic substance in human and rat urine and in placental extracts. He believes the urine and placental factors to be similar since both fail to pass through a cellophane membrane while vasopressin will. This is attributed to the fact that the commercial product is a hydrolytic derivative of the posterior pituitary and therefore may have a smaller molecule than the true hormone.

In summary it may be said that while there may be increased amounts of antidiuretic substances in the blood of toxemic patients, the nature and source of these is not certain. The same is true of pressor substances, hence the role of the posterior lobe in pregnancy toxemia, if any, is obscure.

Preeclamptic and eclamptic manifestations are confined to the gravid state and disappear soon after normal delivery or fetal death. The appearance of identical symptoms during molar pregnancy seems to eliminate the fetal tissues as the etiologic factor. It is not surprising therefore that the placenta, which is the major source of gonadotrophic, estrogenic and progestational hormones during the latter half of gestation has been regarded with more than a little suspicion. While several investigators have found excessive amounts of gonadotrophic substances in the blood of eclamptic patients others have found the values to be low or normal. The results of estrogen and pregnanediol determinations have been equally conflicting. The purported therapeutic value of treatment with estrogen, progesterone or a combination of the two has also been vigorously disputed (215).

Recent investigations have not clarified the status of the toxemias of pregnancy which must still be classified as diseases of unknown etiology in which endocrine disturbances participate in an important, but intangible way.

B. Experimental.

The supposed discovery of posterior lobe hormone in the blood of eclamptic patients stimulated an effort to reproduce the symptoms of eclampsia in animals by means of hormonal injection. Fauvet (126) injected the pressor hormone of the posterior lobe into guinea pigs and observed necrosis and thrombus formation in the hepatic arteries together with changes in the kidneys suggestive of glomerulonephritis. Oligmacher (338) could not confirm this; however he used smaller doses. Watrin and François (488) claimed to have produced cardiac hypertrophy in guinea pigs by injections of vasopressin. However, there were only six animals, three injected and three controls, and the significance of the results is doubtful. Byrom (71) found that the injection of repeated large doses of vasopressin into rats produced gross lesions of the kidneys, liver and other organs and in arteries generally. The renal lesions were accompanied by a transient hypertension and were apparently due to an intense focal arteriolar spasm. If the spasm were maintained there occurrred necrosis of the arterial media and increased permeability of the arterial tree beyond the site of constriction. This was accompanied by delayed water excretion, albuminuria, coma, catarrh and degeneration of renal convoluted tubules and focal hepatic necrosis. The lesions healed spontaneously upon cessation of treatment and there was no evidence of cardiac hypertrophy. There were no pathologic alterations in the brain, heart or pancrease such as are sometimes found in eclampsia. Similar changes did not occur in untreated or oxytocin injected control animals.

The same author later observed that the sensitivity to the toxic effects of vasopressin could be greatly enhanced by preliminary treatment with estrogens (72). Dexter and Weiss (104) were unable to induce renal lesions in either rats or rabbits with pitressin alone or following sensi-

tization with estrogens. Much of the confusion which has arisen as a consequence of the conflicting results seems to be due to the failure to recognize the importance of variable factors in the experimental procedures. In this laboratory it has been observed that, in rats at least, renal vascular lesions may be induced with great frequency by vasopressin injections.

There are many factors influencing the response which have not received adequate attention in the literature. The route of hormone administration; the size and sex of the rat; pretreatment with folliculoid hormone and the amount of water and food intake have all been found to affect the response. Intraperitoneal injection is more effective than the same amount given subcutaneously. Rats of between 120 and 150 gms. are more sensitive to treatment than smaller or larger ones. Older animals are, in general, better test objects than young when the dose given is proportional to the body weight. Sensitization with folliculoid hormone (diethyl-stilboestrol) considerably accentuates the degree and severity of the lesions. Intact females or castrate males respond more markedly and consistently than normal males. Finally, the effect is best observed in animals which have been deprived of both food and water for a period of from 24 to 48 hours before the pituitrin injections are begun (421). If these factors are borne in mind, then, following suitable sensitization with stilbestrol, treatment with the pressor fraction of the posterior pituitary (pitressin, vasopressin or pituitrin) results in extensive renal infarction, gastric ulceration and sometimes acute appendicitis.

These observations indicate that even though it is not certain that there is excess production of posterior lobe hormone during the toxemias of pregnancy, the quantities which are secreted may be rendered more toxic by the increased amount of circulating estrogens. The increased secretion of estrogens at this time may also sensitize the vascular system

to the action of pressor substances released from the placenta or other tissues.

II. The Anterior Lobe

A. Clinical Conditions.

Cases of the association of hypertension and acromegaly are not uncommon in the literature. Hypertension in this condition, which is known to be due to hyperplastic or adenomatous alteration of the eosinophil cells in the anterior lobe, may also be accompanied by evidence of muscular weakness (31). Hechst (200) reports the occurrence of arteriosclerosis in the small and medium sized renal vessels in two out of three patients with acromegaly who came under his observation. Both cases also exhibited a degeneration of nerve cells in the supraoptic nucleus and this was advanced as the probably cause of the hypertension. Brenning (59) reviewed the coincidence of acromegaly and hypertension in 76 patients, twenty-eight of whom were under forty years of age, while forty-eight were over. In the young group only two had hypertension and this was of mild degree, while in the older group consisting of thirty women and eighteen men the incidence was 70% and 11% respectively. He concluded that some malfunction of the pre-hypophysis was responsible since the disturbance was more common in women of post-climacteric age. Renal arteriosclerosis is an extremely common manifestation in such patients at necropsy.

Despite the fact that malignant hypertension is a common finding in acromegalics, the disease is even more commonly associated with basophilic changes in the pituitary. Skubiszewski (440) seems to have been the first to suggest that the hypophysis plays an essential role in primary hypertension. He noted increased basophilia of the anterior lobe in cases of renal disease with hypertension. Cushing (98) was impressed by the coincidence of hypertrophy, hyperplasia or adenomatous transformation of the pituitary and hypertension, usually accompanied by vascular disease, and

listed a series of thirteen cases of the syndrome which now bears his name. Among the more common symptoms of Cushing's syndrome are insulin resistant diabetes, muscular weakness, osteoporosis, hypertension and vascular disease of the kidneys (7). Reports on the association of pituitary enlargement, with basophilic abnormalities, and hypertension, arteriosclerosis or both, are numerous (67, 46, 99, 394, 299, 296, 393, 92, 277, 165, 269, 456, 517, 139, 310). Malignant nephrosclerosis and arterio- or arteriolosclerosis of other organs in the body is an almost constant accompaniment of Cushing's disease (139, 456, 269, 165, 92, 393, 296, 299, 394, 46). Conversely an increase of the number of basophilic cells in the anterior lobe was noticed in eight out of nine patients who had malignant hephrosclerosis, eight out of nine who had hypertension with chronic nephritis and only two out of fifty controls (41). The same was found to be true of patients with essential hypertension, uremia, eclampsia and certain forms of increased intracranial pressure (39). Thus it would seem that hypertension and an increase in the number of basophil cells in the hypophysis go hand in hand, just as do hypertension and arteriosclerosis.

MacMahon et al (296) have shown that both in Cushing's syndrome and in malignant nephrosclerosis as originally defined by Volhard and Fahr there is hypertension, cardiac hypertrophy, increased blood N.P.N., a diminution of the concentrating and diluting power of the kidney, polyuria, retinitis and uremia. They base their conclusions on a large series of cases. Most patients suffering from malignant hypertension do not show the osteoporosis, adiposity and the disturbances of the secondary sex characteristics so typical of Cushing's syndrome. In all probability this is because in the former disease, the adrenal glands are stimulated to produce mainly salt active hormones, while in the latter both sugar active and salt active hormones, as well as adrenal androgens are produced. The reason for believ-

ing the adrenals to be responsible for most of the symptoms of Cushing's syndrome will be discussed later.

It has not been possible to detect any increase in the secretion of pituitrin in cases of hypertension (222), but there is evidence of increased secretion from the anterior lobe. Westphal et al (498) made extracts from the blood of hypertensive patients and found that in about 86% of well over 100 patients with either essential or malignant hypertension, they could extract a pressor substance which, from its ability to enlarge the adrenal glands of animals when injected, they considered to be identical with the adrenocorticotropic hormone of the pituitary. This substance was absent from the blood of control patients. Similar results have been reported by others (409).

Further indication that the pituitary gland is involved in hypertension is offered by the observation that X-irradiation of the pituitary region may improve the condition (111, 227, 96, 97). Irradiation of the pituitary has also led to amelioration of the symptoms in cases of Cushing's syndrome (139, 517). Seligsohn (409) cites a case diagnosed as Cushing's syndrome in which both the hypertension and hyperglycemia returned to normal after treatment with Novuril or Neptal with ammonium chloride. This is interesting in view of the fact that ammonium chloride completely prevents the nephrosclerosis which is induced in rats by treatment with either desoxycorticosterone acetate, or crude anterior pituitary extracts, and sodium chloride (177, 429).

The term "Cushing's syndrome" may be used according to etiology. If so it is restricted to cases where some abnormality of the basophil cells has been demonstrated. Or it may be used according to symptomatology without regard to etiology. In the latter event it becomes difficult to separate conditions where the adrenals seem to be primarily at fault from

those where the hypophysis is to blame. In most cases of Cushing's syndrome, regardless of whether the hypophysis shows basophilic change or not, some alteration of the adrenal glands is present in the form of adenomatous (269, 393, 99, 394), carcinomatous (134, 277, 517), hyperplastic (269, 165), or hypertrophic (299, 67, 92) changes. In rare cases the adrenals are said to be normal (517, 86), however, this is doubtful. Albright (7) has given it as his opinion that basophil changes in the pituitary are always accompanied by hyperplasia of the adrenals, but that the criteria for judging this are not fine enough. In agreement with this view Kepler (249) has stated that probably adrenal hyperfunction may occur in the absence of any detectable histologic change in the glands.

On the other hand cases diagnosed as Cushing's disease have come to autopsy in which a serial section of the pituitary gland has failed to reveal any abnormality. In these cases the symptoms were due to an adrenal cortical carcinoma (134). Instances of so-called Cushing's syndrome have also been reported in which a complete regression of symptoms has followed the removal of a cortical adenoma or excision of parts of hyperplastic adrenals (486). The blood sugar, and also the blood and urine sodium and potassium, in Cushing's syndrome, shows a shift from the normal that is diametrically opposite to that seen in cases of adrenal insufficiency, and in the same direction as that observed in cases of primary adrenal hyperfunction (13).

Anderson et al (12, 13) have found that extracts of the blood or urine of patients with pituitary basophilism contain substances capable of prolonging the life of adrenalectomized rats. This action was not shown by extracts derived from the same amount of blood or urine of normal adults. Weil and Browne (491, 492) have confirmed this and extended it by showing that extracts obtained from the urine of hypertensive patients or those

suffering from the adrenogenital syndrome exhibit a like action.

It is not surprising, therefore that the symptoms of pituitary basophilism and those of primary adrenal hyperfunction are strikingly similar. In general, patients with Cushing's syndrome are more affected by the osteoporosis and less by the hirsutism than are victims of adrenal hirsutism, but a differential diagnosis of the two conditions is difficult.

B. Experimental Effects

Thaon (466) injected a saline suspension of sheep or beef hypophysis into rabbits at variable intervals for six weeks and noted that the animals developed a marked diuresis, a rise in arterial pressure and a mild paralysis of the hind quarters. At autopsy the kidney was hyperemic, while the glomeruli were edematous and showed exudation into the capsular space with signs of cellular proliferation at certain points of the capsule and its glomerulus. The changes were thought to be those of subacute glomerulonephritis.

Blount (52) transplanted pituitary anlagen into the embryos of amphibia (Amblystoma punctatum) and produced thereby a condition which he considered analogous to that of hypertension in man. There was vasoconstriction, slowed heart rate, thickened ventricular wall and edema. The glomeruli did not fill the capsular spaces. The lesions, progressive with age, were accompanied by hypertension which began before the onset of pathologic changes. It was admitted that the pituitary hormones, which were secreted constantly as judged by the pigmentation, might exert their action through the adrenals (53).

Selye (420) has shown that crude extracts of cattle pituitary if given to rats in small doses produces a selective enlargement of the heart, kidney and spleen. If the treatment is more prolonged and intense, and the animals are unilaterally nephrectomized and maintained on a regimen high in sodium chloride, then the animals develop nephrosclerosis, periarteritis nodosa and cardiac changes similar to those of rheumatic fever in man.

CHAPTER XI

The Role of the Adrenal Glands

I. The Adrenal Medulla

A. Clinical Conditions

In 1922 Labbé, Tinel and Doumer (265) first presented a large series of convincing cases that showed the association of paroxysmal hypertension and phaeochrome tumors of the adrenal gland. The raised blood pressure, which sometimes dropped to normal, was accompanied by albuminuria and nitrogen retention. Death usually resulted from lung edema. Despite the fact that uremia was an outstanding symptom during life, necropsy revealed no signs of vascular lesions in the kidney. Langeron and Loheac (267) contrasted cortical tumors with medullary and noted that while the former were characterized by a constantly elevated blood pressure and the latter by a fluctuating hypertension, there was an abnormally high concentration of adrenalin in adrenal tumors regardless of their histologic nature. They considered the hypertension in both cases to be due to the excess liberation of adrenalin. This does not appear to be likely for in patients with adrenal cortical tumors death commonly results from vascular rupture, renal or cardiac failure, but seldomly from lung edema which is the usual sign of death from adrenalin overdosage. The coincidental occurrence of phaeochrome tumors or medullary hyperplasia and cortical adenomas has also been reported (34, 159).

When the hypertension has been of long duration retinal haemorrhages and exudates are a common finding (474, 47). Bouts of hypertension, which can usually be elicited by massaging the area of the tumor or by emotional excitement, together with all other symptoms of the affliction, disappear upon removal of the tumor (474, 47).

It has been noted that, although the hypertension is of paroxysmal nature in the case of medullary tumors, the blood pressure is often mildly elevated between the periods of crisis. This cannot be ascribed to irreversible degenerative changes in the vascular bed because complete normality is still achieved by excision of the tumor. A possible explanation for this has recently been offered by Vogt (482). She finds that either the injection of quantities of adrenalin comparable with those found in the body or direct stimulation of the splanchnic nerves will, in eviscerated dogs and cats, increase the output of cortical hormone to several times the resting value. The sensitive Selye-Schenker test (432) was used to assay the hormones in the blood. The action was not mediated by the pituitary which indicates the possibility of an indirect control over the activity of the adrenal cortex by the sympathetic nervous system.

B. Experimental Observations.

The discovery of adrenalin stimulated investigation into the toxic effects of pressor substances. Josué in 1904 claimed that an unspecified amount of adrenalin administered to rabbits for an unstated period of time led to the production of atheromatous lesions in the aorta of rabbits. There was reduplication of the inner elastic membrane and calcification of the media (241). The chronic administration of adrenalin led to a permanent hypertension (242). Unfortunately there were no controls. It was later found that single doses led to changes in the kidney that were confined to the tubular component (353). Külbs (261) observed a hypertrophy of the media and necrosis accompanied by thickening of the intima in the medium sized arteries of rabbits as a consequence of prolonged treatment with adrenalin. Stief and Tokay (453) administered adrenalin intravenously to dogs and rabbits over a period of four months. They noted medial sclerosis of small and medium sized arteries and arterioles, and intimal changes in the aorta. They did not say just where the lesions were found, nor offer convincing photographs in support of their contention. Controls were not used. Iwanowski (232) noted that in addition to the lesions in the small and medium arteries of rabbits, the prolonged administration of adrenalin also led to damage of the capillaries.

The effects of administered adrenalin are transient owing to the rapidity with which it is destroyed in the body, and large doses are not feasible because of the fatal pulmonary edema which they cause. It is not surprising, then, that comparatively few investigations have been made into the effects of chronic overdosage. In those that have, the results were inconclusive.

II. The Adrenal Cortex

A. Clinical Conditions

Attention has been drawn to the almost invariable association of basophil cell increase in the hypophysis and increased activity of the adrenals. The part played by the adrenal glands, when these are obviously enlarged or hyperactive, will be discussed later, but first there is some indirect evidence implicating the adrenals in hypertensive disease.

In 1910 Neubauer (325) showed that the blood sugar is usually elevated in patients with hypertension, but that glycosuria is most often absent. This finding has been substantiated by most investigators, especially for essential hypertension (511). While, admittedly, organs other than the adrenal cortex may affect the blood sugar, it seems likely, in view of the extensive evidence of morphologic changes accompanying hypertension, that the cortex is hyperactive under these conditions. A further indication of this is that patients with essential or malignant hypertension show a lower level of serum potassium than do normal patients on the same diet and depression is greater in the malignant phase (497). The high serum potassium of patients with adrenal hypofunction or adrenalectomized animals is one of the most characteristic features (62, 66, 309, 330, 473, 260). Conversely, the administration of active corticoids, especially desoxycorticosterone acetate, tends to establish normal levels in either adrenalectomized animals or Addisonians (331, 191, 190, 495, 193, 350, 475, 308, 472, 127) and in large doses even depresses the serum potassium below normal.

Cushing remarked that the symptoms which he ascribed to increased basophilia of the anterior pituitary were more commonly encountered among women, especially during or after the climacterium. The same situation was

found by Brenning (59) to prevail in hypertensive acromegalics. Alvarez (11), who summarized the findings on 15,000 university students, noted a high degree of correlation between the incidence of hypertension and symptoms of ovarian hypofunction. Hypertension is very common in artificially sterilized women (159a). Hutton (226) in 1935 put forward the theory that essential hypertension is an endocrine dysfunction. He noted that adrenal enlargement was common in acromegalics and that essential hypertension usually coincides with menopause in females and decline of potency in males, and suggested that possibly the adrenal was stimulated at this period of life.

As far back as 1910 it was noted that the adrenals of patients dying from advanced Bright's disease, and having contracted kidneys at necropsy, were enlarged and rich in lipoids (469, 4). It has been established that there is an increase of adrenal cortical hormones in the blood and urine of patients with hypertension (491, 369).

In 1904 Aubertin and Ambard (26) recorded nine cases of nephritis and hypertension in which five showed diffuse hyperplasia of the cortex and three others had adenomas of the gland. Achard and Thiers (1) observed the occurrence of hyperplastic adrenals in cases of virilism, hirsutism and hypertension which they called "diabetes of bearded women".

The coincidental occurrence of hypertension and hyperplastic, adenomatous or carcinomatous adrenals, often in the absence of any demonstrable alteration in the morphology of the hypophysis, has been widely observed (54, 134, 250, 251, 268, 279, 289, 310, 334, 339, 340, 384, 385, 486, 468, 499). The high degree of correlation between adrenal cortical tumors and hypertension cannot be merely a fortuitous circumstance (339). Sarason (399) found that there was almost always an enlargement of the adrenal cortex in cases of hypertension, this being most striking when the

hypertension was associated with primary vascular disease. He was unable to offer an explanation of the fact that the adrenals were larger in cases of nephrosclerosis than in other types of renal disease. Bruger et al (68) were unable to confirm this. They failed to detect any difference between adrenals from hypertensive and those from normotensive patients in a series of 65 and 70 respectively. They admitted, however, that this evidence did not preclude the possibility of adrenal cortical hyperactivity in hypertensive disease. Weil and Brown (491) have reported the increased excretion of cortical hormone in the urine of patients suffering from hypertension, Cushing's syndrome or the adreno-genital syndrome, while it was absent from normal urine. They also record the presence of cortical substances in the urine of patients treated with either cortin or desoxycorticosterone.

Beneficial effects have been reported as a result of excision of an abnormal adrenal, by removal of portions of hyperplastic adrenals (103, 250, 268, 485, 486), or by irradiation of the glands (226) in patients with symptoms of hypercorticoadrenalism. Partial removal of the adrenals has also been reported to be of benefit in the therapy of thromboangiitis obliterans and endarteritis (455).

Addison described the disease which now bears his name in 1855. The characteristic symptoms of the malady are hypotension, hypoglycemia, excessive pigmentation, gastrointestinal disturbances, anuria, low blood sodium and chloride and high blood potassium. Inasmuch as destruction of the adrenal glands was the prominent feature at necropsy, and the medulla of the gland was often unaffected, it seemed obvious that the cortex was responsible. This led to the attempt to extract from the glands a substance capable of reversing the symptoms of Addison's disease and maintaining the life of adrenalectomized animals. Such extracts, derived from cattle

adrenals by means of organic solvents were obtained in 1931 by Hartman (192) and also by Swingle and Pfiffner (459-461) and others (520). These extracts also corrected the low blood pressure of schizophrenics (136).

Glycerine extracts of adrenal glands were shown to be active orally, to have a pressor action of long duration and to be as strong in medulla-free preparations as in whole adrenal extracts (218). This seemed to eliminate the possibility of the effect being due to adrenalin. The prolonged administration of these extracts occasionally led to hypertension and had to be discontinued (217).

It was difficult to ascribe the pressor effects of these extracts to any one chemical substance because they consisted of a mixture of steroid compounds. The excessive cost of these whole-gland extracts, to which the name "cortin" was given, stimulated the search for potent crystalline compounds which could be extracted from the adrenal or prepared synthetically.

This was accomplished in 1937 when the 21-hydroxy analog of progesterone was prepared from stigmasterol (452) and given the name of desoxycorticosterone. This compound was later isolated from the adrenal glands (378). The acetate and propionate esters were made available commercially and found to have identical effects.

Administered to patients with Addison's disease, they restored the hypotension to normal or above. Desoxycorticosterone acetate in large doses was found to cause sodium and water retention, hypoproteinemia, marked edema and cardiac insufficiency, but to be without effect on carbohydrate metabolism (51, 128, 449). Correction of the hypotension in Addisonians did not occur as a result of moderate doses of sodium chloride or cortical extract (56, 500). Large doses of desoxycorticosterone acetate were found to cause hypertension (395). Other complications arising from excess amounts of desoxycorticosterone acetate consisted of headache,

cardiac enlargement, neuromuscular pains, muscular weakness and paralysis (211, 472).

Because of its tendency to cause undesirable side effects, the use of desoxycorticosterone acetate was not recommended unless strict observation of the patient was maintained (308). The danger of severe cardiac damage resulting from desoxycorticosterone acetate therapy was considerably augmented if there occurred, simultaneously, an excessive intake of sodium chloride (309) or an extreme curtailment of potassium (309, 160). The toxic cardiovascular effects of desoxycorticosterone acetate, which are so pronounced at high dose levels (371, 391), may also be exhibited by cortin when this is accompanied by high-sodium chloride intake (10).

B. Experimental Observations

Perhaps the most striking property of adrenal cortical extracts is the ability to restore the low blood sugar, liver and muscle glycogen of adrenalectomized animals to normal levels or above (64, 65, 285). In most animals, and man, adrenal deficiency is characterized by low levels of sodium and chloride in the blood and potassium retention. The administration of cortical extracts normalizes the blood chemistry (257, 193, 194).

More recently it has been reported that succesive cortin extractions yields two fractions; one which restores the blood sugar of adrenalectomized animals to normal but is without effect on the level of sodium, and one which restores the sodium levels but is free from carbohydrate activity (195, 196). The latter is said to have the same potency as desoxycorticosterone, but not to be identical with it. The former, which continues under the name cortin, maintains adrenalectomized animals in normal health in spite of the diminished blood sodium levels. Extracts of the adrenal cortex which are particularly potent with regard to decreasing blood potassium levels have also been prepared, and are probably rich in desoxycorticosterone acetate or some similar related compound (331).

The only important effect which these extracts exert upon the vascular system is their ability to decrease the abnormally high capillary permeability which occurs as a result of either carbon arc irradiation (167) or the administration of inflammatory exudates or leucotaxine (314). This may be related in some way to the ability to produce vascular damage, but the relationship is not clear.

When crystalline desoxycorticosterone acetate became available it was tested extensively in both intact and adrenalectomized animals. Administered to intact or adrenalectomized dogs it led to sodium and chlor- [illegible] In the adrenalectomized

rat it prevented serious loss of sodium and chloride even when the intake of sodium chloride was low (380), but if administered for a long period of time the whole blood chlorides of the rat were actually depressed (423). Overdosage resulted in a depletion of brain and liver potassium in intact rats (519) and an increase in muscle sodium at the expense of potassium in the dog (323). Hypervolemia due to increased plasma volume was reported in the rat (423) and dog (85) subsequent to the use of desoxycorticosterone acetate. Prolonged treatment sometimes led to hypoglycemia (380).

