CARDIOVASCULAR RENAL CHANGES ASSOCIATED WITH BASOPHIL ADENOMA OF THE ANTERIOR LOBE OF THE PITUITARY (CUSHING'S SYNDROME)*

H. E. MACMAHON, M.D., H. G. CLOSE, M.B., AND GEORGE HASS, M.D.

(From the Pathological Departments of Tufts College Medical School, Boston, Mass., Guys Hospital, London, England, and the Peter Bent Brigham Hospital, Boston, Mass.)

This brief report is submitted through the kindness and encouragement of Dr. Cushing of the surgical department of the Peter Bent Brigham Hospital in Boston, and Drs. Bishop and Close of the pathological department of Guys Hospital in London, who have allowed us to make histological studies of the kidneys and other organs from patients showing clinical signs of pituitary basophilism.

When one groups together the cases reported of basophil adenoma of the pituitary in order to study and to unravel the complex clinical syndrome one finds recurring with a marked regularity certain signs and symptoms indicative of cardiovascular renal pathology. Emphasis has already been focused on this point by Cushing [1, 2, 3] and others, but we can find no mention in the literature as to just what type of cardiovascular renal pathology occurs in such cases. Is it possible that it is merely a coincidence that a cardiovascular renal picture should be found in patients showing this rather rare disease, or are we dealing here with a cardiovascular renal problem that is definitely an intrinsic part of the syndrome of pituitary basophilism?

In a group of patients showing pituitary basophilism, recently reported by Cushing, none had passed middle life but the blood pressure, both systolic and diastolic, was elevated and at times associated with headache, blurring of vision and retinal hemorrhages. In many cases years passed before signs and symptoms suggesting renal pathology appeared, and then they were sometimes transitory and variable. A clinical study of the "*formes frustes*" of pituitary basophilism offers little help in identifying the nature of the cardiovascular renal lesion associated with basophil adenoma, where an elevated blood pressure together with a large heart may be the only noteworthy finding. A study of the advanced cases, on the other

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hand, offers a possible key to this solution. In such patients one may find in addition to the hypertrophy of the left ventricle and hypertension defective excretion of phenolsulphonephthalein, an elevation of the non-protein nitrogen of the blood, a fixed specific gravity of the urine, a failure to dilute and concentrate fluids or to concentrate urea when taken orally, and lastly, one may find on examination of the urine a variable amount of albumin, hyaline and cellular casts, polymorphonuclear leukocytes, desquamated epithelial cells and varying quantities of erythrocytes. Edema may be present. Such findings as these have led to the following diagnoses: chronic nephritis, vascular nephritis, and granular atrophy of the kidney.

If one disregards for a moment such symptoms of pituitary basophilism as adiposity, kyphosis, amenorrhea, hypertrichosis, a plethoric appearance of the skin, polycythemia and backache, and focuses on the cardiovascular renal problem alone, one sees at once a striking similarity to the clinical picture of malignant nephrosclerosis, as originally described in 1914 by Volhard and Fahr.[4,5] This is characterized by an elevated blood pressure, a large heart, an increase in the non-protein nitrogen in the blood, a diminution in the concentrating and diluting power of the kidney, polyuria, neuroretinitis and uremia. Edema may or may not be present. An examination of the urine in these cases will show albumin, granular, hyaline and cellular casts, polymorphonuclear leukocytes, and frequently frank blood. One may find similar signs and symptoms in chronic glomerulonephritis, but the course of both disease and the relation and sequence of symptoms to one another in chronic glomerulonephritis and malignant nephrosclerosis differ. In the latter disease, early and even in more advanced cases the cardiovascular symptoms stand far in the foreground. An elevated blood pressure and left ventricular hypertrophy that may by chronic glomerulonephritis be slight or absent are developed in patients with malignant nephrosclerosis to a remarkable degree.

In July of the summer of 1933, while visiting the pathological laboratory at Guys Hospital, London, two of us with Dr. Osman had the opportunity to study histologically tissue from a case of basophil adenoma of the anterior lobe of the pituitary, which had recently been reported by Bishop and Close.[6] To our surprise the histological picture was similar to that of malignant nephrosclerosis. On returning to America, Dr. Cushing, who has long been interested

in this same problem, allowed us to study sections from the kidney from one of his cases of basophilic adenoma of the pituitary,* and this, like the case of Bishop and Close, showed without question the histological findings of malignant nephrosclerosis.

Malignant nephrosclerosis, neither clinically nor at the autopsy table, is a common disease: in contrast to the frequency with which one meets patients with benign essential hypertension, malignant nephrosclerosis is rare. The purpose of this paper, however, is neither to describe nor to discuss in detail the clinical and histological changes of malignant nephrosclerosis, but rather to point out an extremely interesting clinical and pathological finding, namely, the presence of malignant nephrosclerosis in two patients with basophil adenoma of the anterior lobe of the pituitary.

Case Reports

Case 1. C. P. (case reported by Bishop and Close[6]), was a normal child until the age of 11 years, when she stopped growing and began to gain weight. She developed a ruddy complexion and her hair began to fall out. Menstruation began normally at the age of 14, but after a year the periods ceased, and except for 3 consecutive months, when she was 18 years of age, she suffered from amenorrhea. From the age of 14 onward she experienced severe headaches which occurred regularly every month. Six months before death the sight of the left eye became affected and 2 months later symptoms of excessive thirst and polyuria became manifest. There was also frequent backache.

At the age of 22, in November 1930, she was admitted to Guys Hospital. She was kept under observation for some time and was then discharged, but was readmitted a short time before death. On admission the most striking features were the very red complexion, dry scaly skin, hairiness of the face, chest and abdomen, and the stunted growth. A beard sufficient to necessitate the use of a razor was present. There was a patchy red erythema localized particularly to the left arm. She was slightly knock-kneed and there was a deformity of the left wrist and right hand. A radiogram showed a fissured fracture of the lower end of the left radius and a rarefaction without evidence of inflammation of the head of the fourth right metacarpal bone. While in the hospital the patient slept badly and complained mainly of thirst. Occasionally there was a feeling of suffocation. The headaches were troublesome and on many occasions the blood pressure was as high as 300 mm. Hg. After she had been in the ward for about a fortnight she had the first of a series of fits, which were relieved on three occasions by venesection, while lumbar puncture was performed about twice a week. Her intelligence was in no way impaired although her illness worried her a great deal, and she frequently resorted to tears. Her eyesight troubled her and there was a marked degree of retinitis with silver wire arteries and a scotoma of the left eye. Examination showed the heart to be slightly enlarged to the left with a loud aortic second sound. The average

* See Ref. 3, page 521.

blood pressure readings were 250/180 mm. Hg. The hemoglobin was 95 per cent. Records of the blood picture are unfortunately not available but it is believed that a red cell count was never higher than 5,000,000. The blood urea was 43 mg. per 100 cc. Blood sugar tolerance test showed delayed return to normal with a high fasting figure (0.14 gm. per 100 cc.). The blood sugar went up to 0.25 per cent and was still raised after 2 hours (0.21 per cent). The blood cholesterol was also slightly above normal (0.185 per cent instead of 0.150 per cent). The Wassermann reaction was negative. The serum calcium figure was within normal limits.

An investigation of the urine showed albumin and sugar to be present but no acetone. Pus, fatty and hyaline casts were also demonstrated. The concentrating power of the kidney was slightly defective. Shortly after the second admission to the hospital signs of acute edema of the lungs developed suddenly and death occurred.

When we examine this report and focus our attention on the cardiovascular renal problem alone, we find a young person with marked hypertension and a large hypertrophied left ventricle, suffering from headaches and disturbances in vision. An examination of the eye grounds revealed a marked degree of retinitis. The blood urea was considerably elevated and the blood cholesterol was above normal. The urine showed albumin, casts of various sorts and defective concentration. Surely from such findings our clinical diagnosis would rest between chronic glomerulonephritis and malignant nephrosclerosis, and when one considers the sequence of events the latter diagnosis is much more likely.