Kuhlmann et al (260) and others (127, 316) noted that periodic spells of paralysis supervened when dogs were chronically treated with desoxycorticosterone acetate and, inasmuch as these were accompanied by a serum potassium deficiency and could be overcome by the administration of potassium chloride, they thought the condition to be similar to that of familial periodic paralysis in man (368). However, other factors must be involved because even more striking depressions of serum potassium are observed in man as a result of testosterone therapy, without there being signs of muscular weakness (70). Nevertheless, desoxycorticosterone acetate is the most effective of the crystalline compounds derived from the adrenal cortex with respect to the ability to affect the potassium balance of the body (495).

One of the most characteristic features of desoxycorticosterone acetate overdosage is the condition of polydipsia and polyuria, simulating diabetes insipidus, which develops in dogs (374, 321, 127, 316) and rats (63, 374, 422). These symptoms are aggravated by a high intake of sodium chloride (321, 374).

Selye (411) and others (258, 290) have observed that desoxycorticosterone acetate causes marked renal enlargement in either intact or hypophysectomized (410) rats, although in hypophysectomized animals the

kidney is not restored to normal size. Durlacher et al (117) found that the renal enlargement, which consists mainly of dilatation, hypertrophy and hyperplasia of the tubules, could be prevented by the addition of KCl to the drinking water. Others have not been able to confirm this (302).

Increases in the blood pressure of rats (61, 174) and dogs (380, 386) have been noted to occur as a consequence of desoxycorticosterone acetate treatment, and the low blood pressure of adrenalectomized rats and dogs is restored to normal levels (270, 458). Pathologic changes in the vascular system or kidneys, however, has not been reported.

Darrow (100, 101) found that either the administration of desoxycorticosterone acetate or maintenance on diets low in potassium led to necrosis of myocardial fibers and replacement by fibroblasts. The potassium deficiency seemed to be responsible inasmuch as the lesions could be prevented by giving KCl and were most severe when rats were maintained on both desoxycorticosterone and a low potassium diet.

Selye (414, 415, 416) observed that the administration of desoxycorticosterone to young chicks resulted in cardiac dilatation ahd hypertrophy, tissue edema, ascites, pericardial fluid accumulation and nephrosclerosis. This could also be produced by 0.9% NaCl solution alone given as drinking water (413). A concentration of sodium chloride in itself innocuous proved highly toxic when given together with desoxycorticosterone acetate (433). Although it has not been possible to produce vascular changes in the mammal by means of NaCl alone with any degree of consistency, Leopold (273) has reported the occurrence of a secondarily contracted kidney in a dog that was chronically treated with it. Hoessli (213) found that the intraperitoneal injection of more than 10% of the body weight of 0.9% NaCl solution to guinea pigs caused hyperemia of the glomeruli and fatty degeneration of the heart and kidney. Other sodium salts were found to

have the same effect. Rössle (390) noted the development of ascites, tissue edema and parenchymatous nephritis in patients who had received excessive infusions of NaCl. Proger et al (367) observed that in patients suffering from heart failure a moderate increase in sodium chloride intake sometimes led in three or four days to a clinical picture indistinguishable from that of congestive heart failure. It is possible that under conditions of adrenal hyperactivity small increases in the intake of sodium chloride would prove to be highly damaging.

The nephrosclerosis observed in the kidneys of chicks as a result of desoxycorticosterone acetate, NaCl, or both, is essentially similar to the corresponding disease of man. There is cloudy swelling of the tubular cells and an increase in the height of the epithelium throughout the nephron, especially in the proximal and distal convoluted tubules. Cellular and hyaline cast formation is prominent in the tubular lumina. The glomeruli, owing to hyalinization of the capillary walls and proliferation of epithelioid cells in and around the capsule of the renal corpuscles, are greatly hypertrophied. This leads to the formation of epithelial crescents, typically present in human nephrosclerosis. In the chronic stage the tubular changes become less prominent than the vascular. The glomerular sclerosis is more pronounced and a hypertrophy of the walls of the small and medium sized arteries and arterioles is observed. Thus there are two stages in the progression of the lesion; the first, or edematous stage, which resembles the so-called "large white kidney" of human pathology, and the chronic stage in which contraction leads to the development of a secondary contracted kidney.

It has been reported that the grafting of adrenal glands into rabbits produced widespread vascular changes in which endarteritis was the conspicuous feature. Thickening and hypertrophy of the intima and media

C. The Pathology of Non-Specific Damage

If the rat is subjected to treatment with an agent which requires intense adaptive adjustment, not of local but of a general nature, it responds in a predictable manner. The sum total of the changes, both physiologic and morphologic which it undergoes, constitute what is known as "the alarm reaction". This has been defined by Selye as follows: "The alarm reaction is the sum of all biological phenomena elicited by sudden exposure to stimuli to which the organism is, quantitatively or qualitatively, not adapted". Typically this consists of two phases, shock and counter shock. In the first stage there is tachycardia, decreased muscular tone, decreased body temperature, ulceration of the gastrointestinal tract, haemoconcentration, anuria, edema formation, acidosis, a depression of the blood sugar, leucopenia followed by leucocytosis and the discharge of adrenalin from the adrenal medulla. The second phase, which sets in anywhere from a few minutes to twenty-four hours later depending on the intensity of the alarming stimulus, is typified by hypertrophy of the adrenal cortex which is rich in lipid granules, involution of lymphatic tissue throughout the body and a general reversal of the symptoms of the shock phase (418, 419). This lasts for a time and then blends into the stage of resistance (which may last for days or weeks) in which the adrenals are large and rich in lipoids. Finally the adaptation breaks down and the stage of exhaustion begins. This leads to death of the animal if the stimulus continues (412).

In general, adrenalectomized animals react in identical fashion during the first stage except, of course, for such reactions as depend upon the presence of adrenals (i.e. discharge of adrenalin), but are unable to develop a well-marked counter shock phase. The same may be said of hypophysectomized animals, although in both death rapidly supervenes if the

the response, the degree of which is proportional to the amount of general damage caused. Among these may be cited traumatic shock, obstetrical shock, muscular exercise, drugs, infectious disease, haemorrhage, nervous shock, exposure to cold, temporary blood vessel ligation, reduced oxygen tension, burns, X-rays, radium rays and solar rays.

The role of the adrenal in the general response to such stimuli is evident in view of the absence of marked counter-shock phenomena in the adrenalectomized or hypophysectomized animal. D.C.A., which causes involution (compensatory atrophy) of the adrenal, and thereby deprives the animal of the protective corticoids for which D.C.A. cannot compensate, considerably reduces the resistance to damaging agents (424). The enlarged adrenal of the counter-shock and resistance phases is apparently producing only corticoid hormones, since it is not possible to detect the presence of folliculoids or testoids in the gonadectomized rat at this time (3).

Following the observation that D.C.A. causes nephrosclerosis in the rat, and that the ability to do so is considerably facilitated by unilateral nephrectomy and a 1% saline regimen, (which is to be reported in the experimental section) it was reasoned that animals suitably sensitized and chronically exposed to damaging stimuli should develop the disease as a consequence of adrenal hyperactivity. A series of experiments proved this to be so. Animals subjected to cold for long periods were shown to develop nephrosclerosis when given 1% NaCl ad lib. The same was found to be true of muscular exercise or formalin although to a lesser degree (417). It has also been observed that the myocardial level of adrenal hormones is increased after treatment with D.C.A., strophanthin or insulin, or following exposure to cold or forced physical exercise (370).

In view of the experimental evidence at hand it would appear to be very likely that many human diseases of hitherto unknown etiology,

characterized by evidence of adrenal hyperactivity are due to the excess production of hormones from the adrenal cortex.

Attention has already been drawn to the important role of the adrenal glands in hypertension, Cushing's syndrome, the adrenogenital syndrome, idiopathic nephrosclerosis and periarteritis nodosa, but it is more difficult to elucidate the cause of the adrenal hyperactivity in these cases. It would not be possible to enumerate all the pathologic conditions in which hyperfunction of the adrenals might be implicated, but it is possible to indicate a few examples of non-specific damage leading to disease conditions.

Reference has been made to the fact that the blood and urine of patients with Cushing's disease, adrenal hirsutism, or hypertension contain abnormally large quantities of adrenal cortical substances. It has also been observed that patients subjected to a variety of surgical interventions excrete from three to thirty times as much cortin-like substance in the urine as normal individuals. These substances, which are presumably metabolites of the cortical hormones, are also more abundant in the urine of patients suffering from burns or infections (479, 490). It therefore would seem that a number of unrelated stimuli are capable of initiating, through the mediation of the pituitary, adrenal hyperfunction. This is usually of a temporary nature, but it is not difficult to conceive of the process continuing unabated and leading to a pathologic state.

Klotz (256) cites two cases of periarteritis nodosa which apparently had their inception at a time when the patient was subjected to one or more successive exposures to cold and rain. One of the patients had previously suffered from a variety of other diseases, but these were not considered to play an important role. Periarteritis nodosa is one of the diseases of obscure etiology, and it has been pointed out that typhoid

fever, syphilis, serum disease, rheumatic fever and a large number of other conditions have all been implicated in the etiology at one time or another. Often a disease has been blamed even when all signs of it had been absent for a period of many years. Repeated illnesses undoubtedly render the subject more likely to develop pathologic lesions. Unless they initiate some process of a durable nature, however, it is unlikely that they could be directly responsible for causing a condition which appears after several years of normal health.

There are several cases of Cushing's disease on record in which the patient dated the onset of symptoms from exposure to a particularly severe condition. Swan (456) reports a case where the initiating stimulus was a leg injury followed by a septic condition. Brown (67) cites a case in which the symptoms began after hysterectomy. Wright (517) mentions a patient who developed all symptoms of Cushing's disease immediately following a severe emotional shock. Undoubtedly other cases could be found, but unfortunately it is seldom that the clinician thinks of such apparent trifles in a case history nor, in all likelihood, does the patient. All three cases cited showed adrenal enlargement or evidence of adrenal hyperactivity, all suffered from hypertension, and in every respect the cardiovascular and renal lesions found at autopsy resemble those produced in the experimental animal by chronic exposure to damaging agents or following D.C.A. overdosage.

The similarity in the symptomatology of patients with Cushing's disease and those with the adrenogenital symdrome is striking, but understandable in view of the adrenal hyperactivity in both cases. It seems that the first is a compensatory process while the second is a primary pathology. This hypothesis is based on the fact that the administration of methyl-testosterone decreases the 17-ketosteroid excretion of Cushing's

patients considerably, but only slightly affects that of patients with the adrenogenital syndrome (379). It is possible, however, that either malady could be induced by sudden exposure to conditions of severe stress and strain. Albright (7) has recently re-examined the etiology of Cushing's syndrome in the light of the evidence provided by the " alarm reaction ", and considers that the possibility of non-specific noxious stimuli giving rise to the condition has, unfortunately, been neglected by clinicians. This hypothesis derives additional support from the well known observation that Cushing's syndrome is most commonly observed in women during or immediately following the menopause, and in men at the time of the so-called male climacteric, notoriously times of great emotional instability and physical stress.

PART IV

EXPERIMENTAL

Cardiovascular-Renal Lesions Produced by Hormonal Intoxication

Chap. XII

Desoxycorticosterone Overdosage

A. Manifestations in the Rat

1. Nephrosclerosis and Cardiac Hypertrophy

In view of the fact that several corticoid compounds (D.C.A., progesterone and acetoxy-pregnenolone) had been found to induce nephrosclerosis in the chick, an attempt was made to determine whether the first, and most active of these, D.C.A., could elicit a similar response in the mammal.

Experimental:

Twenty male albino rats, weighing 76 to 105 grams with an average of 92 gms. were divided into two equal groups. Group I received 0.1 cc. of an aqueous suspension of D.C.A. twice daily by subcutaneous injection. This amount contained 5 mg. of the steroid. Group II served as uninjected controls. The experiment was continued for a period of 57 days, during which time the animals were kept in individual metabolism cages and the daily urine output was measured. For the first ten days tap water was given to drink, while for the remaining period a 1% sodium chloride solution was substituted. The diet consisted of "Purina fox chow". Thus the diet and salt intake was identical in both experimental and control groups, but only the former re-

ceived D.C.A.

Treatment with the steroid resulted in the development of marked nervous disturbances and during the course of the experiment seven of the animals succumbed, in each case with severe motor symptoms. Most of them showed varying degrees of tremor and hyperirritability, and, in some of them, certain muscle groups became paralyzed. This was especially prominent in one animal, which became unable to move the extensor muscles of one forepaw. These symptoms will be considered more fully in a succeeding section. It is noteworthy that all the animals which died during the period of treatment showed varying degrees of nephrosclerosis and cardiac hypertrophy. These lesions were even more pronounced in the three surviving animals, which were autopsied at the end of the 57 day period.

As early as the fourth day of treatment polyuria began to be manifest in the injected animals even though both groups were, at this time, receiving tap water to drink. The symptoms were much more obvious on the saline regimen. On the eleventh day of injection, at which time the water was replaced by 1% NaCl solution, the treated animals excreted an average of 10.5 c.c. of urine while the controls excreted only 3.5 c.c. Twenty-four hours after the change had been made the treated animals excreted an average of 45.6 c.c. per 24 hour-period while the control figure rose only to 9.5 c.c.

Gross and Microscopic Findings:

The most striking change observed in the D.C.A.-treated animals at autopsy was the enormous enlargement of the kidneys, the surface of which was mottled and rather irregular (Fig.I). A cross section through the kidneys viewed at low magnification (Figs. 2 and 3), revealed that the renal

papilla remained normal in size and the medulla showed only slight structural abnormalities; whereas the cortex was approximately twice as wide as that of the control animals, and exhibited great irregularities due to patches of sclerosis and obstruction of the tubules by casts. Under higher magnification wedge-shaped areas of dense sclerosis were noticeable (Fig.4). Throughout the kidney most of the glomeruli were sclerosed. The tuft capillaries exhibited marked hyalinization, and the glomeruli were often surrounded by masses of proliferating epithelioid cells. The stroma was either infiltrated by small round cells or consisted of thick bands of dense connective tissue. The frequently dilated tubules contained many hyaline casts (Fig.5). Frozen sections stained with Sudan III revealed lipid deposition in the proximal convoluted tubules and in many of the sclerotic glomeruli, as well as in some of the casts. Certain of the medium-sized arterioles were likewise rich in lipid granules and their walls showed marked proliferation of the fibromuscular elements. In general, the appearance was that of the "large white kidney" in the process of transformation into the nephrosclerotic kidney, although the secondary contraction had not progressed far enough to compensate for the initial enlargement.

The heart was likewise greatly enlarged in all the D.C.A.-treated animals, and, in cross section under low magnification, it appeared that both the left and right ventricles were hypertrophied, although the change was much more obvious in the latter (Figs. 6 and 7). Under high magnification (Figs. 8 and 9) it was evident that the enlargement was due to an increase in the width of individual myocardial fibers and not merely to edema. The enlargement of both heart and kidneys is even more striking if we consider that the body weight of the D.C.A.-treated animals was much less than that of the controls owing to growth inhibition. Table I gives the average body and organ weights, expressed in grams (with the range in

brackets), of both groups at the end of the experiment. Since seven of the D.C.A. injected animals died during the course of treatment, the weights of these were not included in the table since they were not comparable to the remaining treated and control rats, all of which were killed on the same day.

TABLE I

Effect of Desoxycorticosterone Acetate on Organ and Body Weights of Rats Sensitized by Sodium Chloride Administration

	CONTROLS Wt. in Gms.	D.C.A. TREATED Wt. in Gms.
Body Weight	226 (185-265)	176 (145-190)
Kidneys	1.75 (1.3-2.0)	3.41 (2.9-4.4)
Heart	0.89 (0.82-1.0)	1.36 (1.34-1.37)
Spleen	1.1 (0.6-1.6)	2.49 (1.82-2.96)

The lesions observed in the treated animals could not have been due to the sodium chloride per se, for the controls received the same amount as the D.C.A. injected rats. Experiments have since shown that D.C.A. in itself can produce the same lesions on a normal diet, that is without added NaCl, but the speed of onset and severity are greatly augmented by increased sodium chloride intake.

From this experiment we may condlude that, if the NaCl intake is excessive, desoxycorticosterone acetate regularly produces nephrosclerosis, with cast formation in the renal tubules and hypertrophy of the renal arteri-

ɔles as well as marked cardiac hypertrophy. These observations have been published elsewhere (425).

2. Malignant Hypertension

In view of the findings of the previous experiment an attempt was made to repeat the conditions in a larger series of animals with the design of more thoroughly examining the vascular alterations in the different organs. Because the changes appeared to be essentially similar to those observed in the malignant hypertension of man, blood pressure recordings were made in an effort to determine whether or not the treatment caused hypertension. The remote possibility existed that the lesions in the preceding experiment were due to bacterial invasion of the injection site, therefore the experimental technique was varied by injecting the controls with cholesterol.

Experimental

Four groups of young albino rats weighing 30 to 46 grams were used. Each group consisted of four males and four females and had an average body weight of 35 grams. Throughout the experiment they were fed "Purina fox chow". The animals of the first group received two daily subcutaneous injections of 3 mgm. of D.C.A. in the form of a crystal suspension containing this amount in 0.1 c.c. of water. At the end of one month the dose was increased to two daily injections of 5 mgm. also given in 0.1 c.c. of water. To this group tap water was given to drink. The second group received the same treatment as the first, but a 1% NaCl solution was substituted for the tap water. Group III was treated exactly as the second group except that they were injected with cholesterol in the same amount and manner as the animals of the other groups were given D.C.A. Cholesterol possesses the sterol nucleus, but is devoid of hormonal properties, and thus it was felt that the animals treated with this compound would serve as in-

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Experimental

Four groups of young albino rats weighing 30 to 46 grams were used. Each group consisted of four males and four females and had an average body weight of 35 grams. Throughout the experiment they were fed "Purina fox chow". The animals of the first group received two daily subcutaneous injections of 3 mgm. of D.C.A. in the form of a crystal suspension containing this amount in 0.1 c.c. of water. At the end of one month the dose was increased to two daily injections of 5 mgm. also given in 0.1 c.c. of water. To this group tap water was given to drink. The second group received the same treatment as the first, but a 1% NaCl solution was substituted for the tap water. Group III was treated exactly as the second group except that they were injected with cholesterol in the same amount and manner as the animals of the other groups were given D.C.A. Cholesterol possesses the sterol nucleus, but is devoid of hormonal properties, and thus it was felt that the animals treated with this compound would serve as in-

jected and NaCl treated controls. The rats of the fourth group were not injected and received tap water to drink. They served as entirely untreated controls.

During the course of the experiment one animal in group I and two animals in group II died from haemorrhagic lung edema and several animals in the second group evinced peculiar nervous symptoms consisting of tic or spasmodic muscular twitchings. Most animals in the second group showed fatigue and collapse upon the slightest exertion, and dispnoea even at rest, symptoms indicative of circulatory failure. The skin and mucous membranes were observed to be cyanotic in most of them, and in a few a mild subcutaneou edema developed.

On the 52nd day of treatment the blood pressure was measured in the animals of all groups by the plethysmographic method of Friedman (472). The average pressure of all groups except group II was 110/80 and the highest pressure observed in any of these groups was 120/90 (if we disregard a single, apparently abnormal, animal in the cholesterol-treated group in which the pressure was 140/100. In group II on the other hand, the average blood pressure was 187/130 with a range of 185/130 to 190/130.

These observations demonstrate that a pronounced rise of both diastolic and systolic blood pressure, accompanied by clinical signs of cardiac insufficiency, results from combined treatment with D.C.A. and NaCl; while NaCl in combination with the hormonally inactive cholesterol is without effect. It is of special interest to note that D.C.A. is relatively less active when the sodium chloride intake is not excessive.

Supporting the results of the preceding experiment was the observation that the diuretic effect of D.C.A. was considerably enhanced by the high NaCl intake. The average daily urine volume, at the sixth week of treatment, was 8.8 c.c. in group I, 49 c.c. in group II, 28 c.c. in Group II

and 6.0 c.c. in group IV. The average daily chloride excretion at this same period (method of Van Slyke) (478) was 0.64, 5.2, 2.8, and 0.61 meq., respectively, and the average daily sodium excretion (method of McCance and Shipp (307) slightly modified by Dr. A. Neufeld) was 1.5, 5.9, 3.3 and 1.1 meq., respectively, in the four groups. Qualitative tests (biuret reaction) revealed the presence of considerable amounts of protein in the urine of all animals in group II, but not in the other groups.

Pathologic Findings

On the 53rd day of treatment all animals were killed and their organs fixed in Suza mixture for histologic examination. Mere naked eye inspection revealed that the kidneys of the animals in group II were definitely abnormal. In each case the surface of the organ was irregular and spotted. In some animals white, slightly depressed, areas prevailed; while in others the surface exhibited the "flea-bitten" appearance characteristic of small intraglomerular hemorrhages. There was marked cardiac hypertrophy in all animals of this group and the aorta appeared to be particularly rigid, although definite sclerotic patches were not detectable. Rather slight irregularities were also noted in the renal surfaces in group I. In the animals of group II pancreas edema was commonly observed and this change was not seen in any of the other groups.

A histologic study of the internal organs revealed that the kidneys were only slightly affected in group I and remained normal in groups III and IV. In group II, on the other hand, the characteristic lesions of malignant nephrosclerosis were evident (Fig.10). The glomeruli were large and showed signs of capsular fibrosis. There was marked hyalinization of the tuft capillaries, and degenerative changes in the afferent glomerular arterioles were particularly pronounced, indeed the walls of these arterioles

were completely necrotic in many cases. The convoluted tubules, especially the distal segments, were dilated and often occluded by the presence of hyaline casts. Erythrocytes were only rarely observed in the capsular space or tubular lumina. Wedge-shaped infarct-like areas, with their apex directed toward the renal pelvis, were of common occurrence. These consisted of degenerating nephrons and proliferations of connective tissue stroma.

The most severe lesions, with the exception of those occurring in the kidney, were encountered in the pancreas. The vascular changes in this organ were qualitatively similar to those in the kidney and equally as pronounced. Proliferation of the perivascular connective tissue, leading to the extension of sclerotic patches between the acini and around the islets of Langerhans, was the most marked feature. Many of the islets exhibited signs of degeneration while others were considerably enlarged, perhaps in an attempt to compensate for the loss of those which had ceased to function because of the infiltrative sclerosis. The media and intima of the pancreatic arterioles were also seriously affected. Fibromuscular proliferation was a conspicuous feature, while in other instances hyalinization and even complete necrosis of the walls was observed. Not infrequently the vascular lumen was completely occluded by a more or less homogeneous necrotic mass (Figs. 11, 12 and 13).

Vascular changes in other organs were less conspicuous except for the vessels of the adrenal capsule which were always severely affected showing fibromuscular proliferation, hyalinization or complete necrosis (Fig. 14).

These experiments indicate that if rats are treated with D.C.A. and maintained on a high NaCl intake there occurs a pronounced rise in both systolic and diastolic blood pressure, marked diuresis with increased excretion of sodium and chloride, proteinuria and clinical evidence of severe cardiac decompensation. Death commonly supervenes due to the development of

3. Vascular Lesions Produced with Small Doses

It became apparent that large doses of desoxycorticosterone acetate exerted a definite cardiovascular toxic effect in rats maintained on a high sodium chloride intake. Inasmuch as the doses used were admittedly large, the action might have been pharmacologic and reproducible only under conditions of heavy overdosage. For this reason it was decided to investigate the response elicited by smaller amounts of the steroid, in order to determine whether chronic treatment with quantities of a more physiologic nature would exert similar effects. At the same time a group of adrenalectomized rats was also injected with D.C.A. in order to see whether they were more or less sensitive to treatment than intact animals.

Because it had been shown that the male sex hormone, testosterone, exerted a protective action against the toxic effects of D.C.A. (431) and that unilaterally nephrectomized rats were more sensitive to the development of nephrosclerosis than intact (430), unilaterally nephrectomized and orchidectomized male albino rats were used in the present study.

Technique of Nephrectomy and Adrenalectomy

The animals to be nephrectomized are anaesthetized in an ether chamber and then placed on their sides on a board especially devised for rat operations The operational site is shaved, and swabbed with 70% alcohol. The left kidney is approached by the posterior route. A longitudinal incision is made about 3/4 of an inch to the left of the mid-dorsal line above the kidney and the lumbo-dorsal fascia exposed. Following the line of incision, and cutting through the muscles in the direction of their fibers, the peritoneal space is exposed and entered. The kidney is externalized by gentle pressure on either side of it. The capsule is stripped and a haemostat clamped below the renal

pelvis so as to occlude the renal vessels. A thread ligature is applied to the vessels distal to the haemostat, and the kidney removed. The muscle walls and skin are taken up in a single stitch which serves to close the wound.

The method of adrenalectomy is essentially identical except that the incision is made a little further forward so that the anterior pole of the kidney is exposed when the peritoneal cavity is entered. The whole adrenal is then carefully grasped with a pair of curved forceps and teased free of the kidney. Care is taken not to rupture the adrenal capsule and the gland is removed in its entirety. The incision is closed by a single stitch as in the case of kidney removal. The operation is then repeated on the contralateral side.

Technique of Male Gonadectomy

The rat is anaesthetized, as described above, and placed ventral surface upward on the rat board. An incision is made through the skin and then through the mid-ventral line of the abdominal muscles in the direction of their fibers. The testes are withdrawn from the scrotal sac by pressure from below, mobilized to the wound and extruded through it. A single ligature is placed around the internal spermatic vessels, the deferential vessels and the ductus deferens. The testes and epididymes are excised together. The muscle coats and skin are closed with a single stitch through both

Experimental

Forty male albino rats weighing between 80 and 105 grams were orchidectomized, unilaterally nephrectomized and divided into four equal groups, each averaging 95 grams. While groups I and II were bilaterally

adrenalectomized, groups III and IV were otherwise unoperated. All animals were given 1% sodium chloride solution to drink and were fed a diet of "Purina fox chow". Groups I and III were injected twice daily, subcutaneou ly, with 0.5 mgs. of finely ground D.C.A. crystals suspended in water, this amount being contained in 0.1 c.c. of fluid. The remaining two groups received no injections. The experiment was carried on for a period of 38 day During this interval four animals in group I, eight in group II and five in group III succumbed, while group IV remained intact.

Gross and Microscopic Observations

At autopsy all animals in the D.C.A.-treated group exhibited marked vascular lesions in the kidneys, and most of them showed cardiac and pancreatic involvement as well. Renal and cardiac hypertrophy was a most striking feature. None of the uninjected rats, adrenalectomized or not, were found to have developed vascular lesions. The peculiar neuromotor symptoms, consisting of a paralytic involvement of the fore and hind limbs and tics of the head and neck, previously referred to as being characteristic of D.C.A. intoxicatiion in the rat, were manifested by several animals of both injected groups. The surviving rats were sacrificed on the 38th day and the organs taken for histologic examination. Table II summarizes the essential data on the body and organ weights. The weights of the heart and kidneys are given both in grams and as the percentage of body weight, the latter with the standard errors. Animals which failed to survive for the full length of the experiment have been excluded from the table.

A perusal of the table reveals that the hormonal treatment exerted a retarding effect on body growth. At the same time it caused a pronounced increase in the heart and kidney weights.

Vascular Pathology

Histologic examination revealed that both the intact and adrenal ectomized animals which received D.C.A. had severe renal and cardiac lesion while the salt-treated controls for each group were entirely free of vascul abnormalities. Not a single animal in either of the treated groups escaped pathologic vascular changes in the heart, kidney or both. The lesions were graded in order of increasing severity from 0 to 3, and the heart and renal lesions observed microscopically were each found to average grade 2 for both the adrenalectomized and intact D.C.A.-treated rats. The lesions were similar in most respects to those already described and depicted in the previous two experiments, and for this reason pictorial representation of them will be confined to a few especially well developed lesions.

Enlarged and hyalinized glomeruli were prominent in both treated groups. One of these, from the group of adrenalectomized and D.C.A.-injected animals, is shown in Fig. 15. Sub-endothelial hyalin deposits were marked in the arterioles of the heart (Fig. 16) and kidney (Fig. 17). In the hearts of many of the animals there were lesions resembling those seen in rheumatic endocarditis, clearly proliferative in type. These consisted of highly vascular, nodular accumulations heavily infiltrated with lymphocytes (Figs. 18 and 18a). In these nodules, which usually contain an eccentrically placed arteriole, there was marked proliferation of fibroblas and large polynuclear cells resembling "Aschoff" cells. In addition to the lesions in the heart, myocarditis was a prominent manifestation. Throughou the myocardium numerous small foci, the center of which often consisted of necrotic or hyaline material surrounded by large epithelioid cells with bulky vesicular nuclei and a more or less basophilic cytoplasm, were abunde Proliferating fibroblasts and infiltrating lymphocytes, plasma cells and

polymorphonuclear leucocytes were often present in such regions. In other areas replacement of degenerating muscle fibers by ordinary, sometimes edematous, connective tissue was observed.

TABLE II

The Effect of D.C.A. on the Body and Organ Weights of Intact and Adrenalectomized Rats Sensitized by Castration and the Administration of Sodium Chloride

Group and Treatment	Final Body Wt. In gms.	No. of Survivors	Kidney Weight		Heart Weight	
			In gms.	as % of Body Wt.	In gms.	as % of Body Wt.
I D.C.A. adrenalectomy	165	6	1.854	1.13±0.07	1.091	0.66±0.04
II adrenalectomy	212	2	1.136	0.53±0.00	0.959	0.45±0.05
III D.C.A. controls	138	5	1.719	1.25±0.03	1.190	0.81±0.03
IV controls	195	10	1.191	0.62±0.02	0.717	0.40±0.02

4. Renal and Cardiac Lesions Elicited by Subcutaneously Implanted Pellets

In view of the fact that rather small doses of D.C.A. were found to cause malignant nephrosclerosis and cardiac lesions in sodium chloride sensitized animals, considerable interest attached to the possible toxic effects of this compound when administered in pellet form. This arose from the fact that the subcutaneous implantation of D.C.A. pellets is the most commonly employed method of administering the compound to Addisonian patients. It is known that small quantities of the substance are continuously absorbed by the subcutaneous tissues under such conditions and, for this reason, it has been suggested that this method affords a more physiologic means of hormone administration than the injection of an oily solution or crystalline suspension. In spite of the small quantities thus liberated, there have been numerous reports of undesirable manifestations arising clinically as a result of this form of therapy (e.g. hypertension); therefore an attempt was made to determine whether actual vascular lesions could be induced in the experimental animal. In addition adrenalectomized, hypophysectomized, ovariectomized, orchidectomized and thyroidectomized groups of rats were treated with D.C.A. in an effort to determine whether the ablation of these glands would affect the response to treatment.

Operational Methods

Ovariectomy

This is carried out in the same manner as nephrectomy except that the incision is made a little more caudally so that the posterior border of the kidney is exposed when the peritoneum is entered. The ovary is then apparent, lying in adipose tissue close to the kidney, and is dis-

sected free of attachments and removed. No ligation of vessels is necessary.

Thyro-Parathyroidectomy

The anaesthetized rat is placed on its dorsal surface upon a rat board and the upper incisor teeth engaged by a wire loop in such a way as to permit the animal to be drawn out at full length and immobilized by means of elastic bands. A ventral midline incision is made extending slightly beyond the upper and lower borders of the submaxillary gland. The salivary glands are separated at the midline by blunt dissection and retracted laterally. The muscle coats lying over the trachea are thus revealed, and they are divided in the midline. Smooth, curved forceps with closed tips pointing upward and directed toward the head are inserted through the incision at the level of the thyroid and are spread apart to expose the glands. The isthmus of the thyroid is divided in the midline. Each gland is then removed separately by seizing the caudal border with a pair of curved forceps and pulling upward and laterally, freeing the organ from attachments while progressing slowly. Following the removal of each gland, a pledget of absorbent cotton is inserted at the site of operation to prevent excessive bleeding from the thyroid artery. Care is taken to avoid trauma or fission of the recurrent laryngeal nerve. The incision is closed with one or two stitches through the skin flaps, avoiding the submaxillary glands.

Hypophysectomy

This operation was performed by the retropharyngeal approach as described by Collip, Selye and Thomson (89a).

Experimental .

Ninety-four albino rats weighing between 40 and 60 gms. with an average body weight of 53 grams were unilaterally nephrectomized and divided into nine groups. All groups consisted of ten rats each except group IV which contained fourteen animals. Group I was composed of female rats; group II consisted of male rats: group III contained bilaterally adrenalectomized females; group IV was made up of hypophysectomized females; group V consisted of oöphorectomized females; group VI rats were orchidectomized males; group VII rats were thyro-parathyroidectomized females and groups VIII and IX were duplicates of groups I and II respectively. All animals, except those of groups VIII and IX which served as controls for I and II, received a cylindrical pellet of crystalline D.C.A. once each week by subcutaneous implantation for the first three weeks of treatment, after which no more were given. The pellets which were made at a pressure of 150 lbs. per pellet, averaged 10 mgs. (range 9 to 15). The experiment lasted for 32 days during which time all rats were given 1% NaCl solution to drink. The diet consisted of "Purina fox chow" except for group IV which received Pablum moistened with 1% saline and group VII which was given Pablum fortified with a small quantity of calcium lactate for five days following thyroid removal.

At autopsy the pellets were removed, dried for 48 hours in a drying oven, and weighed to determine the amount of hormone absorbed. The pertinent data on the number of survivors and their average body weight (in grams), together with the average weight of the hearts and kidneys (expressed as the percentage of final body weight) and the amount of hormone absorbed from the pellet (in mgs.) are given in Table III. The standard error is given for all weights.

Perusal of the table reveals that the kidneys and hearts of all animals receiving D.C.A. were enlarged above controls, except in the

thyroidectomized group. It is not possible to draw conclusions from the hypophysectomized group since only two animals survived for the period of treatment.

Pathologic Findings

Microscopic examination of the heart and kidneys revealed the presence of typical lesions, as previously described, in all of the D.C.A.-treated groups except the hypophysectomized and thyro-parathyroidectomized. These were not as severe as those seen following the administration of large amounts of D.C.A., but then the experiment was of comparatively short duration and only approximately 8 milligrams of the steroid were absorbed during the 32 day period. Nephrosclerosis of grades 1 to 3 was found in most animals of all groups excepting those of groups IV and VII which were entirely free of vascular pathologic manifestations. This lesion was of about grade 1 severity in groups I, III, and V and of grade 2 severity in groups II and VI. There was some variation in response within the groups which seemingly bore no relation either to the size of animal or to the amount of hormone absorbed. It may well be that the more severely affected animals drank more of the saline solution than the others, since experiments in metabolism cages have shown that there is considerable variation in the quantity of fluid voluntarily consumed. The cardiac lesions were not as well developed as those which have been described following the administration of large doses of D.C.A., but seemed to be of about grade I severity on the average and closely paralleled the degree of renal involvement in the same animal, although this was not so apparent when the renal lesions were minimal. Diffuse scarring and replacement of myocardial fibres by edematous connective tissue were of more common occurrence than

hyalinization of arterioles or accumulations resembling Aschoff nodules.

The thyro-parathyroidectomized animals absorbed as much of the steroid as did those of groups in which cardiovascular lesions were elicited, and therefore the absence of lesions cannot be ascribed to deficient absorption. It has since been found that while thyroxin in itself cannot cause nephrosclerosis, in the unilaterally nephrectomized and salt-treated rat, it enhances considerably the ability of either D.C.A. or anterior pituitary extracts to do so (434). In all likelihood the absence of endogenous thyroid hormone in the thyroidectomized rats of the present series protected them against this toxic action of D.C.A. Subsequent to this experiment it has been shown in this laboratory that thyroidectomized animals are more resistant to D.C.A.-induced nephrosclerosis even when the dose is as high as 4 mgs. daily, although the lesions will ultimately develop to the full extent if the treatment is protracted.

Although only two hypophysectomized rats survived the full period of treatment in the present experiment, both were free from vascular abnormalities. It may be that certain hypophyseal hormones enhance the toxicity of D.C.A., but this cannot be stated with certainty. These animals, however, received a Pablum diet, and it has since been shown that high carbohydrate diets of this type protect against the toxic vascular effects of nephrosclerosis-producing hormones (40). In this connection it should be emphasized that the thyro-parathyroidectomized rats of the present series also received Pablum for the first five days of treatment, and while it is unlikely that this would account entirely for the failure to develop lesions, still it may well have played a subsidiary role in this instance.

TABLE III

The Effect of D.C.A. Pellets on the Body and Organ Weights of Unilaterally Nephrectomized Intact, Gonadectomized, Adrenal-, Thyroidectomized and Hypophysectomized Rats

Group	Treatment	No. of Survivors	Final Body Wt. In gms.	D.C.A. Absorbed In mgs.	Organ Weights	
					Kidney as % of Body Wt.	Heart as % of Body Wt.
I	D.C.A. females	6	99±5	7.8±0.21	0.98±0.03	0.56±0.02
II	D.C.A. males	7	118±9	8.3±0.38	1.00±0.02	0.59±0.02
III	D.C.A. adrenal-ectomized females	7	120±6	8.1±0.30	0.84±0.04	0.55±0.03
IV	D.C.A. hypophys-ectomized females	2	85±5	7.5±0.15	0.80±0.08	0.52±0.04
V	D.C.A. castrate females	10	114±10	8.0±0.18	1.07±0.02	0.55±0.02
VI	D.C.A. castrate males	8	125±6	8.9±0.10	1.16±0.02	0.57±0.02
VII	D.C.A. thyroid-ectomized females	7	89±3	8.3±0.27	0.80±0.02	0.48±0.02
VIII	control females	10	126±2		0.65±0.02	0.42±0.01
IX	control males	9	153±5		0.69±0.02	0.41±0.02

5. Periarteritis Nodosa and General Vascular Damage From a Single Implanted Pellet

It has been pointed out in the section dealing with dietary constituents, that high protein diets cause greater renal hypertrophy than normally balanced diets, and that this effect is not so marked if the proportion of vitamin B complex is the same in both the experimental and control diets. Reference has already been made to the fact that under certain conditions high protein diets in themselves may produce vascular lesions if administered for long periods of time. With this in view an endeavor was made to test the effect of two types of diet, one high in protein and the other enriched with the vitamin B complex, on the vascular lesions normally elicited by D.C.A.

Experimental

Forty-six male albino rats weighing between 100 and 150 grams were unilaterally nephrectomized, castrated and divided into four groups each having an average body weight of about 114 grams. One week after the operations a single pellet of D.C.A., weighing about 40 milligrams and made at a pressure of 1,000 lbs. per cm^2, was implanted subcutaneously into the animals of groups I, II, and III. Group IV served as untreated controls and contained 10 rats, while the other groups each consisted of 12 animals. All animals were then given a 1% solution of sodium chloride to drink. Groups I and IV received ordinary "Purina fox chow" rations, while group II was given a diet consisting of two-thirds fox chow and one-third (by weight) brewer's yeast and group III received a diet composed of two-thirds fox chow and one-third casein. The animals were placed on the different diets immediately after unilateral nephrectomy and, when they

were found to thrive on it at the end of one week, a pellet of crystalline D.C.A. was implanted into the animals of groups I, II, and III. The hormone treatment was continued for a period of 46 days, at the end of which the survivors were sacrificed and their organs taken for histologic study.

Between the third and fifth weeks of treatment several of the animals developed peculiar motor symptoms. These were of varying intensity and duration. In the milder cases they consisted of clonic contractions of the forepaws. In more severe cases the head and shoulder muscles underwent rapid contractions which, if unilateral, resulted in a characteristic clonic rotatory movement of the shoulder girdle and head. More rarely the movements were bilateral and caused sudden backward jerks of the head and shoulders. They have been described in detail elsewhere (422a). Some of these rats died before the end of the experiment and they, together with the survivors that had shown motor disturbances, invariably revealed characteristic cerebral lesions which could account for the motor symptoms. Four, eleven, six and six animals in groups I, II, III, and IV respectively survived for the full period of the experiment.

Gross and Microscopic Findings

At autopsy it was evident that all of the hormone treated animals had developed the most severe vascular lesions. The brains of the animals which had shown motor symptoms revealed a characteristic, macroscopically visible, pathology (Fig. 19). Along the superior sagittal sinus, in the cortex or just beneath its surface, small hemorrhages were visible in one or both cerebral hemispheres. Histologic examination showed that many of the small arterioles in the subarachnoid space showed sub-

intimal hyalinization and round cell infiltration within the vessel walls. The lesions were characteristic of periarteritis nodosa. In the region of such vascular damage there often occurred extensive destruction of brain tissue with diffuse hemorrhages (Figs. 20 and 20a).

Perhaps the most conspicuous feature at autopsy was the presence of many reddish nodules along the mesenteric blood vessels. These were most numerous in the vascular territories of the upper large intestine, but were also detectable in the vessels of the rectum and stomach. A typical macroscopic view of these nodules is given in Fig. 21 (compare with control Fig. 22). These lesions were obvious in all animals of groups I, II, and III. They were graded in order of increasing severity from grade 0 to grade 3 and, inasmuch as all animals had well marked lesions, the average lay between grades 2 and 3 for all groups.

Microscopically, the nodules proved to be due to an enormous thickening of the vascular walls. The earliest stages are characterized by the presence of a thin layer of hyaline, eosinophilic material, just beneath the endothelium, accompanied by thickening of the muscularis and adventitia due to edema and connective tissue proliferation (Fig. 23). In more advanced cases there is a thicker subendothelial hyaline deposit and the endothelial lining is cast off in places. The entire muscularis shows more extensive necrosis or hyalinization and is heavily infiltrated with leucocytes, many of them eosinophilic. Erythrocytes appear in the connective tissue spaces of the muscularis, and occasionally there are phagocytes containing pigment presumably derived from decomposing red blood corpuscles. Large cells, which may be polynuclear, bearing strong resemblance to the Aschoff cells of rheumatic nodules are usually prominent in this layer. The adventitia shows similar, but less pronounced, alterations and usually remains edematous even in the late stages (Fig. 24). In the

most advanced cases the lumen of the blood vessel is completely, or almost completely, obliterated by the hyaline deposits on the vascular wall and by thrombi consisting mainly of fibrin and leucocytes. This stage is strongly reminiscent of the changes seen in thromboangiitis obliterans. (Figs. 25 to 27). A low power view of a large nodule is shown in fig. 28.

The renal lesions were similar to those which have already been described. All animals of the three hormone-treated groups showed a severe degree of nephrosclerosis, the average intensity lying between grade 2 and grade 3. The lesions have been depicted in a previous section and so will not be described in detail.

In the heart, changes similar to those of rheumatic myocarditis were commonly observed. Throughout the myocardium there were small foci, often with a necrotic or hyalin center, around which large epithelioid cells with bulky vesicular nuclei were disposed. Certain of these cells were polynuclear and seemed to be identical with those seen in rheumatic fever. In such nodules there was usually proliferation of fibroblasts and infiltration with lymphocytes, plasma cells and polymorphonuclear leucocytes. (Figs. 29 and 30). In other cases there was a more or less extensive and diffuse replacement of muscle fibers by connective tissue (Fig. 31).

The vascular lesions in the pancreas were similar to those described in a previous section and do not warrant special attention.

The essential details as to the body, kidney and heart weight (ventricles only) are given in Table IV. The organ weights are expressed both in grams and as percentages of the body weight, the latter with the standard errors. A perusal of the table reveals that the kidneys of the group receiving both D.C.A. and a high casein diet were significantly larger than either those of the group receiving D.C.A. and the fox chow diet ($t = 2.9$) or those of the group on the vitamin B fortified diet ($t = 3.2$).

The kidneys of the animals on D.C.A. and a normal diet were not significantly larger than those of the animals on the yeast fortified diet ($t = 1.6$). The calculations were made according to "Student's" method for small samples (130). From the data presented it is not possible to state whether this enlargement is due to potentiation of D.C.A. by casein or merely a summation of their independent actions.

(Note: Since they were readily available, certain of the photographs depicted were obtained from another series of similarly treated rats. These correspond to histologic changes in the present series which were not photographed).

TABLE IV

The Effect of Diets Supplemented With Yeast and Casein on the Heart and Kidney Hypertrophy Elicited by D.C.A.

Group and Treatment	No. Survivors	Final Body Wt. gms.	Kidney Weight		Heart Weight	
			gms.	as % Body Wt.	gms.	as % Body Wt.
I D.C.A. Basal Diet	4	133	1.677	1.26±0.01	0.83	0.63±0.01
II D.C.A. Yeast Diet	11	172	1.956	1.13±0.08	0.89	0.52±0.03
III D.C.A. Casein Diet	6	181	2.443	1.38±0.09	1.15	0.65±0.03
IV Controls Basal Diet	6	201	1.280	0.64±0.04	0.70	0.35±0.06

B. Effects on the Dog

6. Nephrosclerosis and Cardiac Hypertrophy

The dog has been widely used to test the toxic effects of D.C.A. administration and, as it has been pointed out in the review section, such treatment has been found to cause periodic spells of muscular paralysis (260, 316, 127), and symptoms of diabetes insipidus (374, 381, 127, 316) which are aggravated if the intake of sodium chloride is excessive (381, 374). The administration of potassium chloride was claimed to induce recovery from the paralysis (127). Following the observation that prolonged treatment with D.C.A. at high dose levels induced extensive cardiovascular-renal lesions in sodium chloride sensitized animals of various species, it was decided to investigate the possibility of duplicating these effects in the dog by more intensive treatment than had previously been employed.

Experimental

Four recently weaned puppies, weighing from 900 to 1,300 gms., were used in this experiment. The males were slightly heavier than the females, but the average weight of each group, which consisted of a male and a female, was the same. The animals were about one month old at the beginning of treatment. They came from the same litter and, although they were mongrels, they were almost identical in appearance when the experiment was started.

The two treated pups each received 5 mg. of D.C.A. in 0.1 c.c. of peanut oil subcutaneously twice daily for a period of one week, after which the dose was doubled. On the fifteenth day the daily dose was raised to

20 mg. of D.C.A. in 0.4 c.c. of peanut oil, given subcutaneously twice daily. This dose level was maintained for the remainder of the experimental period. Desoxycorticosterone acetate is not soluble in oil at such a high concentration; hence it was administered in the form of a fine crystal suspension. The delayed absorption of crystals from a suspension probably increases their hormonal effectiveness. In order to obtain as good absorption as possible, the site of injection was varied over almost the entire cutaneous area, and gross inspection at autopsy revealed that the removal of crystals from the subcutaneous surface was almost complete. The diet consisted of "Purina fox chow" supplemented with meat.

No unusual manifestations were observed in either of the treated pups by the end of the first month. At the end of this period enough sodium chloride was added to the milk of both groups to make a 1% solution. No other fluid was permitted. Forty-eight hours after the change in diet had been made marked paralysis developed in the D.C.A.-injected pups, especially of the neck and shoulder muscles. They did not appear to be affected otherwise and continued to eat and drink normally and wagged their tails when approached. Slow intravenous injection of 20 c.c. of 2% potassium chloride solution failed to effect a dramatic recovery in the animals, but when plain milk was given the pups regained their normal condition within two days. Ten days later saline-milk of the same concentration as before was given to the pups and again muscular weakness developed within forty-eight hours. This time the muscles of the legs were involved and both dogs, especially the female, became comatose. It is not clear whether these symptoms were indicative of an involvement of the central nervous system or were merely a sign of generalized muscular weakness. In this instance, as before, complete recovery from the symptoms within two days occurred when plain milk was substituted for the saline milk.

Two days later the male doges of both groups received an intravenous injection of 40 c.c. of a 5% NaCl solution, administered slowly during a period of one hour. While this was without effect on the control dog, the D.C.A.-treated animal exhibited signs of muscular weakness, vomiting and diarrhea. Recovery from this was rapid in spite of the continued administration of D.C.A. Two days later a similar experiment was performed on the two female dogs. This time 100 c.c. of a 5% solution of NaCl were given in four injections over a period of two hours. Following this treatment vomiting occurred in both animals, but while the control animal rapidly recovered, the treated animal showed marked muscular weakness and tremor which passed within six hours into a condition of deep coma. Twenty c.c. of a 2% solution of potassium chloride administered intravenously failed to facilitate recovery and the animal died.

This bitch had been treated for a period of 47 days and, although the D.C.A. was administered continuously, paralytic seizures were observed only when excessive quantities of NaCl were given either orally or intravenously. Conversely, an attack of paralysis invariably ensued when the salt was given. A control female was sacrificed at the time the treated bitch died and the details of gross and microscopic observations are given together with those relating to the two males.

The two surviving males were maintained without the addition of saline to their diet until the 62nd day of treatment at which time 1% saline-milk was again given to them. Paralysis, reversible by withdrawal of saline-milk, was again elicited in the steroid-treated dog but not in the control. On the 70th day of treatment NaCl was added to the milk so as to make a 2% solution, and although the control dog tolerated this high concentration without untoward manifestations the D.C.A-treated dog developed rapid paralysis. This began at the neck and shoulders and progres-

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sively extended so as to involve practically all muscles of the body. The experimental animal died about thirty hours after this last initiation of salt treatment and the control male was killed for comparison.