Postmortem Examination

External examination of the cadaver showed an obese, stunted body with hair over the entire abdomen and on the chest. There were many hemorrhages beneath the skin of the limbs. The pituitary fossa and its contents were preserved. There was considerable edema of the lungs with an excess of frothy fluid in the bronchi. The left ventricle was hypertrophied and dilated, and the heart muscle pale and mottled. Extensive arteriosclerosis was found throughout the vessels. The liver was passively congested and the pancreas greatly reduced in size. The spleen and suprarenals were normal. The kidneys, which were rather small, showed scarring of the surface, which had a "flea-bitten" appearance. There were several hemorrhages beneath the mucosa of the bladder. The uterus was infantile in type while the ovaries were small and without visible evidence of Graafian follicles.

Again to review this report, focusing our attention once more on the cardiovascular renal problem, we have marked hypertensive hypertrophy of the left ventricle, diffuse arteriosclerosis, a granular kidney, with hemorrhages into the kidney, bladder and skin, and finally terminal pulmonary edema, which is so commonly seen in death associated with malignant nephrosclerosis.

Microscopic Examination

The entire kidney is severely injured by a chronic diffuse pathological process involving the vessels, the glomeruli, the tubules and stroma, leading to an almost complete reconstruction of the parenchyma and sclerosis of the interstitial tissue. The vessels show a varied picture. In a branch of the *renal artery* the intima is thickened by a narrow polster made up of a fibrillary ground substance staining blue by the Mallory anilin blue stain and showing flecks, shreds, and clumps of fibrin near the endothelial surface. The most recently formed portion of this polster is adjacent to the endothelium where it appears to have an almost semifluid appearance in which fibrils are poorly formed and appear more like lines and threads of coagulated protein, which show no definite order or arrangement. Farther away from the lumen this polster varies in structure and takes on rather a band-like arrangement in which cells are separated by well formed collagen fibrils. Just inside the original elastic interna there is seen in the Mallory anilin blue stain a bluish yellow, clear hyaline band, very narrow and showing fine reddish dots. This lamella in the elastic tissue-stained preparation is moderately positive so that we have here probably the beginning of a second elastic lamella arising in ground substance. The original elastica interna is fragmented, stains irregularly and in places is impregnated with calcium. The media of this vessel shows two interesting features: first, a hypertrophy of the individual muscle fibers, and second, a great increase in fibrillary ground substance between the muscle fibers. The adventitia is little changed. This vessel is large, the wall is generally thickened and the lumen is larger than normal. As one follows the large artery to the *interlobar* branches one finds in the latter a similar change, namely, a slight intimal and medial thickening, and the lumen is wider than that of a normal interlobar artery in a patient of the same age. In places the smooth muscle fibers show regressive changes, with disintegration and disappear-

ance. In the *arcuate arteries* one again sees this vascular hypertrophy, with dilatation of the lumen and regressive changes in an already hypertrophied muscular media. The *lobular arteries* show a striking change from the three sizes of vessels already described (the renal, interlobar and arcuate). Here the media is devoid of muscle fibers. It is represented merely by a blue-staining fibrous wall that in some places is not clearly defined from the surrounding stroma. Here and there an occasional muscle fiber is still recognizable. The basement membrane is not swollen and, except for areas where it has disappeared or ruptured, appears unchanged. Between the endothelium and the basement membrane one finds a bluish fibrillary substance (using the Mallory anilin blue stain) often containing delicate fibrin threads and not infrequently filled with large coarse clumps of fibrin and red blood cells. Occasionally fibrin and red blood cells may be traced throughout the wall. In these vessels the lumina are greatly narrowed and not infrequently obliterated by fibrin thrombi, or simply by the accumulation of subendothelial ground substance or the accumulation of nests of large "foam cells." There is no lamellar elastosis in these lobular arteries. The *afferent arterioles* to the glomeruli show changes resembling those in the lobular vessels just described, with necrosis of the wall and fibrin thrombi in the lumen on the one hand and old healed sclerotic vessels with occluded lumina on the other. The type of sclerosis here is characterized by a lamellar arrangement of fibrous tissue beneath the endothelium in which cells and fibrils form concentric whirls within one another, greatly narrowing the lumen.