Gross and Microscopic Observations

The kidneys of both steroid-treated dogs were enlarged and pale in color (Fig. 32). The kidneys of the two female dogs, which were treated for the same length of time, weighed 27.5 grams for the hormone treated (body weight 2.6 kg.) and 19.2 gms. for the control (body weight 2.3 kg.). Those of the males weighed 50.5 gms. in the treated (body weight 4.25 kg.) and 34.0 gms. in the control (body weight 5.3 kg.). The surfaces of the kidneys in the D.C.A.-treated animals were slightly irregular and the organs exhibited the appearance of the "large white kidney". Histologic examination revealed that the diameter of both the proximal and distal convoluted tubules was increased, due to cellular hypertrophy and dilatation of the lumina. In many of the tubules the lumen was obstructed by hyalin casts. Desquamation of cells into the lumen was also quite common. Many of the glomeruli were observed to contain large dark cells, especially in the vicinity of the hilus. Similar epithelioid cells were observed in the connective tissue surrounding the glomeruli (Figs. 33 and 34). The walls of the afferent glomerular arterioles were also thickened, but there was no conspicuous abnormality of the large renal vessels.

The heart was also enlarged and pale in the treated animals, especially in the female. In the females the heart weighed 27.0 gms. in the treated and 19.2 gms. in the control, while in the males the weights were 36.5 and 35.5 respectively. This difference is especially striking when it is recalled that both male and female D.C.A.-treated dogs had a lesser body weight than their respective controls at the end of the experi-

ment. Sections of the heart stained with Sudan III revealed that the cardiac pallor of the treated animals was not due to fat. However, haematoxylin and eosin stained sections revealed a slight degree of hypertrophy and edema in the latter.

Although there was no definite signs of sclerosis in the blood vessels of the treated animals, the arteries sppeared somewhat thickened. In the arcus aortae, gross inspection revealed an irregular yellow spot which was barely detectable in the female, but quite marked in the chronically treated male. Histologically this region was characterized by irregularities in the elastic membranes between the muscle layers. In many places the elastic fibers were swollen and in the process of degeneration (Fig. 38).

An analysis of blood samples, taken from the heart of the two male dogs at the time of death, revealed that the non-protein nitrogen content was 37 mg. per hundred cubic centimeters in the control and 62 mg. per hundred cubic centimeters in the treated dog. This suggests a definite impairment in the renal excretion of nitrogenous end products in the latter.

C. Effects on the Cat

7. Nephrosclerosis

In view of the ability of desoxycorticosterone acetate to induce severe renal and cardiovascular lesions in the rat, dog and chick, it became of interest to see whether similar alterations could be produced in other animal species by the same means. The object of the present experiment was to test the effect of D.C.A. overdosage on the cat.

Experimental

Three ten-day old kittens were injected subcutaneously twice daily with 5 mg. of a finely gound crystalline suspension of D.C.A. in water. The suspension contained 50 mg. of D.C.A. per c.c. This dose level was maintained for the first ten weeks of treatment and then doubled for the remaining period of the experiment. Three litter mates were taken to serve as controls. Both groups were maintained on a diet of liver, beef and fish, and milk was given to drink. At the end of the first month of treatment sodium chloride was added to the milk of both groups so as to form a 1% solution. In the treated group there was a male and two females, while the control group consisted of three females. The average body weight of the treated group was 255 grams at the beginning of the experiment and 560 gms. at the end. The control group averaged 230 gms. at the start and 1,176 gms. at the end.

After 15 days of treatment the male kitten contracted an eye infection and, owing to its rapidly deteriorating condition, had to be sacrificed. A female control was killed at the same time for comparison. It was not expected that any pathologic manifestations would be apparent

after such a short period of treatment and this proved to be the case. Neither gross inspection nor histological examination revealed the presence of lesions.

On the 78th day of treatment one of the two treated animals displayed marked anorexia and on the following day nervous manifestations became apparent. These began as slight muscular twitchings and spasmodic movements; and by the following day profound weakness, loss of co-ordination and general lassitude were evident. On the 81st day of treatment the cat was comatose, exhibited coarse fibrillar twitchings and attempted to crawl about the cage, but being unable to either orient itself or attain an upright position it could move only by dragging along on the back or sides. At this time ordinary milk was substituted for the saline-milk and some was administered forcibly by gavage in an attempt to produce recovery. This failed and the animal died on the 82nd day of treatment, at which time the remaining animals were sacrificed and the organs taken for histologic examination.

Gross Pathology

Autopsy revealed that the dead animal had succumbed to multiple cerebral hemorrhages similar to those which have been described as occurring in the rat following similar treatment. Gross examination of the two treated animals revealed that, in both, the kidneys were small and exhibited the appearance of the secondary contracted kidney seen in chronic nephrosclerosis of man. The capsules showed patchy fibrosis and stripped from the kidney with difficulty. The surface of the renal cortex was mottled in appearance and was covered with numerous small, pitted depressions (Fig. 36). Both of the treated animals also had fatty livers, but

otherwise there were no striking pathologic lesions. The control animals showed no lesions at all.

Microscopic Findings

Histologic examination of the kidneys from the D.C.A. injected animals revealed marked scarring and interstitial fibrosis with round cell infiltration. In many areas these changes book the form of wedge-shaped, infarct-like areas such as are seen in cases of human nephrosclerosis. Dilatation of the renal tubules, with the formation of homogeneous hyaline casts, was apparent throughout the kidneys (Figs. 37 and 38). The larger renal vessels were not markedly affected, but some of the medium sized arteries and arterioles showed round cell infiltration and hyalinization of the walls. The adrenals, heart, ovaries and pituitary gland exhibited no significant histological deviations from the normal.

This experiment shows that the cat responds to overdosage with D.C.A. in essentially the same way as the rat or dog. Marked vascular lesions, first detectable in the kidneys, are the most prominent feature. In addition, the cat develops the same motor symptoms and muscular weakness that have been reported to occur in the dog. The impression gained from watching the spasms is, however, that in the cat the symptoms of muscular weakness are not so localized as in the dog. Not merely the shoulder and neck muscles, nor only those of the limbs are involved, but the entire musculature is affected. It appears that a longer period of treatment is necessary before the cat displays these motor disturbances than is the case with the dog, but once it does the symptoms are more severe and rapidly fatal.

D. The Response in the Monkey

8. Renal Lesions

The experiments hitherto reported indicated that D.C.A. in large doses acted as a toxic substance in such a variety of animal species that there did not seem to be any substantial reason for supposing that it would prove inactive in the monkey. Nonetheless the monkey, being more closely similar to man than lower mammals, is usually a necessary intermediate test object when extending observations on biological phenomena to humans. For this reason the rhesus monkey (Macaca mulatta) was employed in the present study.

Experimental

Two male rhesus monkeys weighing 2,900 and 2,950 gms. at the beginning of the experiment were obtained. One of these served as a control while the other was injected twice daily, subcutaneously, with 20 mg. of desoxycorticosterone acetate in 0.4 c.c. of peanut oil. The duration of the experiment was sixty-three days. The animals were fed a diet of "Purina dog chow", carrots and water for the first twenty-five days of treatment, at which time 1% sodium chloride solution was given to drink in place of water. After six days on the sodium chloride solution, the treated monkey became extremely weak. This was especially evident in the neck and shoulder muscles and the animal was usually to be found huddled in a corner of the cage with its hands clasped about the back of the neck. The condition became progressively more severe and within a week paralysis was almost complete, necessitating withdrawal of the saline solution. Although marked polyuria had developed by this time the animal refused to take plain

water and had to be given milk. Complete recovery was evidenced within twenty-four hours.

On the forty-third day of treatment both animals were given intravenous injections of 100 c.c. of a 5% NaCl solution administered over the period of an hour. While the control animal tolerated this treatment without evincing any untoward symptoms, the D.C.A.-treated monkey showed definite signs of weakness in the neck and took up the usual position in the cage, with hands clasped behind the head, immediately upon cessation of injection. Within two hours a spastic paralysis affecting practically the entire musculature ensued in this monkey. This condition was interrupted by epileptiform attacks of violent convulsions. These passed off and within six hours the animal recovered and took nourishment.

Two days later a 1% NaCl solution was again substituted for the drinking water. The monkey manifested an aversion to this fluid, refused to drink it and attempted to get along on the water content of the carrots which it consumed in large quantities. For this reason fluid was withheld for twenty-four hours on the 60th day of treatment in order to make the animal thirsty. At the end of this period a 3% NaCl solution was offered, and, since this highly concentrated salt solution greatly increased thirst, the monkey took large quantities of it. Within two days marked muscular weakness set in and on the third day the animal passed into a stage of deep coma which strongly resembled a condition of general anaesthesia. In this state the motor responses to painful stimuli were not completely abolished, but the corneal reflex could not be elicited. The respiration was regular, but the body temperature showed a progressive decline and death supervened.

•Gross and Microscopic Observations

The outstanding feature at autopsy was again, as in the case of the dog, the large white kidneys, which weighed 17.2 gms. in the treated animal and only 12.3 gms. in the control. The heart was also enlarged weighing 14.2 gms. in the former and 12.3 gms. in the latter. The other organs showed no marked alterations although the adrenal glands of the injected animal were somewhat smaller than those of the control.

Histologic examination of the kidneys revealed dilatation of both the proximal and distal segments of the convoluted tubules and hypertrophy of the lining cells in the D.C.A.-treated animal. The most conspicuous change, however, was an invagination of the proximal convoluted tubules into the space of Bowman's capsule (Figs. 39 and 40). Glomerular sclerosis was rarely observed, but most of the glomerular tufts were distinctly hyperemic. These observations have been reported elsewhere (426, 427).

Chap. XIII

Anterior Pituitary Overdosage

Manifestations in the Rat

9. Vascular Lesions and Their Prevention with Ammonium Chloride

It has been mentioned in the review that lesions similar to those produced by D.C.A. treatment may be elicited by non-specific damaging agents which enlarge the adrenal cortex. This was attributed to hyperactivity of the hypophysis and liberation of abnormally large quantities of adrenocorticotropic hormone. Further investigations in this laboratory revealed that, in the unilaterally nephrectomized and saline treated rat, these could also be elicited by the administration of potent extracts of the anterior pituitary (420). Earlier experiments had shown that the lesions induced by D.C.A. could be prevented if the animals were given ammonium chloride together with the sensitizing sodium chloride (429); hence it was felt that if the ammonium chloride could also prevent the lesions caused by anterior pituitary extracts, the view that the adrenal cortex is the mediating agency between the hypophyseal extracts and the damaged end organs would be strengthened.

Experimental.

Twenty male albino rats weighing 118 grams on the average (range 105-130 gms.) were castrated, unilaterally nephrectomized and divided into two equal groups. The experiment was carried on for 27 days, and during this period all animals received 0.5 c.c. of a suspension of lyophilized cattle anterior pituitary tissue twice daily by subcutaneous injection.

This preparation was obtained by suspending 1 gm. of the finely ground anterior lobe powder in 20 cc. of a 10% alcohol solution. Both groups were given a 1% NaCl solution to drink for the first thirteen days of treatment. This was done in order to facilitate the development of nephrosclerosis which, under these circumstances, develops in about three weeks. During the remaining two weeks group I received 3 c.c. of a 10% NaCl solution by gavage twice daily, while group II was given the same amount of a solution containing 10% NaCl plus 10% NH_4Cl. Both groups were allowed tap water ad lib during this period. Thus both groups received the same amount of both hormone and NaCl thoughout the course of treatment, while group II was given NH_4Cl in addition. On the 27th day of treatment the rats were weighed, sacrificed and the adrenals, hearts and kidneys were fixed in "Suza" mixture.

Macroscopic Findings

At autopsy it was evident, by mere naked eye inspection, that 7 out of the 8 surviving animals in group I had severe renal lesions. In group II only one animal among the nine survivors showed a trace of nephrosclerosis. The weights of the heart, kidney and adrenals proved to be significantly greater in group I than in group II when expressed either in absolute values or as a percentage of the body weight. The body weights of the two groups were equally matched until the third week of treatment after which the average weight of the animals in group I decreased from 219 to 214 grams, while that of group II rose from 211 to 234 gms. This loss of weight is probably a reflection of the debilitated condition of the rats which developed a severe hypertensive state, while the continued gain in weight in group II is probably evidence of the amelioration of this

condition by ammonium chloride. Blood pressure determinations were not made on the animals of the present series, but it will be remembered that hypertension accompanies the nephrosclerosis caused by D.C.A. overdosage and the occurrence of identical lesions, together with pronounced cardiac hypertrophy in the animals of group I, suggests that these were hypertensive.

The pertinent data are summarized in Table V. The final body weight and the adrenal, heart and kidney weight are given, the last three with their standard errors. An analysis of the figures was made to test the statistical significance of the organ weight changes. This was done in accordance with "Student's method for the evaluation of small samples" (130). The probability of the difference being due to chance alone is given in Table I under the heading "Value of P". Since P=0.05 is considered to be the upper limit of statistical significance, and the values obtained were all below this point, it is obvious that the differences in organ weights between the two groups are statistically significant.

TABLE V

Organ Changes in Male Castrate Unilaterally Nephrectomized Albino Rats Treated With Anterior Pituitary Extract

Group and Treatment	Final Body Wt. in gms.	Adrenal Wt. in mgms.	Kidney Weight		Heart Weight	
			in gms.	as % of Body Wt.	in gms.	as % of Body Wt.
I NaCl	214	147±9	3.493±132	1.6	1.307±06	0.61
II NaCl plus NH_4Cl	234	118±6	2.585±100	1.1	1.016±06	0.43
Value of P	0.02	0.02	<0.01		<0.01	

Microscopic Findings

The heart and kidneys of all animals were histologically examined. The incidence of renal and cardiac lesions was found to be 100%, that is all animals had both types of lesion, in group I. The average intensity of lesion was 83% for the renal and 63% for the cardiac. In group II the incidence of renal lesions was 37% with an average intensity of 13%; while the incidence of cardiac lesions was 50% with an average intensity of 16%. (The tissues of one of the autopsied animals in group II were lost, and therefore not histologically examined).

The renal lesions in group I were essentially the same as those described as occurring in the rat following overdosage with D.C.A. The most striking change was the dilatation of the proximal and distal convoluted tubules due to obstruction by hyaline casts. Not infrequently the stroma between the tubules was heavily infiltrated by polymorphonuclear leucocytes, thus exhibiting the typical picture of an interstitial nephritis (Figs. 41, 41a, and 42). In all animals of this group inflammatory changes, sometimes with marked edema, were seen also in the loose connective tissue surrounding the renal pelvis. A macroscopic view of a nephrosclerotic kidney and hypertrophic heart from an animal treated with L.A.P. and saline, as contrasted with the corresponding organs from an animal of the same size which received both this treatment and ammonium chloride, is shown in Fig. 42a.

These observations are in accord with the view that true inflammatory lesions may be elicited by hormonal treatment. The periarteritis nodosa, so regularly seen in animals chronically overdosed with D.C.A., and the arthritic lesions occasionally evoked by the same treatment (438) are other examples of such inflammatory responses.

The renal glomeruli of the animals in group I displayed consider-

able enlargement, hyalinization of the capillary loops and afferent arterioles, not infrequently accompanied by thickening of the glomerular capsule and pericapsular fibrosis. These changes are essentially similar to those observed in patients suffering from malignant nephrosclerosis (Fig. 43). Glomerular hemorrhages or infiltration of the glomeruli by leucocytes were only occasionally observed.

The development of pathologic changes in the glomeruli, tubules and connective tissue around the renal pelvis were invariably inhibited, if not completely prevented, in the animals of group II which received ammonium chloride and sodium chloride together. The convoluted tubules were occasionally somewhat dilated and exhibited some hypertrophy of the lining cells, but definite pathologic changes were almost always absent (Fig. 44). Only in a few instances was there an occasional hyaline cast.

Hyalinized patches and foci of scar formation were observed in the heart muscle of almost every animal of group I. Surprisingly, however, giant cells and periarteritis nodosa of the cardiac blood vessels were rarely seen. This is in contrast to the almost invariable occurrence of these changes in combination with the severe nephrosclerosis induced by D.C.A. overdosage. The healthy cardiac muscle fibers were markedly hypertrophic, however, probably due to the hypertensive effect of the nephrosclerotic hormones (Figs. 45 and 46). The myocardium of the animals in Group II, on the other hand, appeared to be entirely normal (Fig. 46).

It should be remembered that both the hormone treatment and the administration of excessive amounts of sodium chloride was instituted thirteen days before ammonium chloride was given to group II. It is improbable that a severely damaged glomerulus could be restored by any therapeutic measure; the experiment shows, however, that ammonium chloride acts not only as a prophylactic but as a curative agent. This is evidenced by

the fact that it prevents the progression of the disease after its initiation in spite of the continued administration of the eliciting agents.

Ammonium chloride appears to inhibit the adrenal enlargement resulting from treatment with crude anterior pituitary extract. This lends added support to the hypothesis that the lesions induced by treatment with hypophyseal extracts are due to the excess liberation of toxic corticoids from the hyperactive adrenal cortices.

Although only one series of rats is reported on in this instance the conclusions which have been drawn are supported by several previous experiments. In these the rats were treated as above except that 1% NaCl was given to one group ad lib, while the other received a solution containing 1% NaCl plus 1% NH_4Cl in the same way. The group receiving the second mixture failed to thrive on this regimen and failed to drink enough of the solution provided; hence it proved impossible by this method to obtain a sufficiently large number of survivors to base definite conclusions upon. Such rats as did survive, however, invariably indicated that the lesions which are normally elicited by treatment with anterior lobe preparations and sodium chloride are inhibited by ammonium chloride (177).

10. The Role of the Adrenals

The results reported in the previous experiment strongly suggested that the adrenal glands were intimately involved in the vascular lesions produced by lyophilized anterior pituitary extract (L.A.P.). The crucial test of this hypothesis, it seemed, would be to test the effect of such an extract on adrenalectomized animals. The failure of these to develop lesions at a time when similarly treated intact animals showed extensive vascular damage, would indicate definitely that the adrenal glands are involved in the vascular response.

Experience had shown that the crude anterior pituitary preparations exhibited a high degree of toxicity. This was great enough to kill adrenalectomized rats within a very short period of time even when these were maintained on a diet which contained optimal amounts of sodium chloride and carbohydrate. It was therefore necessary to maintain the adrenalectomized animals on adrenal cortical extract. Previous experiments indicated that commercial cortical extracts, in doses up to 1 c.c. daily, did not cause evidences of renal or vascular damage in unilaterally nephrectomized and saline treated rats.

Experimental

One hundred female albino rats, weighing between 140 and 160 grams, were unilaterally nephrectomized and divided into eight groups having an average body weight of 153 grams. The animals all received a diet of "Purina fox chow" and were given a 1% NaCl solution to drink. Group I was not treated and served as a control. Group II received 0.33 c.c. of adrenal cortical extract (Connaught Laboratories, Toronto) subcutaneously three times daily. Group III received twice daily, subcu-

taneously, 0.4 c.c. of an aqueous suspension containing 40 mgs. of lyophilized (cattle) anterior pituitary powder (L.A.P.). Group IV received both L.A.P. and cortical extract in the same amount and manner as the animals of groups II and III. Groups V to VIII were treated exactly as groups I to IV respectively, but were bilaterally adrenalectomized the day before the injections were begun. The experiment was terminated on the 89th day, at which time all surviving animals were killed and their organs taken for histologic examination. The results are summarized in Table VI.

Gross and Microscopic Findings

At autopsy nephrosclerosis and cardiac lesions were prominent in almost all animals of groups III and IV. Lesions were not present in any of the other groups although the kidneys and hearts seemed somewhat enlarged in the animals of group VIII. The adrenal glands were markedly enlarged in all animals which had received anterior pituitary extract.

Histologically, nephrosclerosis, myocardial scarring or both were present in all animals of groups III and IV, while no such lesions were observed in any of the others. Twelve of the thirteen surviving animals in group III showed nephrosclerosis of an average intensity of ++ when graded on a scale ranging from 0 to +++. Myocardial scarring was observed in ten animals of the same group. In group IV, seven of the nine survivors averaged ++ nephrosclerosis, while four in the same group showed cardiac lesions. No trace of either of these lesions was to be observed in any of the adrenalectomized rats which received anterior pituitary preparation either alone or in combination with cortical extract.

These observations indicate that the presence of functional adrenal glands is a necessary prerequisite for the induction of cardiovas-

cular lesions by anterior pituitary preparation. Because of the identity of these changes to those brought about by treatment with synthetic D.C.A., and since they are likewise intensified or inhibited by the same agencies, it seems probable that adrenal mediation is essential for their production. Possibly the hypophyseal preparation stimulates the adrenal cortex to liberate abnormally large quantities of desoxycorticosterone-like compounds. It is unlikely that the nephrosclerosis and cardiovascular damage caused by L.A.P. is due to a direct action of the latter upon the kidney and the cardiovascular system. The experiment does not eliminate the possibility that, had the treatment been prolonged further, cardiovascular-renal lesions might ultimately have developed. It may be that both hypophyseal and certain hormones of the adrenal cortex are necessary for the pathologic changes observed.

The experiment also confirms previous observations to the effect that whole adrenal cortical extract, at the dose levels tested, does not induce cardiovascular lesions in the unilaterally nephrectomized and sodium chloride-treated rat. Such extracts are also devoid of any protective action against the lesions induced by anterior pituitary preparations.

This inability of a pituitary extract capable of eliciting vascular lesions in the intact animal to do so in the adrenalectomized rat was confirmed in a subsequent study (36a).

TABLE VI

The Effect of Adrenalectomy on the Nephrosclerotic Activity of L.A.P.

Group and Treatment		No. of rats		Body Wt. in Gms.		Lesions				Organ Weights				
						Renal		Cardiac		Kidney			Heart	Adrenals
		Initial	Final	Initial	Final	Incidence	Severity	Incidence	Severity	In Gms.	as % of Body Wt.	In Gms.	As % of Body Wt.	In Mgs.
I Controls		10	6	152	181	0	0	1	+	1.420	0.78±0.02	0.758	0.42±0.02	62±2.3
II Cortin		10	10	152	180	0	0	0	0	1.316	0.72±0.02	0.759	0.43±0.02	54±1.9
III L.A.P.		20	13	153	253	12	++	10	+	3.042	1.18±0.08	0.272	0.50±0.08	155±13
IV Cortin & L.A.P.		19	9	152	259	7	++	4	+	2.817	1.08±0.07	1.147	0.44±0.01	127±3.9
Adrenalectomized	V Controls	10	9	153	182	0	0	0	0	1.272	0.70±0.07	0.854	0.35±0.02	
	VI Cortin	10	10	153	182	0	0	0	0	1.380	0.75±0.05	0.672	0.36±0.01	
	VII L.A.P.	10	1	153	252	0	0	0	0	2.367	0.91	1.052	0.40	
	VIII Cortin & L.A.P.	20	7	153	254	0	0	0	0	2.842	0.87±0.03	1.101	0.38±0.02	

DISCUSSION

The experiments indicate that the administration of the adrenal cortical compound desoxycorticosterone acetate results in the induction of widespread vascular lesions in the cat, dog, monkey and rat. Experiments in this laboratory have also shown that these same lesions occur in the mouse (36a) and in the guinea-pig. The high incidence of spontaneous vascular lesions (especially in the kidney) and the inability to tolerate a 1% sodium chloride drinking fluid, has rendered the rabbit unsuitable for investigation. Nephrosclerosis appears to be the first lesion to develop although, if the treatment is prolonged so that the renal damage is extensive, changes in the myocardium become prominent. These consist of a non-specific diffuse scarring, accompanied in many cases by proliferative nodular accumulations resembling the Aschoff nodule of rheumatic disease. In this stage subendothelial hyalin deposits are commonly found in arterioles and the medium sized arteries in various parts of the body. More chronically-treated animals (rats) show periarteritis nodosa which affects the blood vessels of the heart, brain, adrenals, pancreas, kidney and mesentery.

The observation that, in the rat at least, a typical rheumatoid arthritis may be manifest along with the other changes, strongly emphasizes the relationship of the experimentally induced changes to those observed in rheumatic fever (435). The occurrence of these lesions together with hypertension, which has been determined by direct measurement in the rat and inferred from the left-ventricular hypertrophy in the other species, is reminiscent of the syndrome which occurs in the condition of hypercorticoadrenalism or in Cushing's disease. The similarity is especially marked in view of the fact that the experimental condition may be elicited

by treatment either with D.C.A. or anterior pituitary preparation. Prevention of the lesions induced by the latter agent by adrenalectomy, supports the hypothesis of many clinicians that most of the symptoms of Cushing's disease are referable to a secondary hyperactivity of the adrenal cortex.

Attention has been drawn to the fact that identical lesions may also be elicited by exposure to a variety of non-specific stimuli which, experimental evidence indicates, act by stimulating pituitary adrenocorticotropic hormone production and hence adrenal cortical hyperactivity. Thus the clinical conditions of rheumatic fever, Cushing's disease and hypercorticoadrenalism, in which the pathologic manifestations are so strikingly similar, may, not unreasonably, be classified as "diseases of adaptation" (412).

The findings are in accordance with certain clinically observed undesirable side-effects of desoxycorticosterone and suggest that therapy with this compound should be undertaken only after due caution has been observed, especially with regard to sodium chloride intake.

In this connection it may be stated that, although they have not been reported here, experiments have been conducted on the rat which indicate that sodium chloride alone, even in concentrations as high as 5% of the total water intake, does not cause these lesions to develop. Treatment with 1% sodium chloride in the drinking water for a period of nine months was likewise ineffective in this respect. Thus the electrolyte appears to be effective only when there is endogenous or exogenous excess of adrenal steroids of the salt active type.

SUMMARY

1. Treatment with desoxycorticosterone acetate causes malignant hypertension in the rat. There is a marked rise of both systolic and diastolic blood pressures to hypertensive levels accompanied by cardiac hypertrophy.

2. Concomitantly there is the development of widespread vascular lesions. In the smaller arteries and arterioles this takes the form of medial hypertrophy which progresses to hyalinization of the vessel wall and even complete necrosis if the treatment is prolonged. In the kidney the changes are typical of those occurring in malignant nephrosclerosis; while in the pancreas, mesenteric vessels, brain, adrenals and heart, periarteritis nodosa is the conspicuous pathology. In the heart myocardial scarring and prominent proliferative nodular accumulations resembling the Aschoff nodules of rheumatic fever are frequently observed.

3. The speed of onset and severity of the lesions are both greatly enhanced if the animals are maintained on a high sodium chloride intake.

4. Accompanying the lesions, there may be peculiar neuromuscular motor disturbances which are apparently referable to periarteritis of the cerebral vessels.

5. Pathologic vascular lesions, identical for the most part to those which occur in the rat, may also be elicited in the cat, dog and monkey by desoxycorticosterone acetate. Myasthenia and paralysis are prominently displayed in these species. In the dog and the monkey at least these symptoms may be evoked or abolished at will by varying the sodium chloride intake appropriately.

6. The qualitative response is not affected by the method of administration since, if the treatment is long enough, it does not matter whether the compound is administered in an oily suspension, a water suspension or as compressed crystalline pellets.

7. At minimal dose levels thyroidectomized animals appear to be less sensitive to the nephrosclerotic activity of D.C.A. than intact. This may be related to decreased food intake and decreased metabolism in general. Other experiments have supported the validity of this observation even at high dose levels.

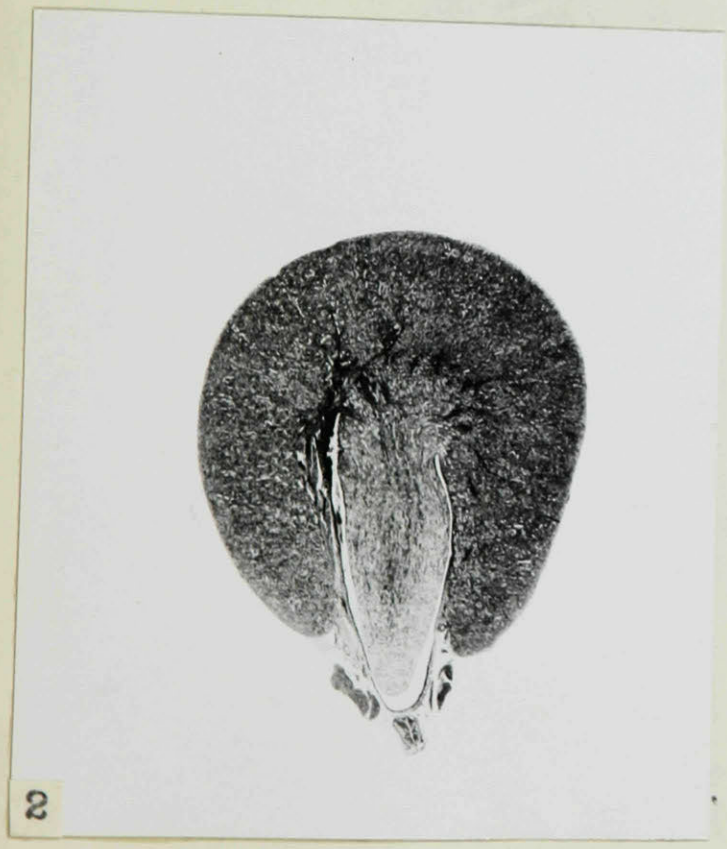
8. The renal hypertrophy caused by desoxycorticosterone acetate is augmented by a high-protein diet.

9. The same lesions may be elicited in the rat by treatment with a lyophilized anterior pituitary extract, if the animal is kept on a high sodium chloride intake, and prevented or inhibited by the simultaneous administration of ammonium chloride. The nephrosclerosis induced by lyophilized pituitary extract is often accompanied by interstitial nephritis.

10. The ability of anterior pituitary extract to induce vascular lesions is attributed to its ability to stimulate the adrenal cortex to secrete excess quantities of desoxycorticosterone-like steroids, since this quality is not manifest in the adrenalectomized animal. It is possible, however, that both pituitary and adrenal cortical hormones are necessary for this response.

PLATE I

Experiment 1.



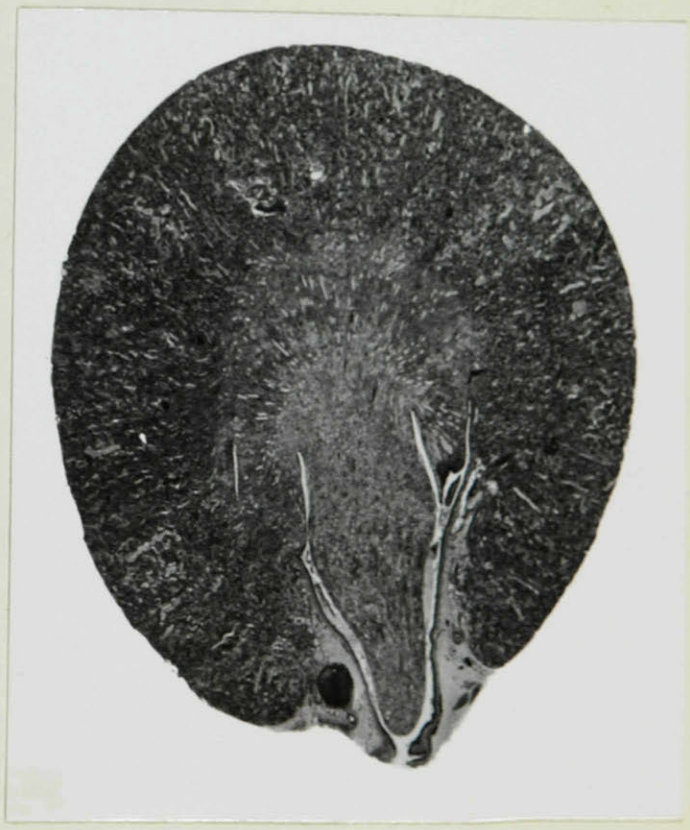


Fig. 1. Macroscopic view of a normal kidney from a rat which received sodium chloride (left), and a hypertrophic mottled kidney from one which received both sodium chloride and D.C.A. (right).

Fig. 2. Low magnification view of a section through the kidney of a sodium chloride treated rat.

Fig. 3. Low magnification view of a section through the kidney of a rat which received both sodium chloride and D.C.A. The cortex is greatly enlarged and exhibits an irregular pattern due to cast-filled tubules and patches of sclerosis.

PLATE II

Experiment 1.

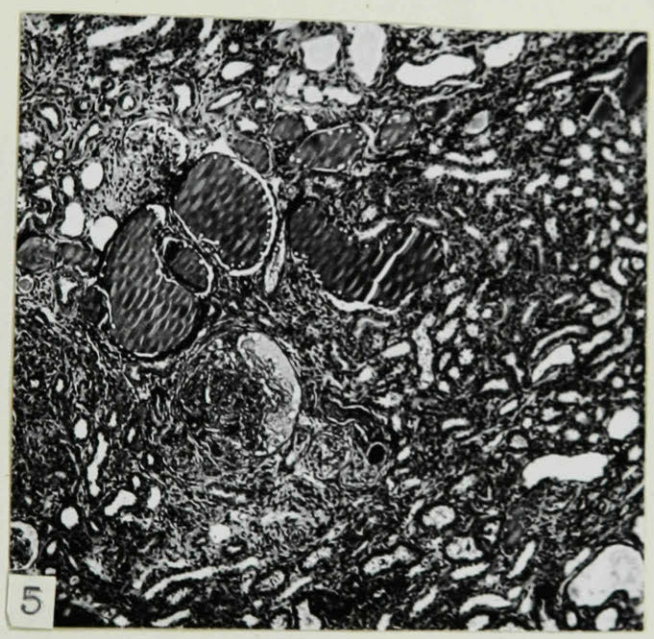
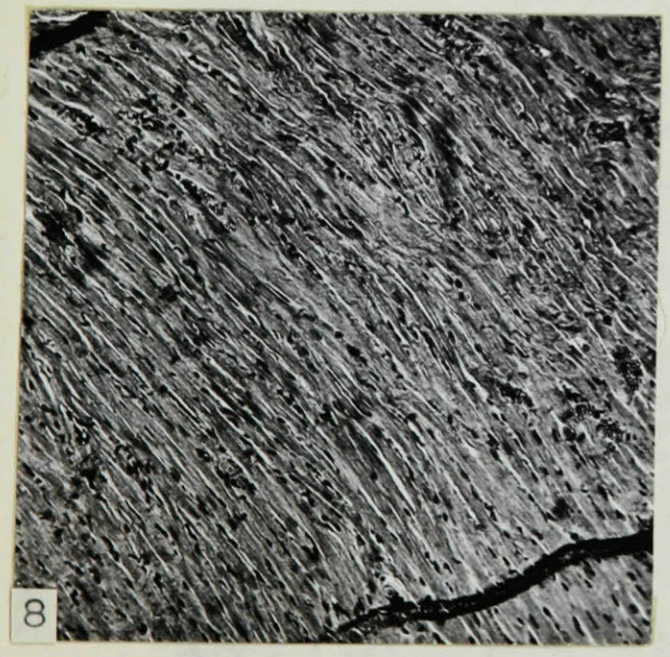


Fig. 4. A V-shaped sclerotic area in the renal cortex of a rat treated with desoxycorticosterone acetate and sodium chloride.

Fig. 5. Several dilated renal tubules containing hyaline casts and one sclerotic glomerulus surrounded by proliferating epithelioid cells. Same kidney as depicted in Fig. 4.

PLATE III

Experiment 1.



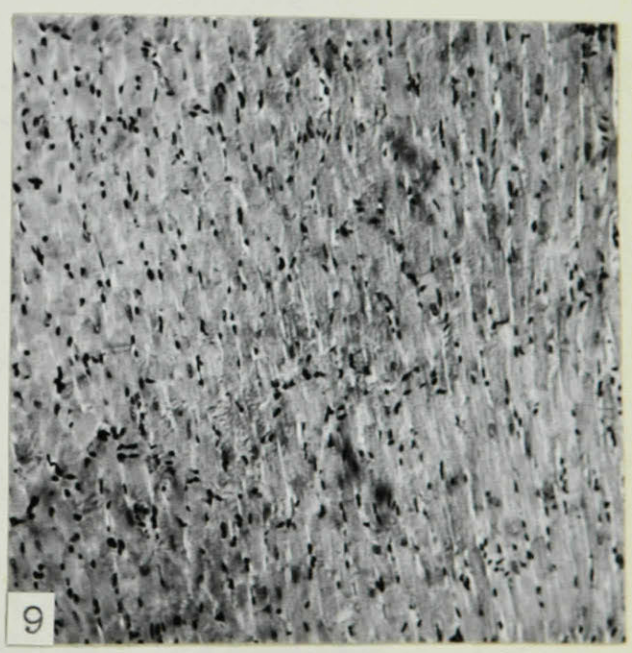


Fig. 6. Cross section through the heart ventricles of a control rat which received sodium chloride alone.

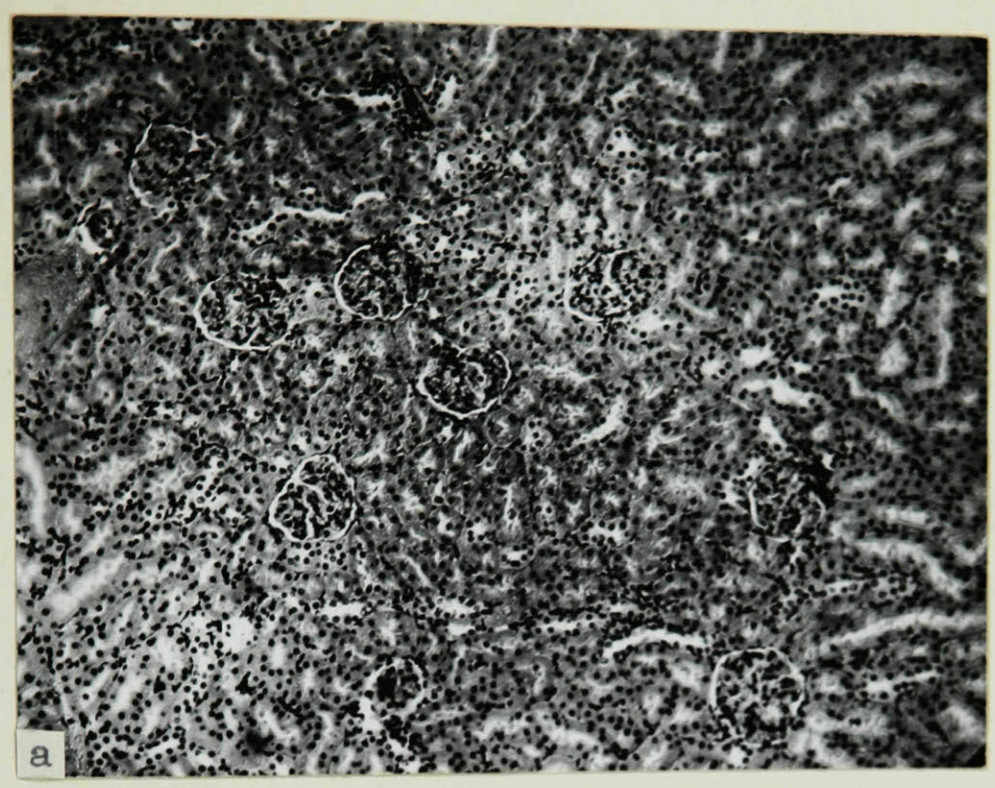
Fig. 7. Cross section through the heart ventricles of a rat which received both sodium chloride and D.C.A. Note the great increase in thickness, especially of the left ventricle. Same magnification as Fig. 6.

Fig. 8. High magnification of a section through the left ventricle of the heart shown in Fig. 6.

Fig. 9. Section through the left ventricle of the heart shown in Fig.7. Note the hypertrophy of the myocardial fibers. Same magnification as Fig. 8.

PLATE IV

Experiment 2.



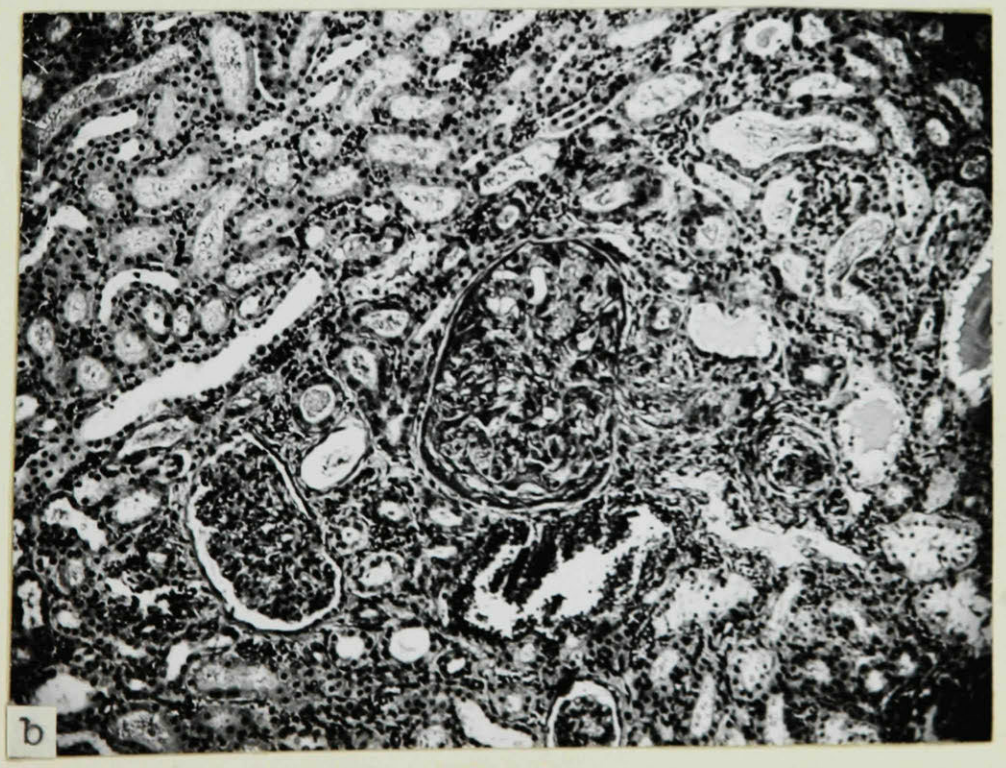
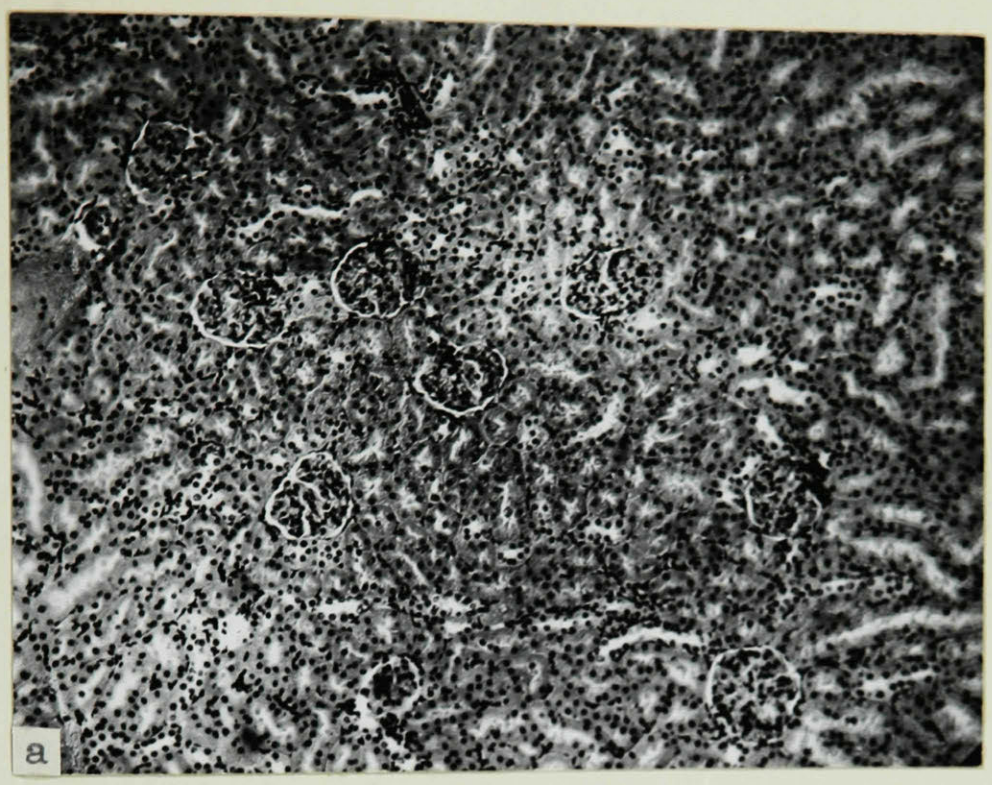


Fig. 10. (a) Section through the renal cortex of a control rat.

(b) Section through the renal cortex of a rat treated with D.C.A. and NaCl. There is marked enlargement and hyalinization of the glomeruli, and capsular fibrosis. The afferent arteriole of the central glomerulus is completely necrotic.

PLATE IV

Experiment 2.



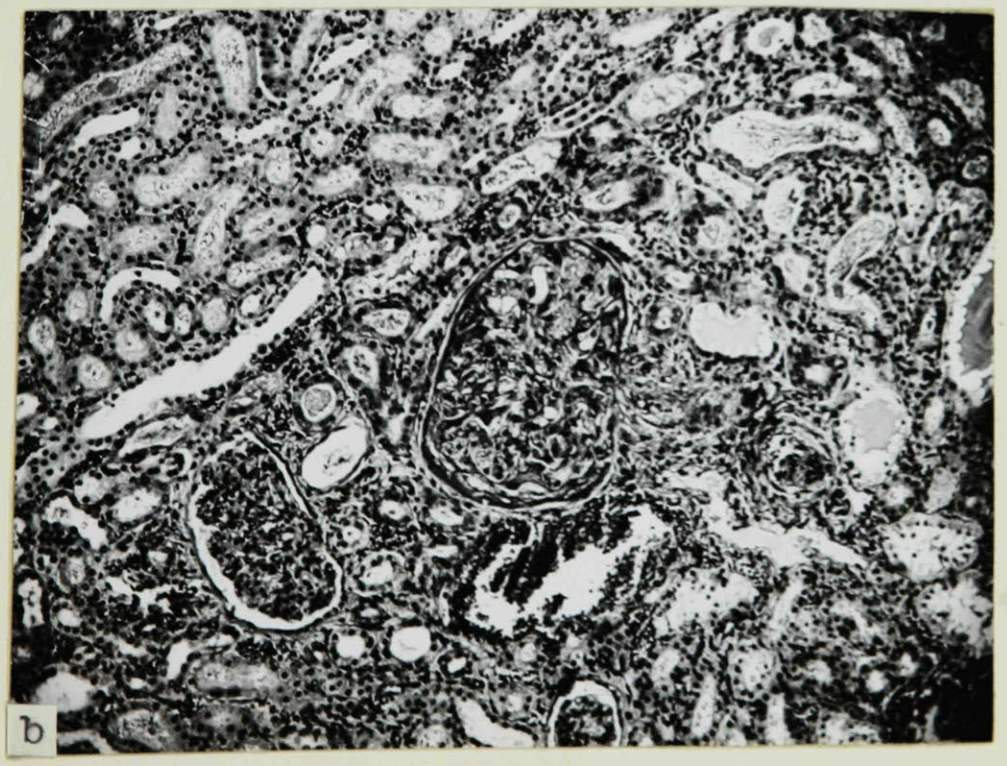


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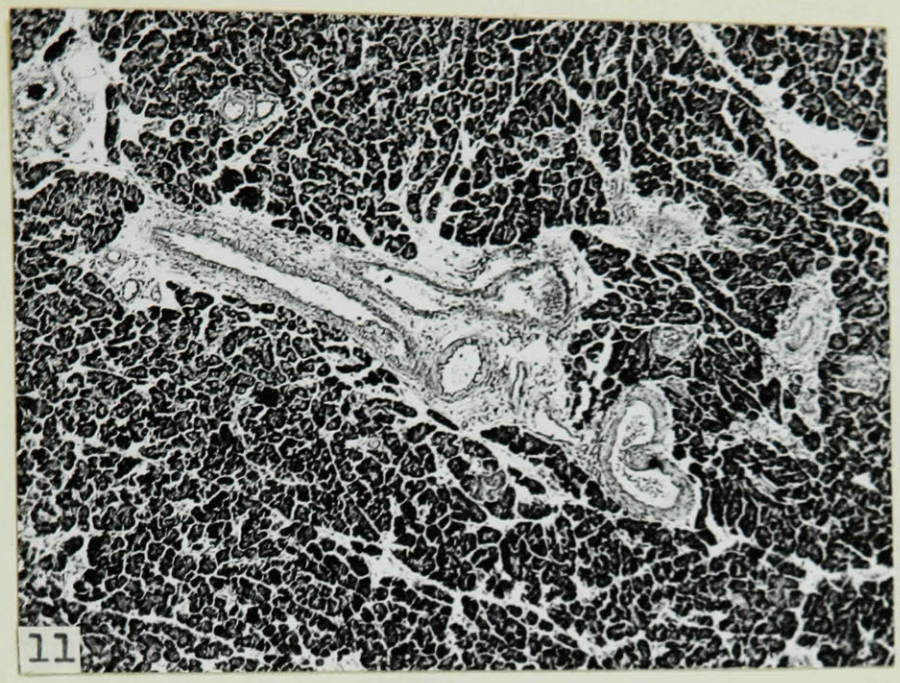
PLATE V

Experiment 2.