The *glomeruli* show a varied picture. About 70 per cent of those seen in the sections examined show a rather characteristic ischemia, together with an increase in cells and ground substance, and in contrast to the normal glomerulus they are large. There are clusters of glomeruli usually just beneath the capsule which show the simple hyaline transformation with thickening of the capsule. The most interesting glomerular lesion is the fresh fulminating degenerative and inflammatory lesion associated with aneurysmal dilatation of the capillaries, hemorrhage and fibrin within the lumina and throughout the ground substance, so characteristic of malignant nephrosclerosis. Where this lesion is somewhat older there is proliferation of both endothelium and epithelial cells with desquamation and adhesions between the capillary loops and from the

capillary loops to the capsular wall. This may be associated with proliferation of the cells along the capsular wall. Where the lesion has healed many of the cells have disappeared and the glomerulus itself may no longer be easily recognizable. One finds acute lesions, others that are healing, others that have healed, and still others showing recurrent fresh lesions in glomeruli that have long ago healed. These lesions appear at times isolated and at times in small clusters of glomeruli fed by the same lobular artery.

The *tubules* show as variable a histological picture as that in the arteries and glomeruli, and like the changes in both of those one finds both fresh and old lesions. The most interesting change is the almost complete absence of well differentiated proximal convoluted tubules. A search for such clearly recognizable proximal convoluted tubules in which one seeks a rather characteristic type of epithelium reveals only here and there small scattered islands; and the cells lining these show albuminous granular degeneration, hyaline droplet degeneration and, in places, necrosis. The great majority of tubules are small, collapsed and poorly differentiated, and lined by small atrophic cuboidal cells. The lumina are narrow and contain little precipitated protein. A third type of tubule commonly found also lacks differentiation and is characterized by marked dilatation with endothelial-like cells lining the wall. Mitoses in such tubules are quite common and their lumina contain precipitated albumin, a few polymorphonuclear leukocytes and red blood cells. In a few areas the tubules have entirely disappeared. This, however, is a rare finding and is best seen at the tips of the papillae.

The *stroma* in both cortex and medulla is increased. When stained by the Mallory anilin blue stain it appears as a blue-staining, finely fibrillar ground substance, which is most marked in areas where the tubules are small and atrophic or where they have disappeared entirely, but is also present, though to a much less degree, about the tubules that form the islands of still recognizable proximal convoluted tubules. This material has the same structure, stain and character as the material beneath the endothelium of the arteries. There are small foci of the lymphocytes limited largely to the areas of sclerosis.

The *veins and capillaries* are dilated, especially the capillaries surrounding the tubules, but there are no hemorrhages from these vessels into the stroma.

The *basement membrane* in vessels, glomeruli and tubules shows a series of interesting changes. In the arterioles, as already mentioned, it is in places broken up and absent. In the glomerular capillaries it is separated from the endothelium by a newly formed, finely fibrillar ground substance. The basement membrane forming the glomerular capsules is here and there thickened. On the tubules, especially where they have collapsed, the basement membrane is thickened and somewhat irregular, and here and there one finds a fine fibrillary ground substance between the collapsed epithelium and the original basement membrane — a picture corresponding very closely to the accumulation of fibrillary ground substance beneath the endothelium in the smaller vessels.

To summarize these histological changes, we find a severely damaged kidney; the larger arteries show vascular hypertrophy, the smaller show regressive changes, necrosis, thrombosis and hemorrhage. Some show healed lesions, others fresh lesions and still others show chronic lesions, occasionally with fresh hemorrhage superimposed. The glomeruli for the most part are still readily recognizable, being large, anemic and rich in cells. There are areas in which the glomeruli show acute, healing, healed, chronic and recurrent degenerative and inflammatory processes characterized by hemorrhage, necrosis and cellular proliferation leading in places to half-moon formation within the capsule. The tubules are severely injured; only nests of recognizable proximal convoluted tubules are present. The majority are small and atrophic while others are dilated, poorly differentiated and filled with coagulated protein, desquamated epithelial cells, polymorphonuclear leukocytes and erythrocytes. The stroma is diffusely increased, the veins and capillaries are congested. Such findings as these are neither compatible with chronic glomerulonephritis nor with benign nephrosclerosis, but are characteristic of chronic malignant nephrosclerosis which has been progressing with remissions for several years.

In keeping with this picture of malignant nephrosclerosis the spleen, liver, intestine and ovary reveal the same variation and character of histological changes in the smaller blood vessels. In the spleen many of the small arterioles show fibrin throughout the wall and occlusion of the lumen, and still others show marked swelling of the basement membrane with partial occlusion of the lumen. In the ovary these changes are especially marked where

some of the small vessels are almost completely transformed into walls of fibrin.

CASE 2. H. P. (case reported by Cushing [3]), an unmarried, white female, 33 years of age, entered the hospital with a history of two periods of amenorrhea. The first attack was of 1 year and 8 months duration, occurring when the patient was 20 years of age. The present attack began 1 year and 3 months ago. She was born of healthy parents and attained normal adolescence at the age of 13, when she later grew into an intelligent, vigorous and ambitious young woman. She entered college at 18 but became unhappy there and withdrew at the end of the second year. She ascribes this to restlessness and emotional instability. In 1919, when she first ceased to menstruate, she developed a ravenous appetite, gained weight rapidly, particularly in the face and abdomen. During the summer of 1919 she broke her ankle. Purplish striae of the body and arms began to appear at that time. In December of 1919, she found herself easily fatigued and acquired a definite polyuria and polydipsia. At the same time headaches occurred, with blurred vision, tinnitus, dizziness and numbness of the hands.

Toward the end of February 1920, because of a sudden fainting attack, she came under the care of Dr. E. P. Joslin, who found there was a moderate hyperglycemia with glycosuria, and a basal metabolic rate of −30 per cent. On March 13, 1920, she was first seen briefly in consultation with Dr. Joslin. The facial hypertrichosis and the peculiar disposition of the adiposity with extraordinarily widespread striae atrophicae, associated with a moderate hypertension of 140/100, indicated a polyglandular syndrome. By January 1921, she had become increasingly hirsute and "bloated" in appearance. At this time she entered the Neurological Institute in New York where she was given baths, exercises and glandular preparations. After 4 weeks the weight was reduced, the hirsuties had disappeared and normal menstruation was resumed. From this time, for a period of 5 years, she continued under various combinations of glandular treatment and regarded herself as reasonably well.

In 1926 the face again began to get heavily bearded, necessitating the use of a razor. A year later tonsils, adenoids and impacted wisdom teeth were removed and it was noticed that the blood pressure was high, 155/115. In 1929 she had a "nervous breakdown," and the following year, while being studied at the Evans Memorial Hospital, it was noticed that the urine showed some albumin and an occasional hyaline cast with a normal phthalein test. She had a low sugar tolerance, a fluctuating hypertension, a basal metabolic rate of −14 per cent and cardiac enlargement. In January 1931 the menstrual periods, after having been essentially regular for 10 years, ceased, and in July she was found to have a marked hypertension varying from 220 to 250 systolic.

In 1932 she fell and fractured the humerus. The following summer polydipsia, occipital headaches, palpitation, shortness of breath and swelling of the feet and ankles were present. The fatness of the face and shoulders, dryness and pigmentation of the skin, cyanosis of the dependent hands and feet had markedly increased. It was observed that large ecchymoses would follow the slightest bruise and that a cut or scratch would bleed excessively. At this juncture, in October 1932, she was referred to the Peter Bent Brigham Hospital for study.