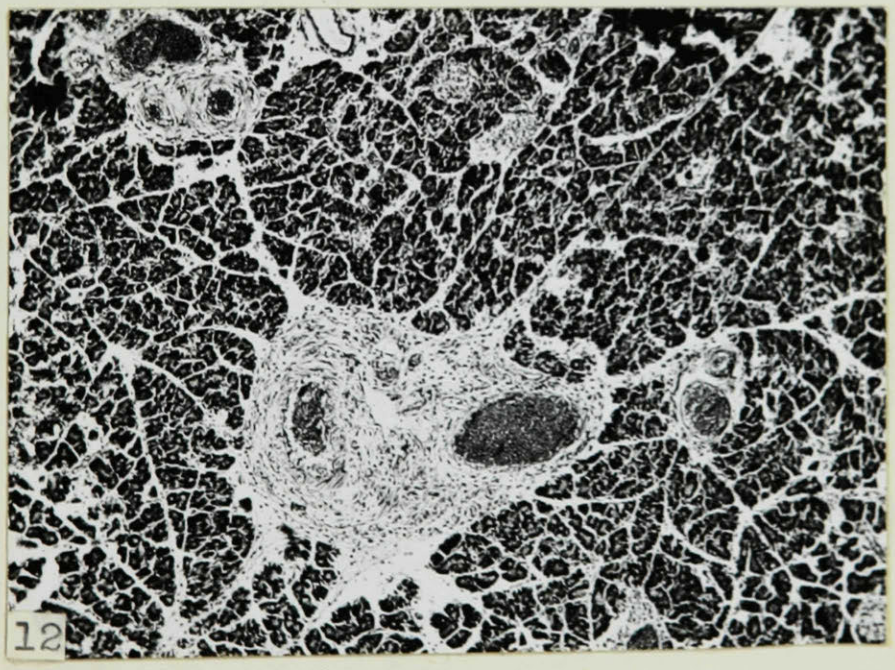
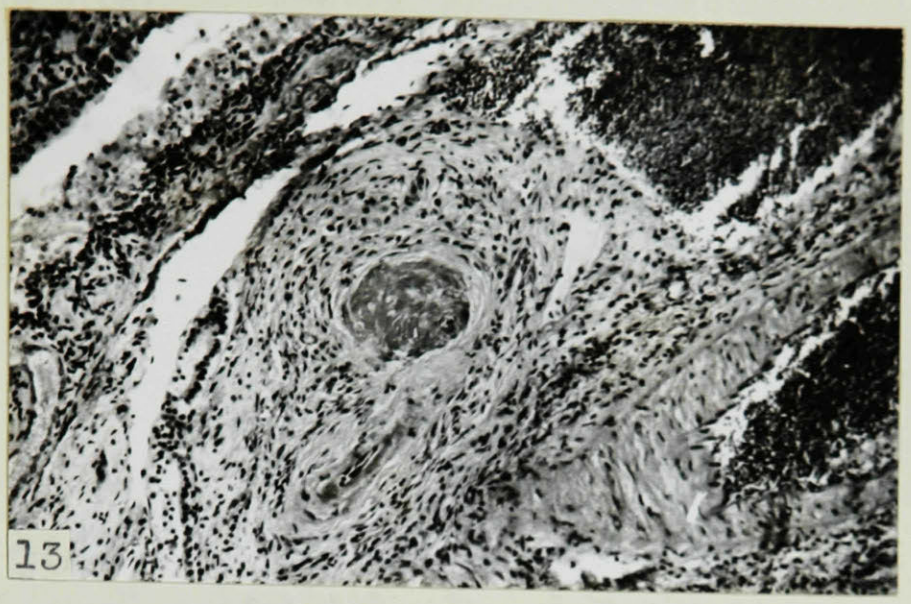


Fig. 11. Section through the pancreas of a control rat.

Fig. 12. Perivascular fibrosis in the pancreas of a rat treated with D.C.A. and sodium chloride.

PLATE VI

Experiment 2.



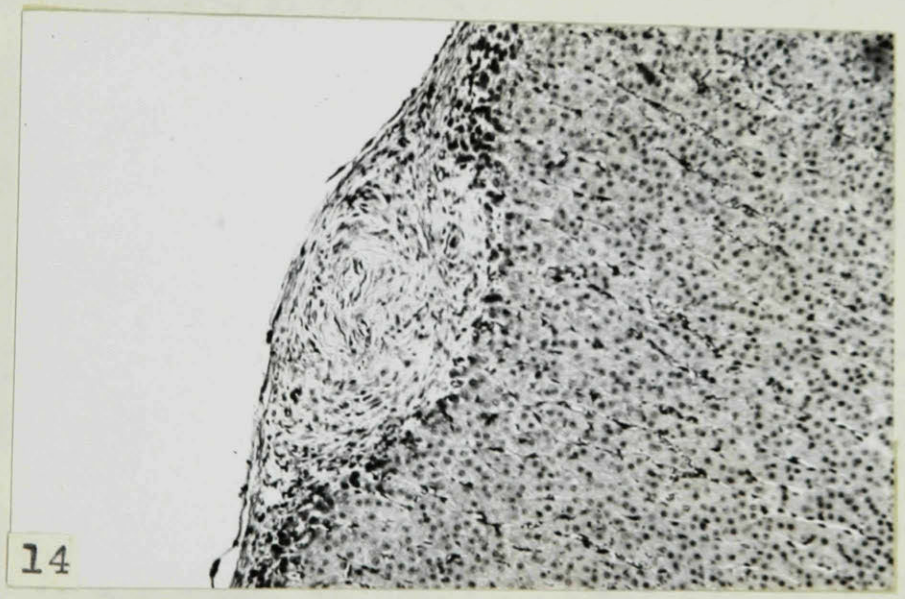
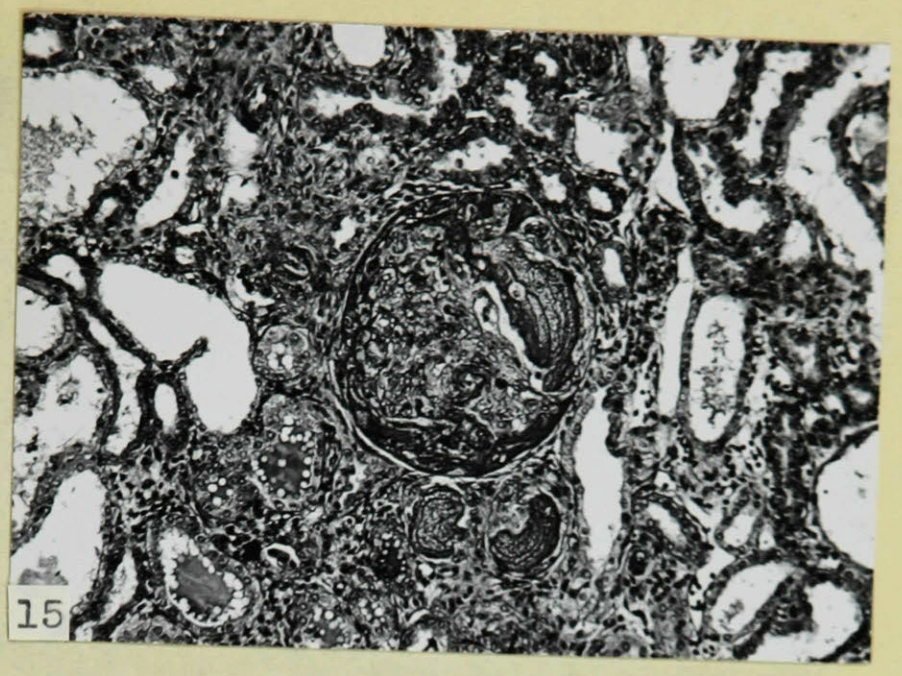


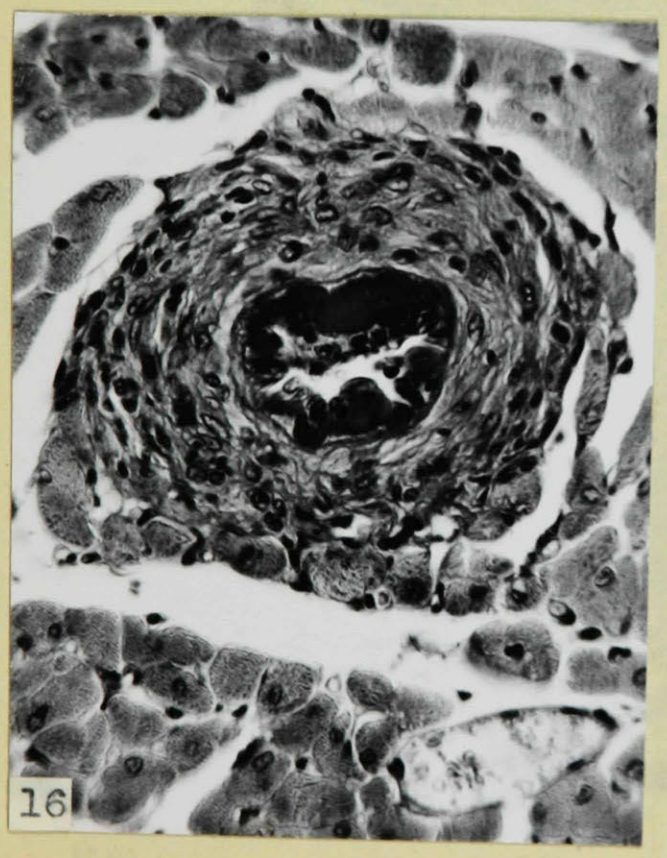
Fig. 13. Hyalinization and necrosis with complete obliteration of the lumen in a medium-sized arteriole of the pancreas. From a rat treated with D.C.A. and NaCl.

Fig. 14. Marked perivascular fibrosis and hyalinization of an arteriole in the capsule of the adrenal cortex. From a rat treated with D.C.A. and sodium chloride.

PLATE VII

Experiment 3.





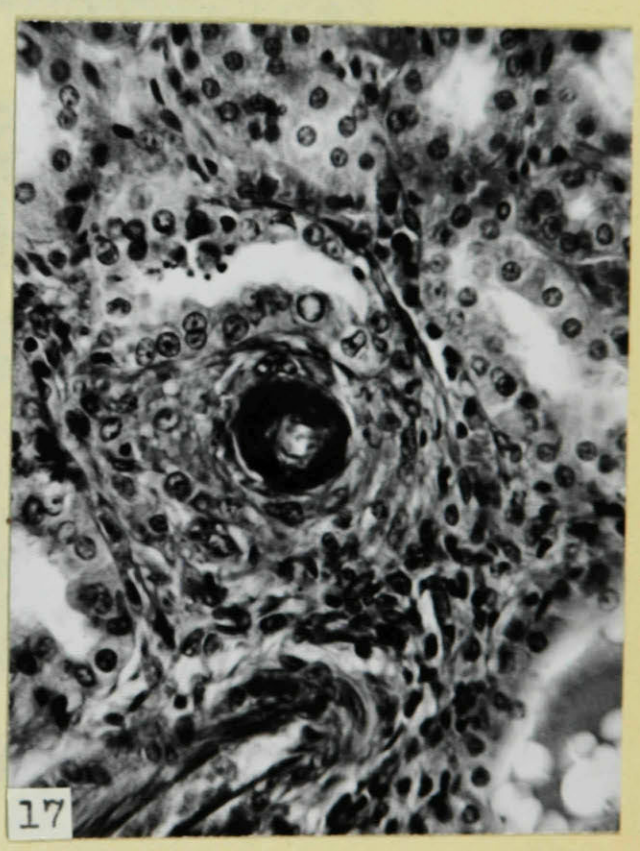


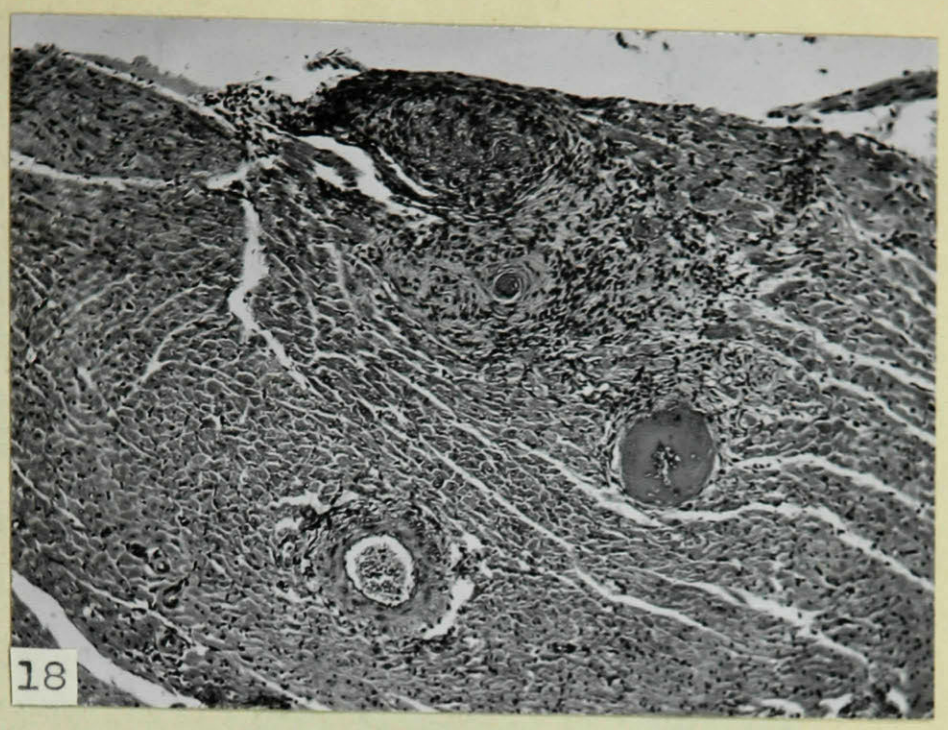
Fig. 15. Hyalinized glomerulus surrounded by dilated and cast-filled tubules. Low magnification view of a kidney from an adrenalectomized rat treated with D.C.A. and sodium chloride.

Fig. 16. High magnification view of an arteriole in the heart of a rat which received D.C.A. and NaCl. Note the extensive sub-endothelial hyalin deposition.

Fig. 17. High magnification view of a renal arteriole in the kidney of a rat which received D.C.A. and NaCl. The sub-endothelial deposition of hyalin material has resulted in almost complete obliteration of the lumen.

PLATE VIII

Experiment 3.



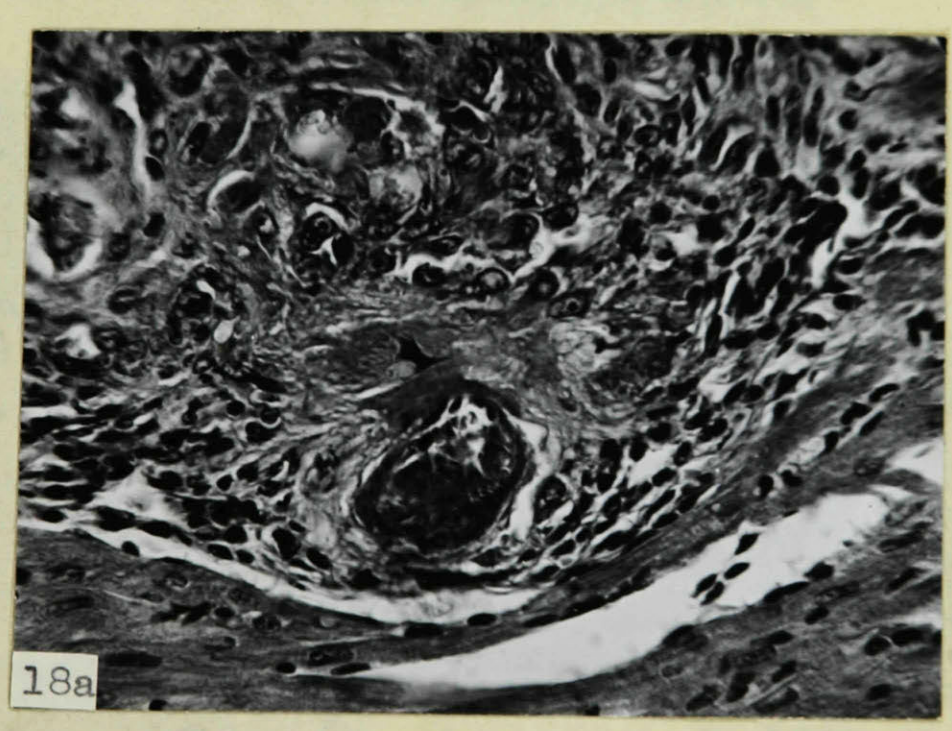
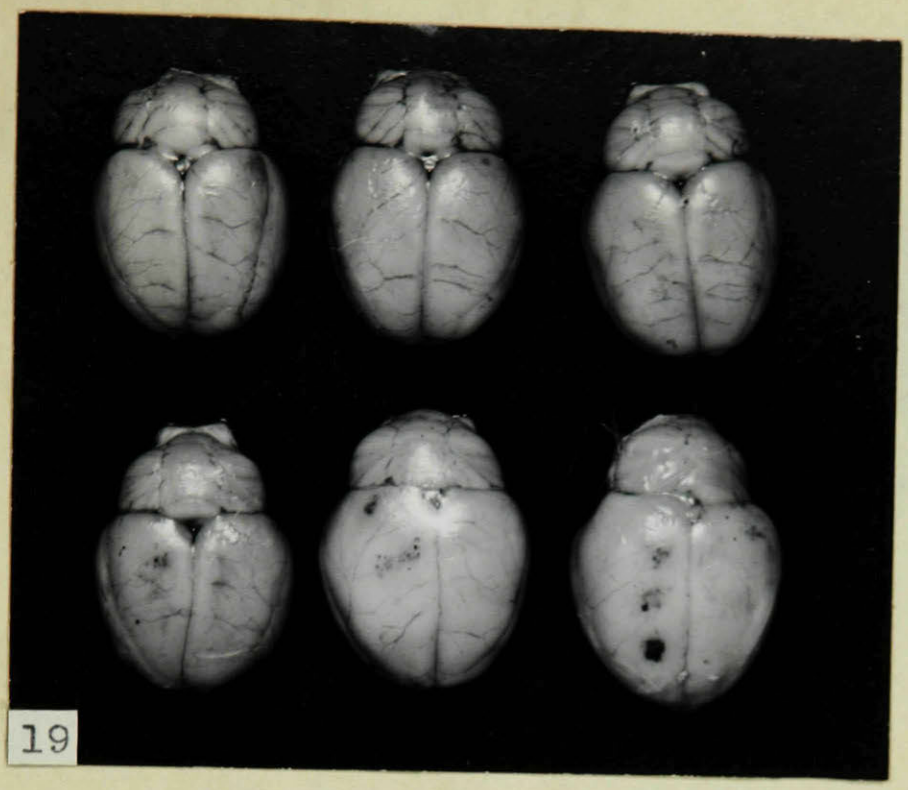


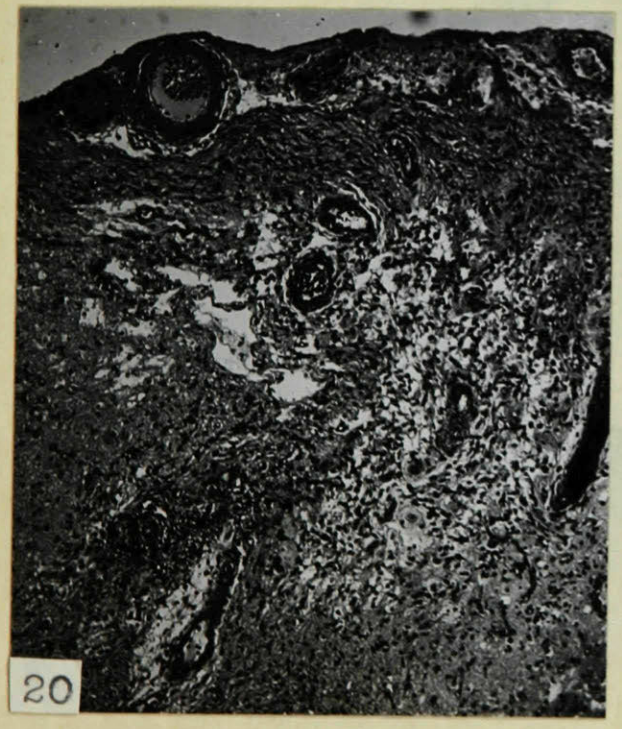
Fig. 18. Typical Aschoff body in the myocardium of a rat treated with D.C.A. and NaCl. The centre of the nodule consists of hyalinized material. The completely hyalinized wall of the arteriole at right centre contrasts sharply with that of the arteriole to the left and below it.

Fig. 18a. High magnification view of an Aschoff nodule. Note the hyalinized arteriole and the large binucleate cells.

PLATE VIIIa

Experiment 5.





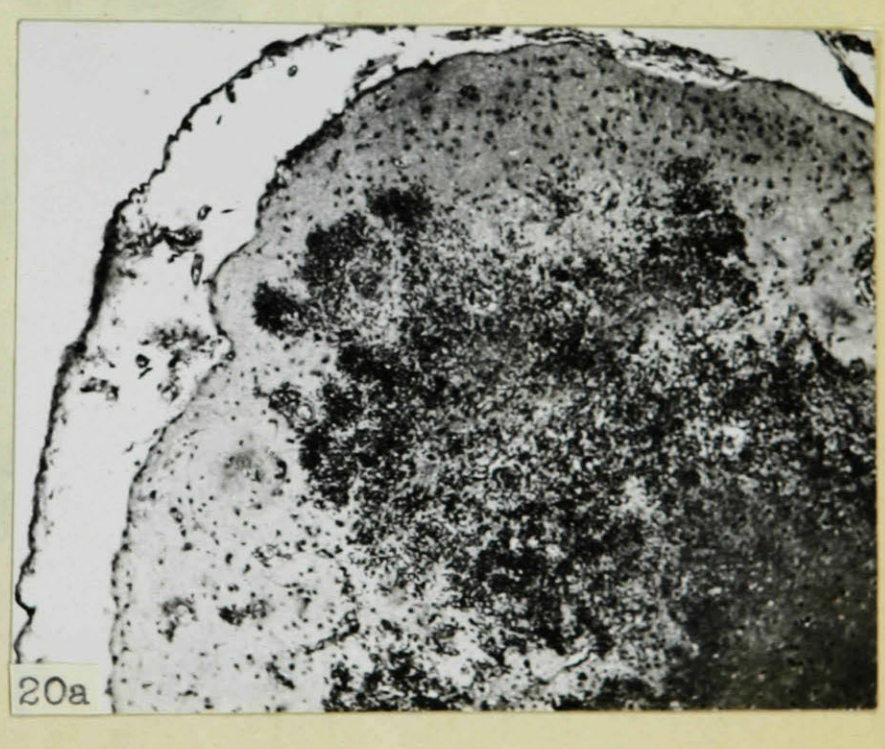


Fig. 19. Macroscopic view of three brains from untreated control rats (top row) and three brains with hemorrhagic patches due to periarteritis nodosa of surface vessels from D.C.A. treated rats (bottom row).

Fig. 20. Section through the brain showing hyalinization of surface arterioles in the cerebral hemisphere. Note tissue edema and small vessel in the depth of the brain surrounded by blood cells. From a rat treated with D.C.A. and NaCl.

Fig. 20a. Marked destruction of brain tissue with diffuse hemorrhages. From a brain similar to those shown in lower row Fig. 19.

PLATE VIIIb

Experiment 5.

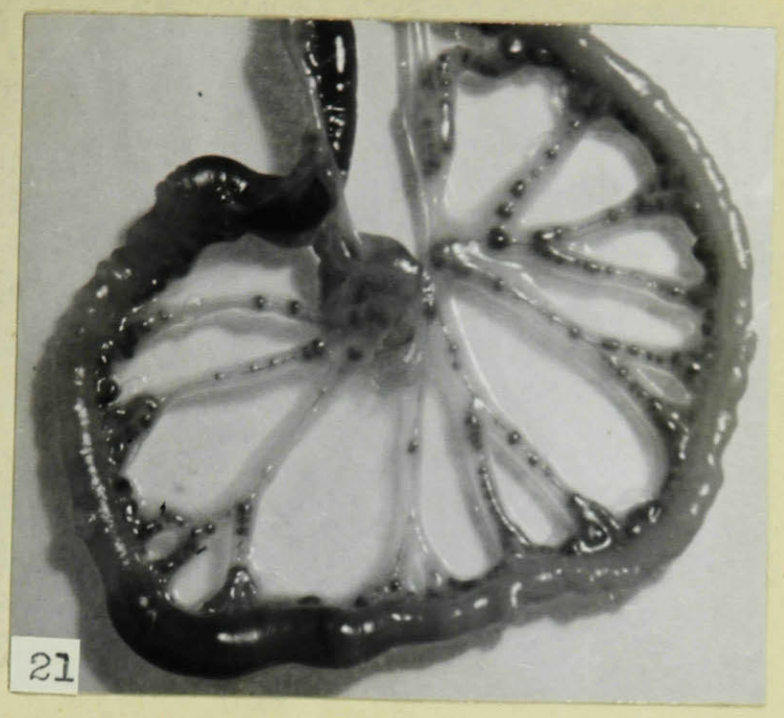
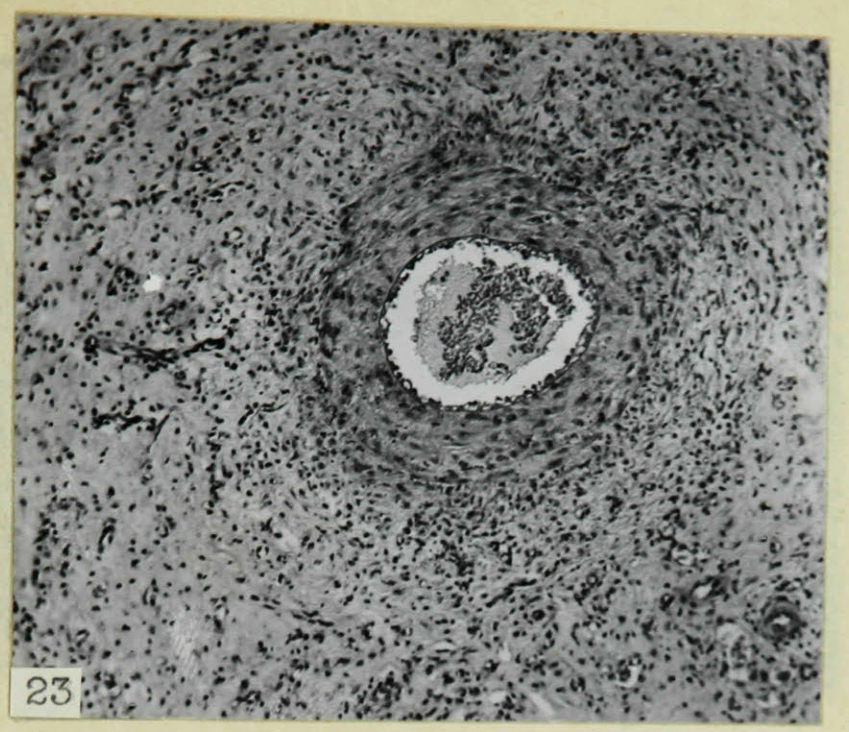


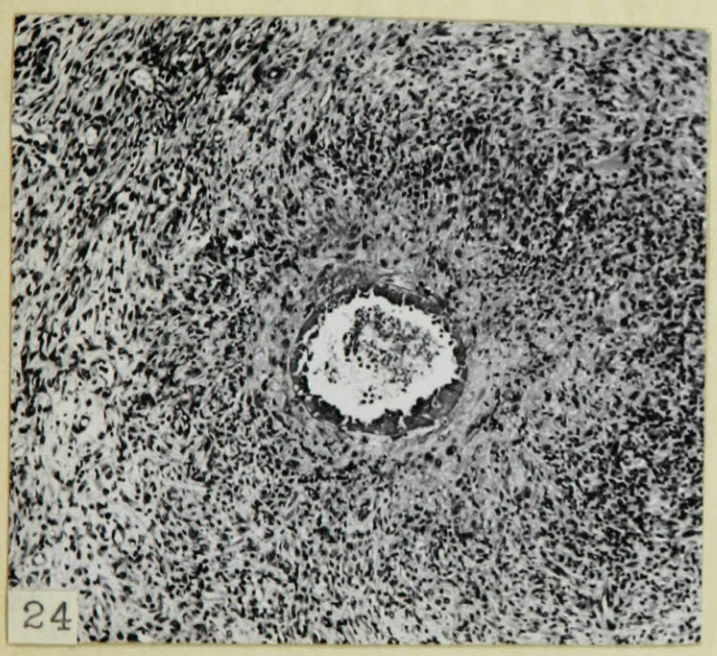
Fig. 21. Macroscopic view of an intestinal loop showing periarteritis nodosa. Note the numerous nodules along the mesenteric vessels. From a rat treated with D.C.A.

Fig. 22. Macroscopic view of a normal intestinal loop. Note thin and regular mesenteric vessels.

PLATE IX

Experiment 5.





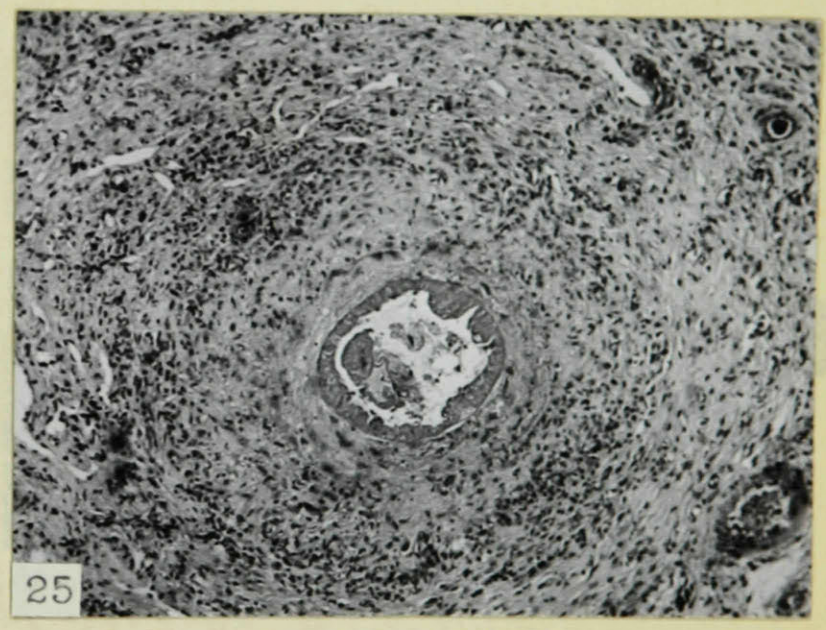


Fig. 23. Cross section of a mesenteric artery showing the first stages of periarteritis nodosa. Note the thin layer of hyalinized material just beneath the endothelial surface.

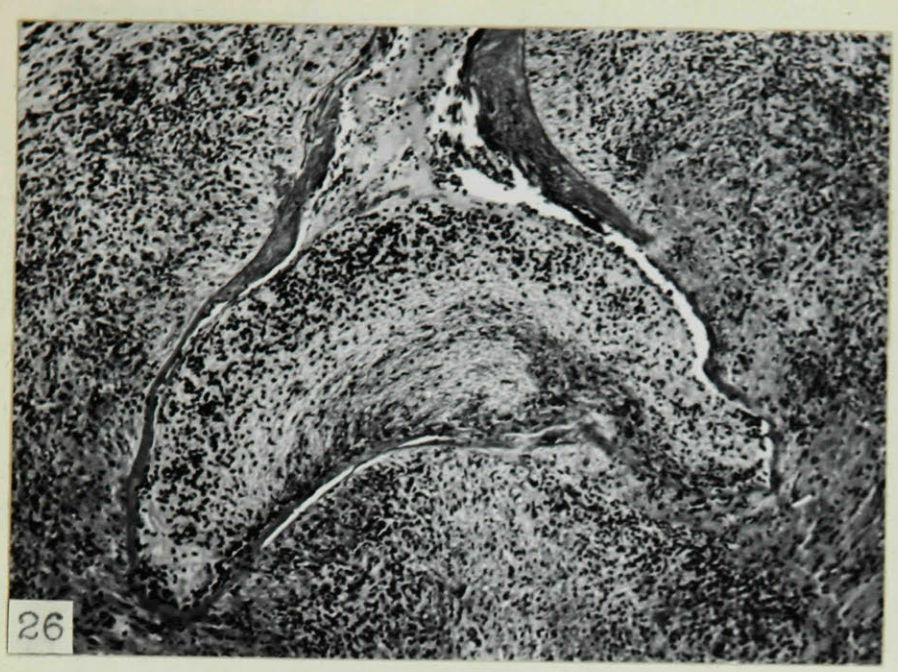
Fig. 24. Cross section of a mesenteric artery showing a more advanced stage of periarteritis nodosa. There is a fairly thick layer of hyalinized fibrin-like material on the vascular wall and almost complete destruction of the endothelium. Note the infiltration of leucocytes and giant cells.

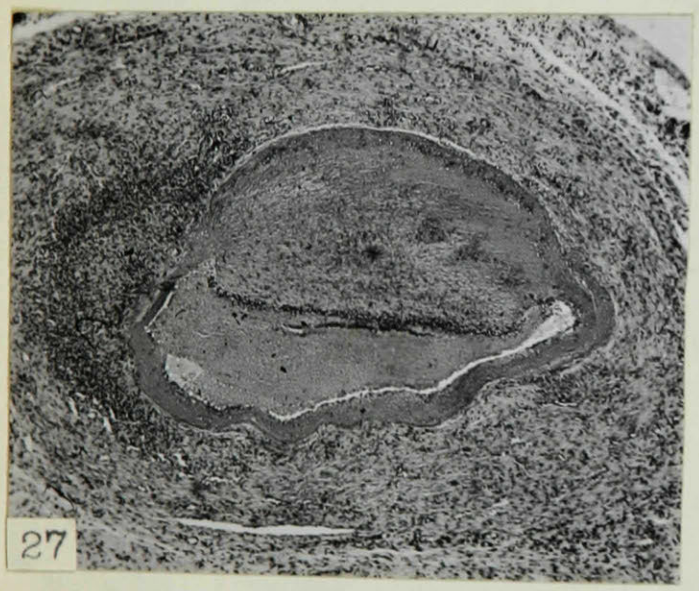
Fig. 25. The final stage of periarteritis nodosa in a mesenteric artery. Hyalinized fibrin lines the lumen, and the vessel wall appears homogeneous since it has undergone partial necrosis.

These figures are of medium magnification and are from rats treated with D.C.A. and sodium chloride.

PLATE X

Experiment 5.





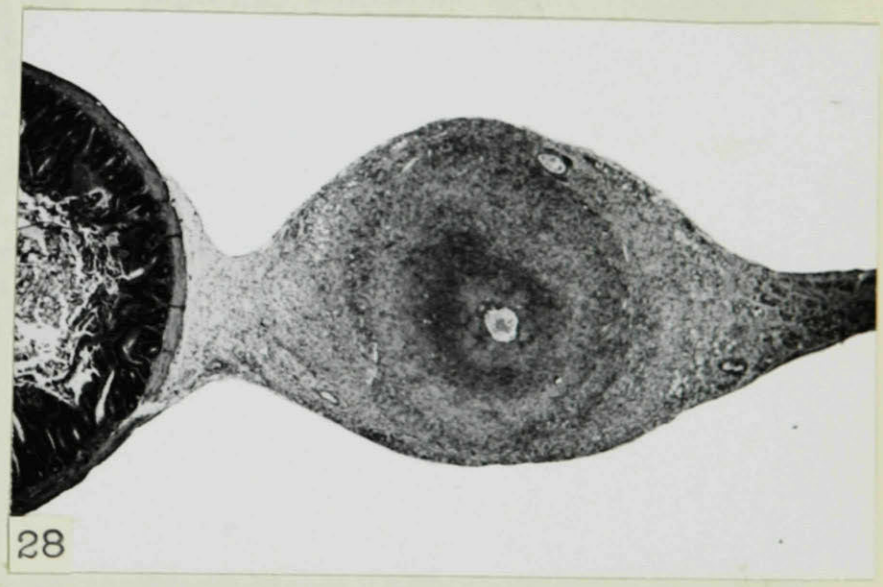


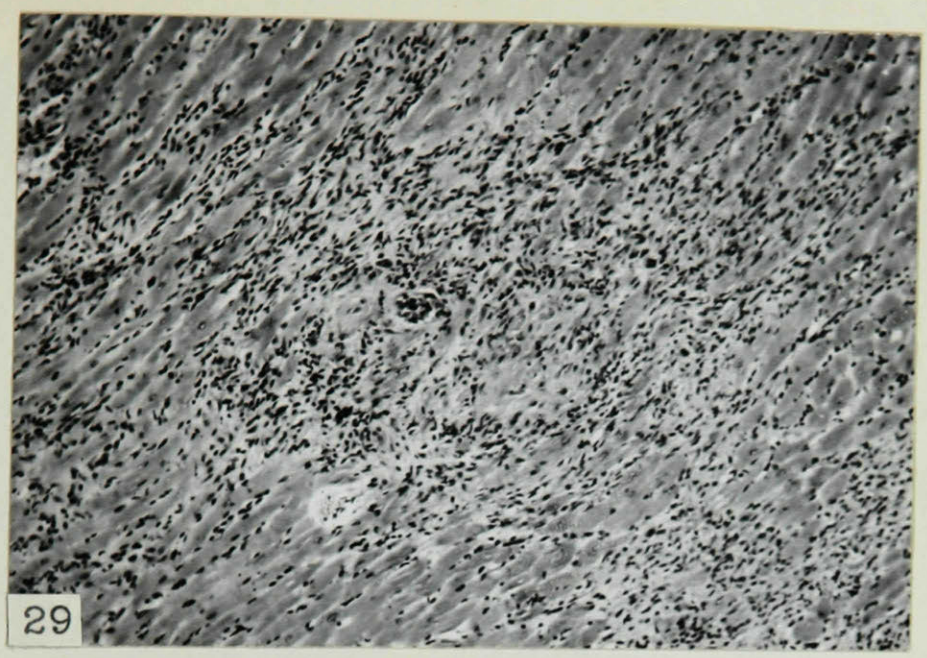
Fig. 26. An arteritic nodule at the bifurcation of a mesenteric artery. A thick layer of fibrin lines the vessel wall and a U-shaped thrombus almost completely occludes the lumen. The thrombus consists mainly of fibrin, platelets and leucocytes. A view at medium magnification.

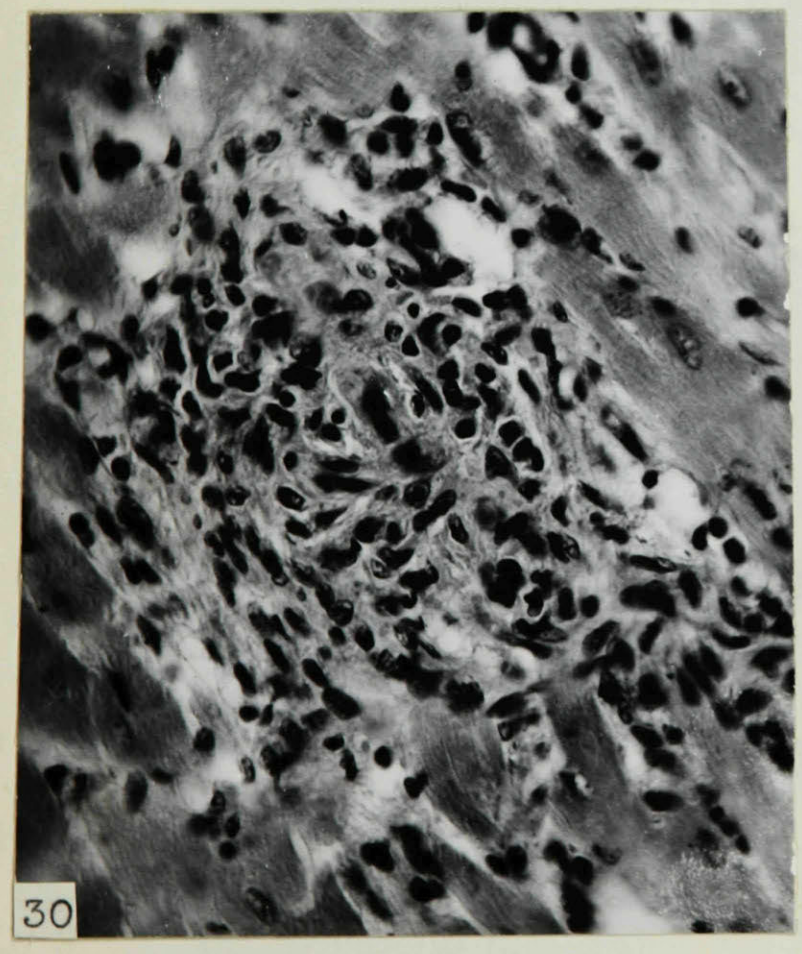
Fig. 27. A low magnification view of a cross section of a mesenteric artery showing a thrombus which almost completely fills the lumen.

Fig. 28. Low magnification view of a transverse section through a mesenteric artery in the region of the mesenteric insertion on the intestinal wall. There is thickening and infiltration of the arterial wall.

PLATE XI

Experiment 5.





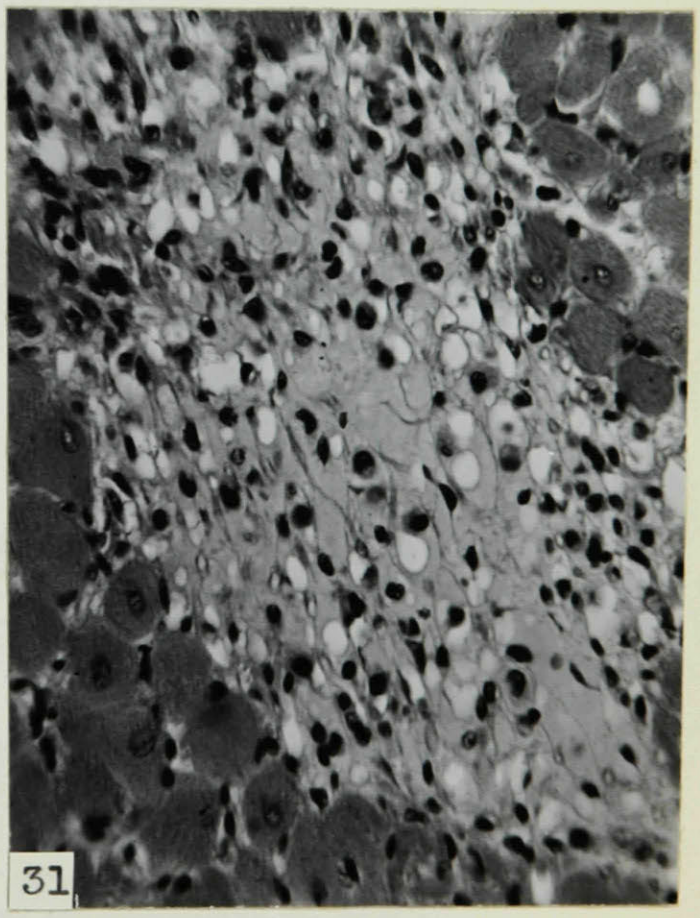


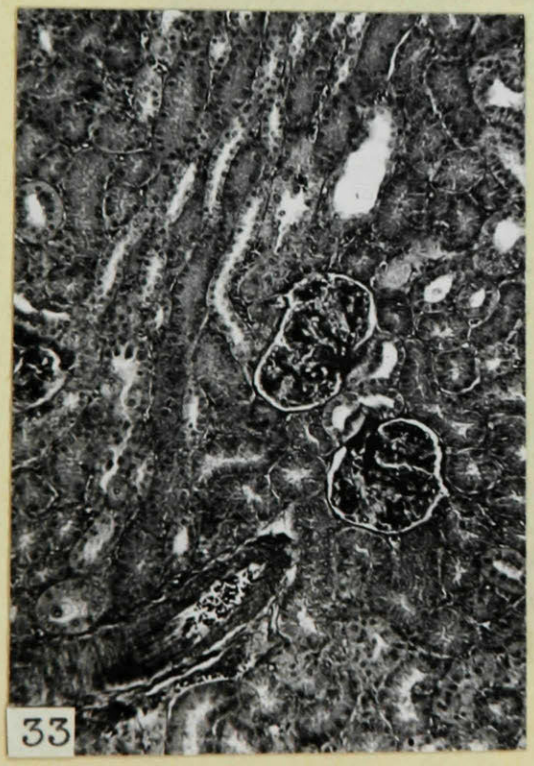
Fig. 29. Typical Aschoff body in the myocardium of a rat treated with desoxycorticosterone acetate and sodium chloride.

Fig. 30. High magnification of an Aschoff body in the myocardium showing several slightly basophilic polymorphonuclear Aschoff cells with characteristic fringy cell borders.

Fig. 31. High magnification of an area showing degeneration of myocardial fibers and replacement by somewhat edematous connective tissue. From a rat treated with D.C.A. and NaCl.

PLATE XII

Experiment 6.



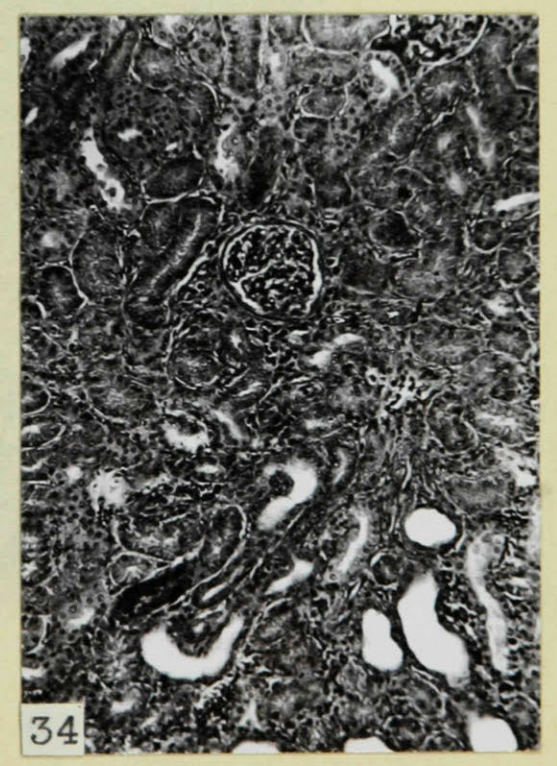


Fig. 32. Macroscopic view of the enlarged and pale kidney from a female dog treated with D.C.A. and NaCl (left) and the normal kidney from a control female dog (right).

Fig. 33. Low magnification view of a section from the above enlarged kidney. The cells of the convoluted tubules are hypertrophic and there are dark cells in the glomerulus.

Fig. 34. A different section of the same kidney as above. Note the thickening of the glomerular basement membrane.

PLATE XIII

Experiment 6.