The patient was a rather tall woman, 5 feet, 9½ inches, weighing 63.5 Kg., with a peculiar moon-shaped, recently shaven face with clipped eyebrows. The eyes were puffy and there were posterior cervical and supraclavicular fat pads. She was not appreciably round shouldered and though not particularly abdominous the parietes were somewhat pendulous and flabby. The extremities did not participate in this adiposity. Over the arms, axilla, breasts, abdomen, hips, groins and thighs were an extraordinary number of broad, pale striae atrophicae. The lower extremities showed marked pigmentation and scarring of the dry and scaly skin, with several large and fading ecchymoses from recent trivial contusions.

The blood pressure averaged 220/170, the urine showed a trace of sugar and of albumin with no renal elements. There was a variable polyuria amounting to about 3 liters. The basal metabolic rate was −10 per cent. The detailed blood examination showed 4,720,000 erythrocytes, with a hemoglobin (Sahli) of 106 per cent. The non-protein nitrogen was 46.97 mg. and the cholesterol 192.3 mg. per cent. Roentgenograms showed slight diffuse atrophy of the vertebral bodies without collapse or deformity, normal detail of the cranial bones, a sella tursica of normal dimensions but hazy outline, and multiple small tiny shadows in both flanks suggesting renal calculi — a common finding in hyperparathyroidism. The patient was transferred to the Huntington Hospital where, through the kindness of Dr. Aub, her elimination was thoroughly studied. He reported essentially normal blood content for calcium phosphorus and phosphotase and normal elimination of both calcium and phosphorus. She showed a low sugar tolerance and a high nitrogen output, as shown by an average loss of 6.7 gm. daily on a balanced diet containing 56 gm. of protein.

On readmission the pituitary body was irradiated on 4 successive days without any immediate effects. She was discharged Nov. 12, 1932, and returned home and resumed her usual activities. On December 3 she retired about midnight, waking about an hour later with dyspnea and increasing cyanosis. She died 12 hours later from what was supposed to be acute pulmonary edema.

When we study this patient in retrospect from a cardiovascular renal standpoint we find that in 1919, when the patient was 20 years old, she began having headaches, blurred vision, tinnitus, dizziness and numbness of the hands. Several months later we find the blood pressure slightly elevated, 140/100. Six years later the blood pressure was again examined and had reached 155/115, and the urine contained albumin and casts. The heart at this time was enlarged. Five years later we find the hypertension had increased to nearly 250 systolic and a year later there were occipital headaches, palpitation, shortness of breath and swelling of the feet and ankles, and the patient observed that large ecchymoses would follow the slightest bruise. The physical examination at the time of hospital entry in 1932 substantiated this high blood pressure with some albumin in the urine. There was a variable polyuria and the non-protein nitrogen and cholesterol values were increased and the

nitrogen output showed an average loss of 6.7 gm. daily on a balanced diet of 56 gm. of protein. Finally, death came suddenly, probably to be explained on the basis of pulmonary edema.

From such a summary our attention is primarily focused upon the cardiovascular problem, with its hypertension, enlarged heart, headaches and disturbances in vision. The disturbances in renal function with albumin, elevated non-protein nitrogen and cholesterol stand rather in the background and yet the sequence of events must be carefully considered, and a clinical diagnosis of benign nephrosclerosis with beginning renal decompensation or malignant nephrosclerosis must be considered. The tendency to bleed when slightly bruised is found more commonly associated with the latter diagnosis.

Postmortem Examination

An autopsy was performed by Drs. Schulz, Hass and Cushing, and only the cardiovascular renal changes will be mentioned here. The heart was enlarged (695 gm.) and the large arteries, including the aorta, showed an advanced degree of atherosclerosis. The kidneys had slightly adherent capsules and on section minute calculi were visible in the calices.