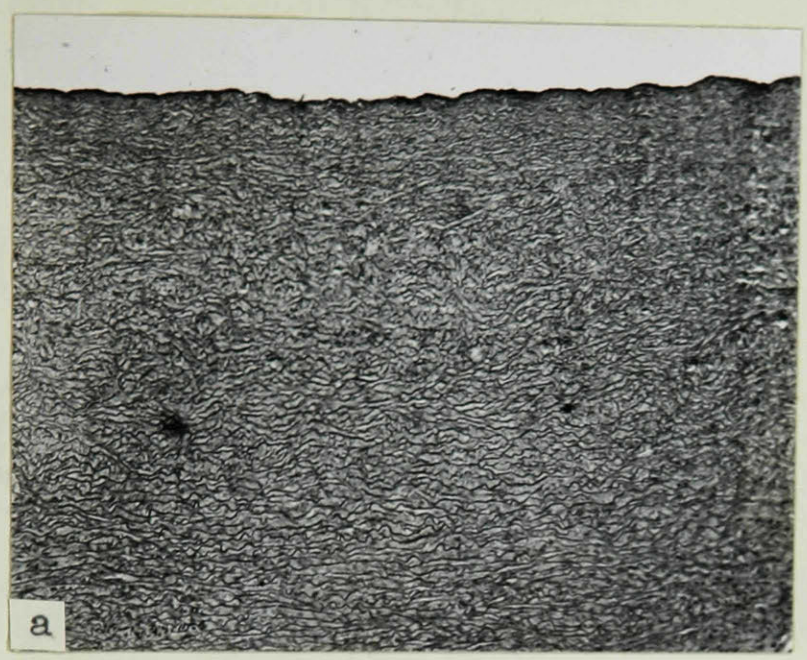
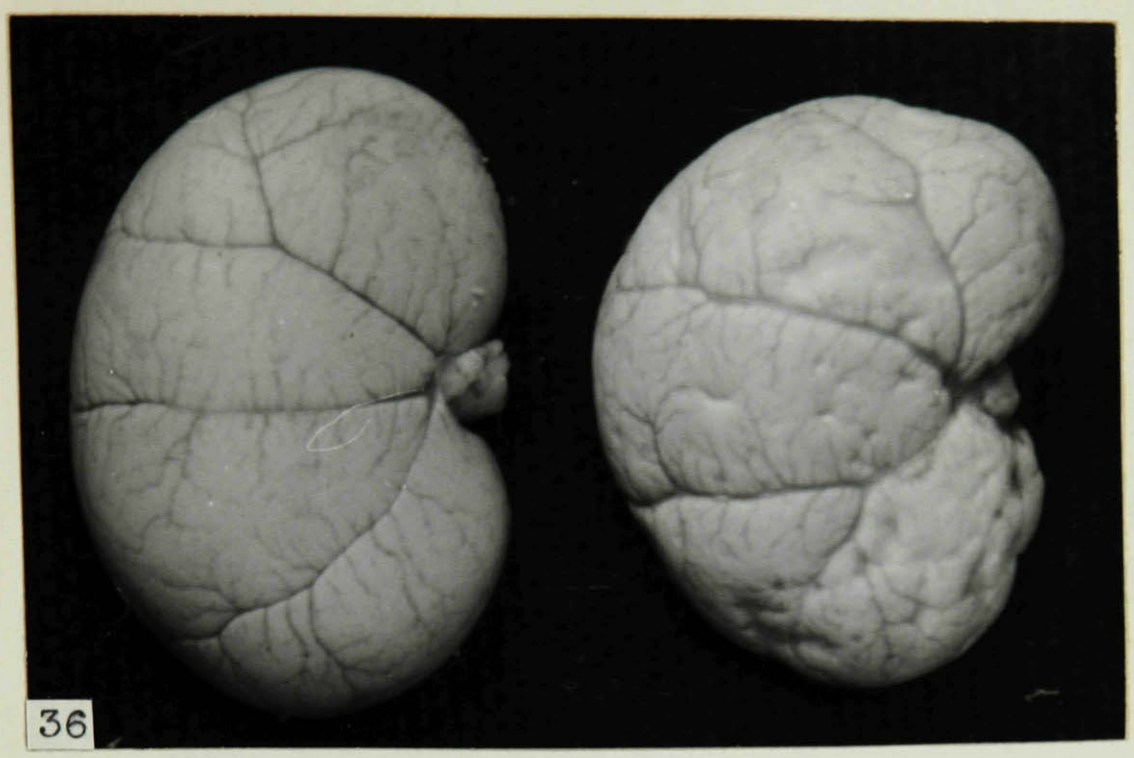


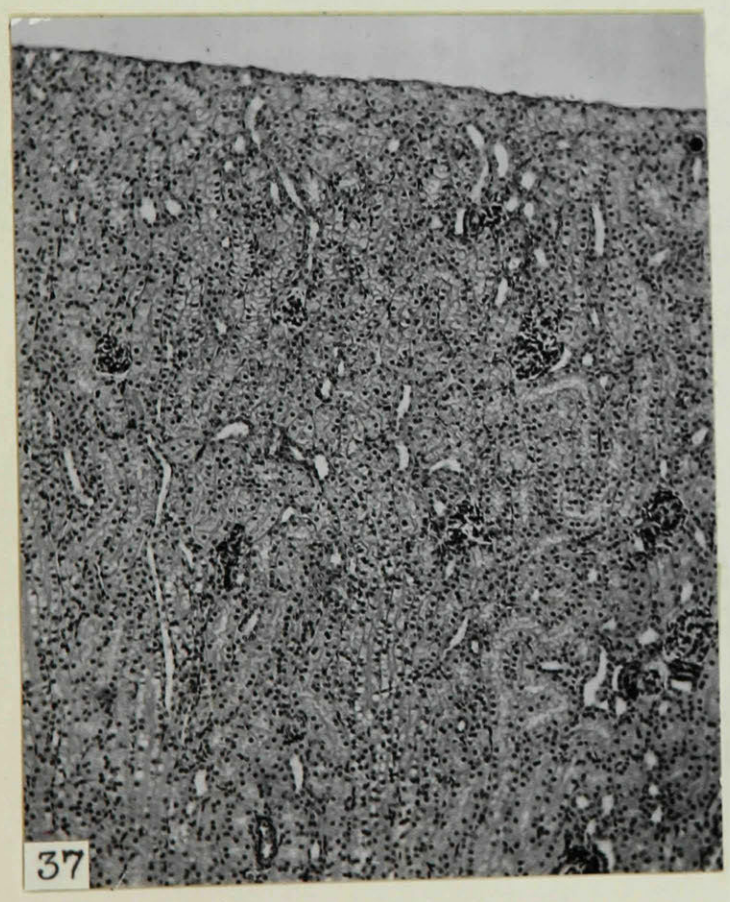
Fig. 35. (a) Low magnification view of the aortic arch of a control male dog.

(b) Low magnification view of the aortic arch of a male dog treated with D.C.A. and NaCl. Note the swelling and beginning degeneration of elastic tissue.

PLATE XIV

Experiment 7.





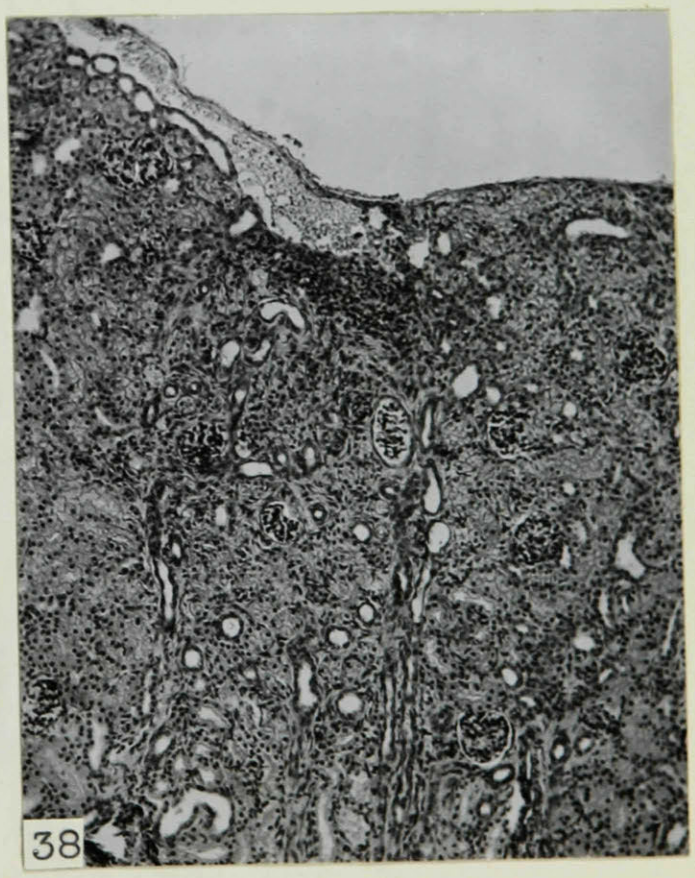


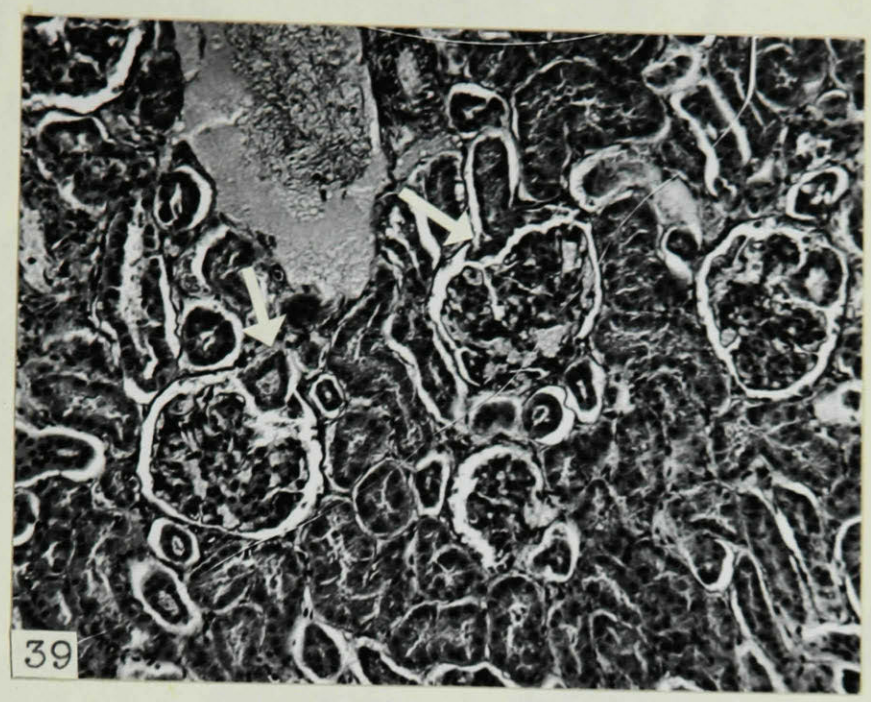
Fig. 36. Macroscopic view of the kidney of a normal kitten which received NaCl (left) and the nephrosclerotic kidney with a contracted and pitted surface from a kitten which received both desoxycorticosterone acetate and NaCl (right).

Fig. 37. View of a section through the cortex of the above normal kidney at low magnification.

Fig. 38. View of a section through the cortex of the above nephrosclerotic kidney. Note extensive scarring and leucocytic infiltration. The tubules are dilated and many of the glomeruli are degenerating.

PLATE XV

Experiment 8.



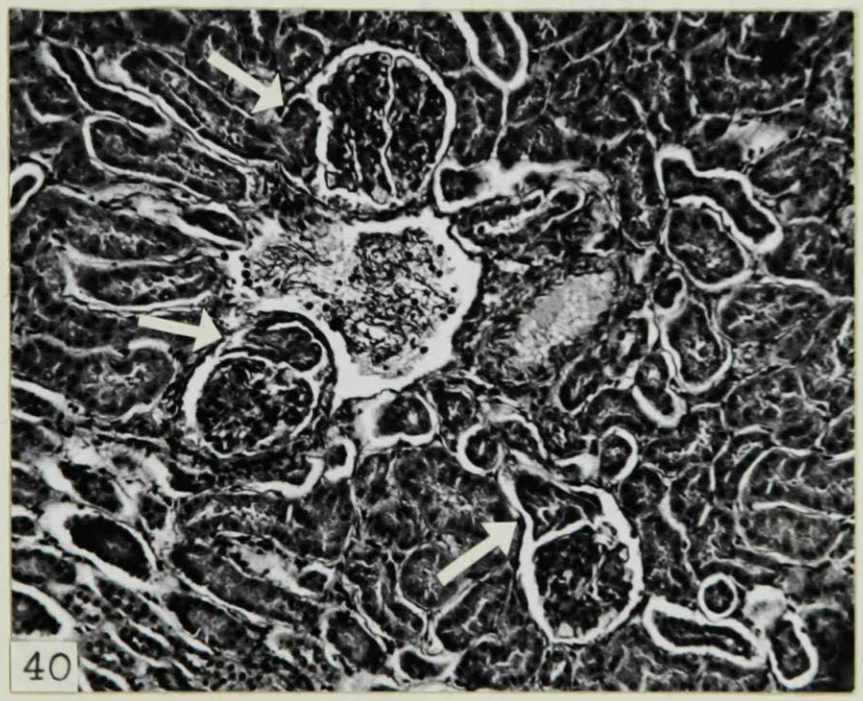
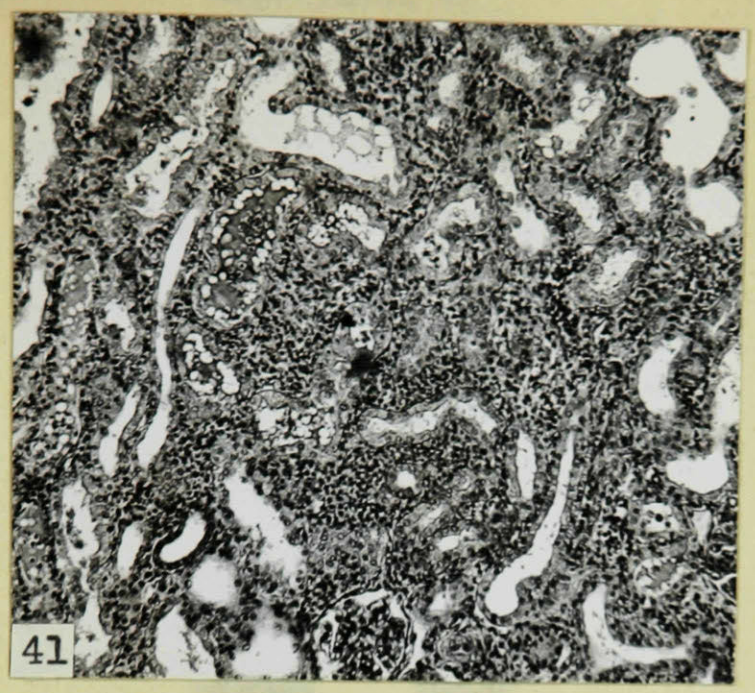


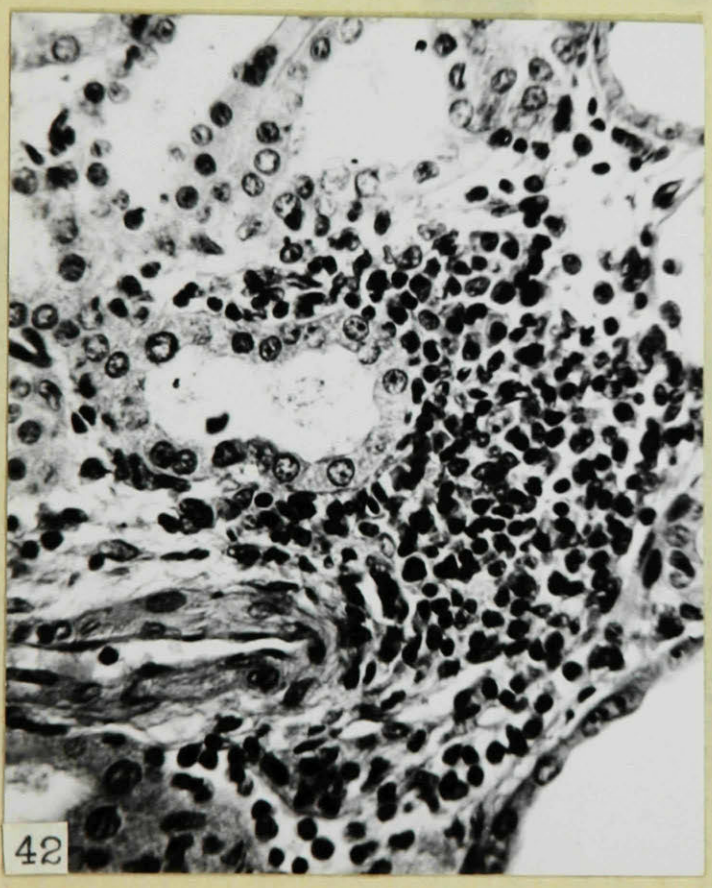
Fig. 39. High magnification view of a section through the cortex of a kidney from a monkey treated with NaCl and D.C.A. Note the invagination of proximal convoluted tubule segments between glomerular capillaries and the parietal layer of Bowman's capsule.

Fig. 40. A similar invagination occurring in three adjacent glomeruli. The points are indicated by arrows.

PLATE XVI

Experiment 9.





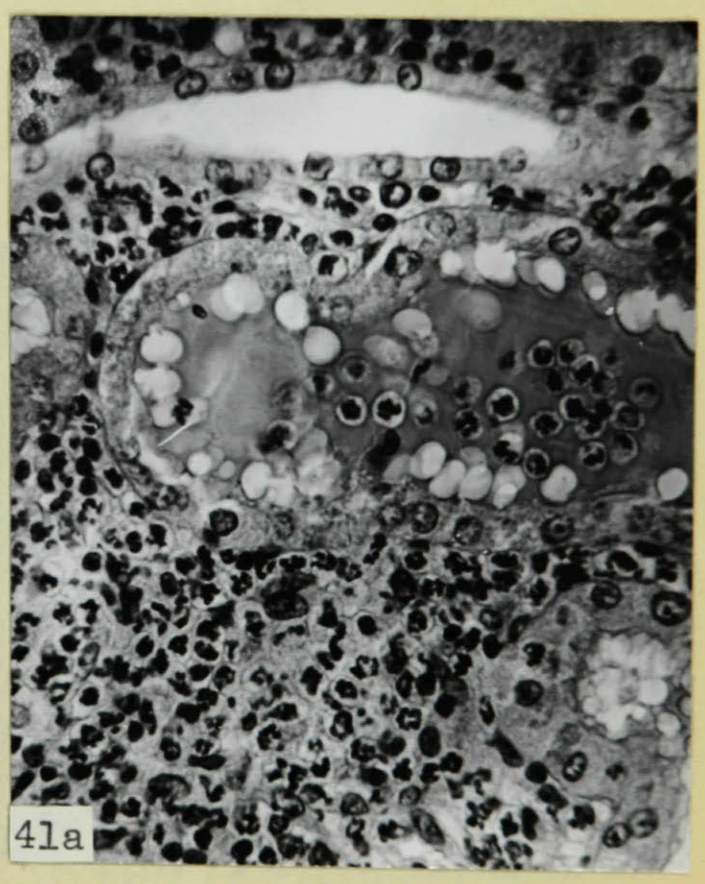


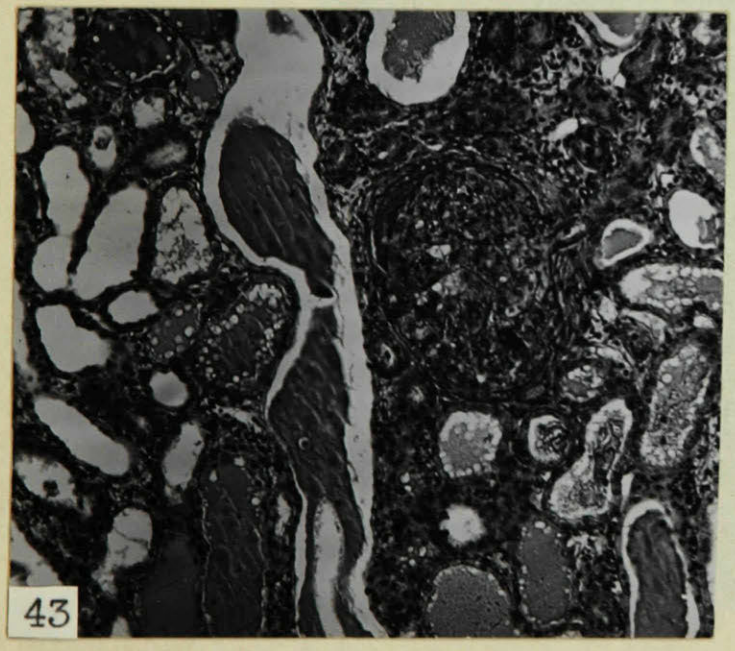
Fig. 41. Section through the kidney of a rat treated with lyophilized anterior pituitary extract and sodium chloride. Note the interstitial nephritis and dilatation of convoluted tubules.

Fig. 41a. High magnification of a section through the kidney of a rat treated as above. Note the accumulation of lymphocytes in the interstitial spaces and the tubular dilatation.

Fig. 42. High magnification of an area selected from Fig. 41. There are many leucocytes, some polymorphonuclear, in the stroma between the tubules. A few may also be observed inside a hyaline cast within a tubule.

PLATE XVII

Experiment 9.



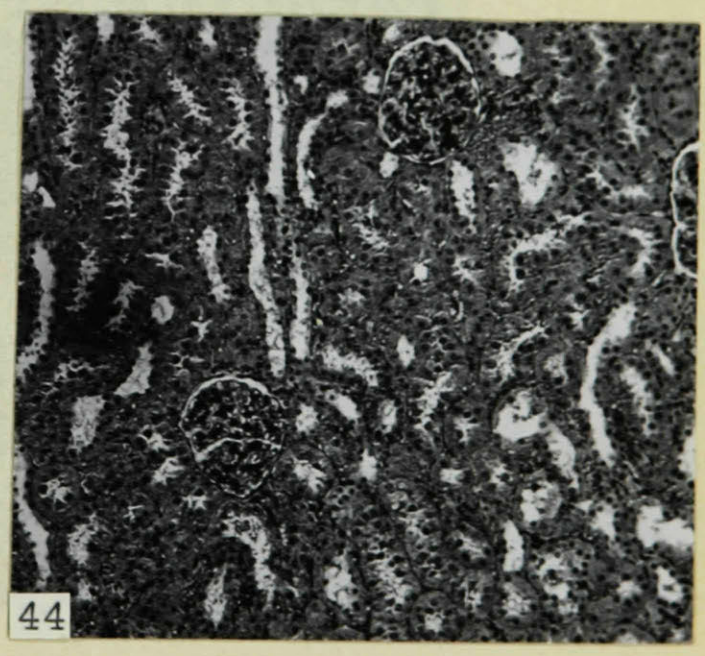


Fig. 42a. Macroscopic view of an enlarged nephrosclerotic kidney and hypertrophic heart from a rat treated with anterior pituitary extract and sodium chloride (left) and the normal organs from a rat of the same size which received the same treatment and ammonium chloride.

Fig. 43. Section through the kidney of an animal treated with L.A.P. and NaCl. Note the enlarged, partly hyalinized, glomerulus and the pericapsular fibrosis, thickening of the afferent arteriole and the cast-filled dilated tubules.

Fig. 44. Section through the kidney of a rat protected by ammonium chloride. Note the absence of pathologic changes.

PLATE XVIII

Experiment 9.

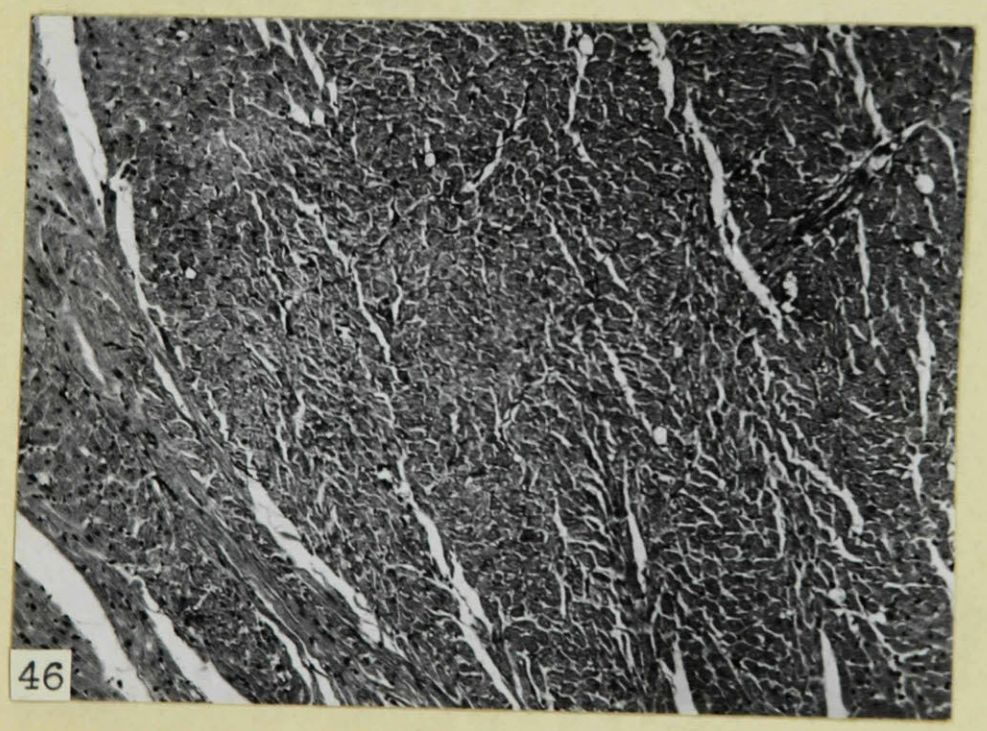


Fig. 45. Section through the left ventricle of a rat treated with anterior pituitary extract and NaCl. There is widespread fibrosis and round cell infiltration between the few remaining hypertrophic muscle fibers.

Fig. 46. Section through the left ventricle of a rat protected by ammonium chloride. The cardiac muscle is free of pathologic change and the individual muscle fibers are thinner than those in Fig. 45.

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FORM 214 Cardiovascular lesion (Thesis)

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