Microscopic Examination

The kidney is finely granular, the capsule thickened, and small hemorrhages are seen over the surface. The kidney as a whole shows only moderately severe changes, the most important of which appear in the cortex and are somewhat irregularly distributed. There is a destruction of kidney tissue and a new formation of tubules with a general reconstruction of the normal architecture. The arteries show a variety of interesting changes. The large *interlobar* arteries show marked medial hypertrophy with large, well preserved muscle fibers. The intercellular ground substance is not remarkably increased. The internal elastic lamina is intact and stains well. The intima is only slightly thickened, showing a lamellar connective tissue thickening. Practically the same changes are found in the *arcuate* and larger lobular arteries; that is, we have in these vessels a form of vascular hypertrophy with an enlargement of the vessel, a thickening of the vessel wall and a lumen larger than that of a normal person of the corresponding age. In the smaller *lobular*

arteries one sees a gradual disappearance of the muscle fibers from the largest to the smallest arterioles. The vessels are abnormally large and the media shows replacement by connective tissue. The internal elastic lamina is still preserved, and the basement membrane of the arterioles is here and there remarkably swollen, irregular, and when stained with the Mallory anilin blue stain appears reddish yellow. In other arterioles the basement membrane is unchanged and between the endothelium and this basement membrane there is an accumulation of watery-like material forming in places a very fine network which, when stained with the Mallory anilin blue stain, appears distinctly blue. This accumulation beneath the endothelium leads in places to almost complete obliteration of the lumen. In other vessels of similar caliber, where the process is older, one sees a lamellated arrangement of cells and connective tissue in which spindle-shaped cells appear drawn out and separated by narrow bundles of collagen, giving a characteristic "onion-like" picture. A still more striking change, though somewhat rarely seen, is the presence of fibrin and red blood cells within the wall, which at times is completely necrotic. Nests of fatty endothelial cells beneath the endothelium and fibrin in the lumen may complicate the picture. Some of the arterioles to the glomeruli are scarcely recognizable. The lumina of the vessels comprising the smaller branches of the vascular tree are greatly reduced. It is not infrequent to find extensive vascular changes without a corresponding change occurring in the capillary loops of the glomeruli.

The *glomeruli* are relatively little changed. By count, between 90 and 95 per cent are still preserved, the most of which, however, are large, ischemic and show an increase in cells and intercellular substance. Here and there, usually occurring in small groups of two and three, glomeruli show simple hyaline transformation with connective tissue thickening of the collapsed capsule. Here and there, even in areas showing rather advanced atrophy of the tubules, one finds well preserved glomeruli, rich in blood, showing neither cellular nor intercellular changes. The most striking change is that so characteristic of malignant nephrosclerosis, namely, the capillary dilatation, hemorrhage into the capsular space and fibrin occluding the capillary lumina and extending out into the somewhat loose intercellular basement membrane and ground substance. Regressive changes in the epithelial cells are occasionally found associated with

proliferation and desquamation. Glomeruli showing these changes are infrequent. They appear singly and in small groups. Somewhat older changes, including the chronic and the healed lesions with simplification of the dilated capillaries, adhesions of the capillary loops with each other, and with the capsular wall, and even half-moon formations are also found, but only rarely.

The *tubules* show the usual varied picture, such as is seen in malignant nephrosclerosis. Unlike the former case, however, many of the proximal convoluted tubules are still moderately well preserved, showing the characteristic type of epithelium. They are moderately hypertrophied and in places show regressive changes leading at times even to necrosis. Most of the tubules are changed. They are small, atrophic, collapsed and bordered with small cuboidal, undifferentiated epithelial cells often containing in the lumina small hyaline casts. Here and there and usually occurring in islands are nests of tubules showing dilatation; such tubules are bordered with elongated endothelial-like cells showing frequent mitoses, and frequently contain remnants of necrotic desquamated cells, precipitated albumin and polymorphonuclear leukocytes. Stains for bacteria are negative. The necrotic cells are incrustated with salts often rich in iron and in places surrounded by large multinucleated foreign body giant cells. It is interesting that even in this group of reformed tubules hyaline droplet degeneration is already present in the cells. In the medulla where casts incrustated with iron have remained fixed the surrounding epithelium has totally disappeared, leaving this foreign body surrounded by connective tissue.

The *veins* throughout the kidney and the *intertubular capillaries* are unusually dilated and one sees very well the very close relation that the intertubular capillaries bear to the tubules, being separated only by a basement membrane, an anatomical relation similar to that of the capillary tufts of the glomerulus. Occasionally one sees petechial hemorrhages into the stroma of both cortex and medulla from these dilated capillaries.

The *basement membrane* of the arterioles is markedly swollen and rich in lipoids but this kidney, like the former, shows no double refractile fat. Along the capillary loops of the glomerular tufts the basement membrane seems loose, lax, and increased and fibrillated, but not swollen like that of the arterioles. The basement

membrane forming the capsule in places is rather coarse but quite uniform and shows no papillary bulging. Along the tubules, and especially those that are collapsed, it is swollen and irregular, and here and there fluid-like material slightly fibrillar has collected between the collapsed epithelium and the basement membrane.

The *interstitial tissue* is unevenly increased and shows foci of lymphocytes, especially in areas of tubular atrophy and disappearance. In the medulla the stroma is diffusely increased, yet there is practically no total disappearance of tubules.

To summarize these histological changes, we find a moderately damaged kidney with changes involving the blood vessels, glomeruli, tubules and stroma. The lesions for the most part are chronic and fairly advanced. From the character and extent of the histological lesion alone there is no basis for one to believe that either through the vascular, glomerular, or tubular changes this patient should suffer from severe renal insufficiency. The lesions, being largely of a chronic nature, warrant the diagnosis of a slowly progressive type of malignant nephrosclerosis. This is substantiated by the finding of similar, if not more severe, lesions of the same character in many of the other organs of the body.

Discussion

A study of the etiology of malignant nephrosclerosis has, since the work of Volhard and Fahr, occupied the attention of many investigators. A recent paper by Schürmann and MacMahon [7] reviews the work that has already been done up to the present time. Without question it would appear that the anterior lobe of the pituitary, and especially the secretion of the basophilic cells, may, in some cases, play a very important rôle in the etiology of this important cardiovascular renal syndrome. Most cases of malignant nephrosclerosis, however, are not characterized by such signs of pituitary basophilism as adiposity, disturbances in secondary sexual characteristics and osteoporosis.

For years clinicians and pathologists considered the bony changes of osteitis fibrosa deformans and osteodystrophia fibrosa cystica as being one and the same fundamental disease. Only with the discovery of the important rôle played by the parathyroid in cystic disease of bone were the clinical and histological differences in these two diseases accepted as definite and distinct entities. Now the

question may be asked — can we distinguish a particular group of cases of malignant nephrosclerosis clinically or histologically which specifically belong to the syndrome of basophil tumors of the anterior lobe of the pituitary? From a study of fifty cases of malignant nephrosclerosis one finds variations in the clinical and pathological picture, but clinically these cases of malignant nephrosclerosis associated with typical signs of pituitary basophilism, as described by Cushing, belong to a very definite and distinct group. Comparing the vascular changes in these two cases of basophilic adenoma of the anterior lobe of the pituitary with the vascular changes in many other cases of malignant nephrosclerosis which did not show pituitary basophilism, we could find no single change or group of changes that would permit us to distinguish one case specifically from another.

SUMMARY

Two cases of basophilic adenoma of the anterior lobe of the pituitary, one reported by Bishop and Close and the other by Cushing, have been discussed again from a cardiovascular renal standpoint in which it is shown that the cardiovascular renal lesion present in these two cases corresponds to the picture originally described as malignant nephrosclerosis by Fahr.

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