RENAL HYPERPARATHYROIDISM ASSOCIATED WITH CUSHING'S SYNDROME *

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The case here reported presents, as the title indicates, a puzzling combination of symptoms which bring up for discussion the complex and still obscure interrelations of kidney, parathyroids and pituitary. So far as can be learned from a rather thorough scrutiny of the literature, no very similar case has been described.

REPORT OF CASE

C. J. M., a 33-year old white, intelligent and very active Puerto Rican merchant, was first seen by one of us (J. A. P.) at the University Hospital of the School of Tropical Medicine on May 25, 1936. He related that in March, 1927, while in Halifax, N. S., he had had an attack of gout and had been found to have had a small amount of albumen in the urine, which also contained a few granular and hyalo-granular casts; blood chemical examination at the time showed urea nitrogen 29.9 mg., uric acid 4.2 mg. and creatinine 2.0 mg. per 100 cc. After recovering from this illness he returned to Puerto Rico and a few weeks later was taken suddenly ill with chills and high fever; albumen in small amounts was again found in the urine; at the end of 15 days, during which time he continued to have fever and became extremely weak, *P. malariae* was found in the blood and under specific (quinine) treatment he recovered very promptly and completely. The blood pressure was not taken during this illness but was found to be "high" a few weeks later. The patient was then 24 years old. Mild albuminuria had been almost constant since then.

Up to the time of his marriage in 1931 he had taken very little care of himself. Since 1932 urine and blood examinations yielded results as follows:

* Received for publication, May 2, 1937.

January 5, 1932: *Urine*—albumen + +, glucose negative, some pus cells, many small hyaline casts.

March 20, 1932: Red blood cells 4.68 millions per cmm.
Hemoglobin 80 per cent (Dare).

July 13, 1932: *Urine*—specific gravity 1.008, albumen + +, glucose negative, some mucus and pus, some vesical epithelium.

Blood Wassermann reaction negative.

Blood Chemical examination:

Glucose 140.0 mg. per 100 cc. blood.
Urea nitrogen 20.44 mg. per 100 cc. blood.
Uric acid 5.0 mg. per 100 cc. blood.

December 4, 1932: *Urine*—Albumen + +, glucose negative, many granular casts.

Blood Chemical examination:

Urea nitrogen 22.5 mg. per 100 cc. blood.
Creatinine 2.142 mg. per 100 cc. blood

Since early in 1934 the patient often had nausea on awakening in the morning, and was forced to wash his stomach by drinking water and vomiting several times before he could eat breakfast; he at times also vomited his first breakfast. In October or November 1935 his systolic blood pressure was found to be 230 mm. of mercury. Shortly before he had noticed that he would tire much more easily than previously and that his capacity for physical exertion was gradually and rapidly decreasing; he would become short of breath and be troubled with palpitations. He became alarmed in February, 1936, when he had nausea and vomiting every morning and noted that he was getting pale and of a dusky color.

On March 2, 1936, laboratory examinations yielded the following results:

Hematology—Erythrocytes, 2.69 millions per cmm.
Hemoglobin, 62 per cent (Wintrobe).
Leukocytes, 3,600 per cmm.

Polynuclear neutrophiles	55.0 per cent.
Lymphocytes	40.5 per cent.
Mononuclears	3.5 per cent.
Eosinophiles	1.0 per cent.

Blood Chemical examination:

Non-protein nitrogen	134.0 mg. per 100 cc. of blood.
Urea nitrogen	62.8 mg. per 100 cc. of blood.
Creatinine	3.0 mg. per 100 cc. of blood.
Glucose	142.1 mg. per 100 cc. of blood.
Uric acid	5.7 mg. per 100 cc. of blood.

Blood Kahn test negative.

On April 7, 1936, results of laboratory examinations were as follows:

Hematology—Erythrocytes, 2.52 millions per cmm.
Hemoglobin, 62 per cent (Wintrobe).
Leukocytes, 3,160 per cmm.

Blood Chemical analysis:

Non-protein nitrogen	200.0	mg. per 100 cc. of blood.
Urea nitrogen	91.5	mg. per 100 cc. of blood.
Creatinine	5.0	mg. per 100 cc. of blood.
Glucose	105.0	mg. per 100 cc. of blood.
Uric acid	4.7	mg. per 100 cc. of blood.

Urinalysis—albumen 0.5 per cent; specific gravity 1.010.

Towards the middle of April the patient entered a private hospital and all laboratory examinations were repeated with almost identical results. Lysis of erythrocytes was found to begin at a concentration of 0.42 per cent sodium chloride and to be complete at a concentration of 0.34 per cent. The basal metabolic rate was minus 22 per cent.

Under a very restricted diet during April and May the non-protein nitrogen in the blood went down (May 22) to 100.0 mg. per hundred cubic centimeters, the urea nitrogen down to 38.69 mg., the creatinine up to 9.5 mg. and the uric acid up to 8.696 mg. He became extremely weak and had vertigo, diplopia, much vomiting, diarrhea. In this condition of great asthenia he came to us and was immediately hospitalized.

Physical findings of the cardio-circulatory-renal systems consisted only of an ashen, dusky, plethoric pallor of the skin, pallor of mucous membranes, a heart moderately enlarged to the left with no murmur or arrhythmia, no evidences of congestive failure, blood pressure of 132 systolic and 92 diastolic, no evidence of marked sclerosis of the larger peripheral vessels, remarkably slight changes of the finer retinal vessels.

The laboratory data obtained were similar to those of May 22 and added no information of any great value.

It became immediately evident that the patient had very serious renal disease which was either of the nature of a chronic glomerular nephritis or an arteriolar nephrosclerosis secondary to arteriolar disease. The sequence of events and the behavior of the case through the nine years of its history seemed to make it much more likely that he had an arteriolar

nephrosclerosis. That diagnosis was made for the cardio-vascular-renal aspects of the picture; obviously he was, at the time, in the end stage of the disease. Death from uremia, or from vascular accident of any kind, seemed imminent.

But the make-up of the patient suggested to us that he might also have some endocrine disturbance and we directed our attention to this aspect of the case. He was definitely obese, with flabby undeveloped musculature, weighing 184 pounds with a height of 68 inches; the adiposity was confined to the face, neck and trunk; the extremities were completely spared. He was round-shouldered and somewhat kyphotic. On the abdominal wall and on the upper third of both thighs there were purplish *lineae atrophicae;* the eyes were somewhat prominent as if from slight exophthalmos, said to be a family characteristic. The hair distribution was normal.

The history of his obesity was as follows: in 1921, when 18 years of age, he went to the United States to study, weighing 110 pounds; when he returned 10 months later he weighed 135 pounds. At the latter weight he remained for 3 years. In 1923 he began to travel between Puerto Rico and Halifax, N. S., spending his summers (May to September) in Puerto Rico and winters (September to May) in Halifax.* In 1925 he suddenly began to gain weight and one year later weighed 180 pounds, some time later 230 pounds. From the beginning fat collected on his face, neck and trunk, the legs and arms remaining as they were when he weighed only 135 pounds. He was weighing 230 pounds when, in Halifax, he had his first attack of gout (there were 3 or 4 more such attacks during the following 9 years). Since 1925, when he began to gain weight, he had had tremendous polyphagia and polydypsia; there was also a corresponding polyuria. He was not impotent.

Course.—It was thought that the history of rapidly acquired adiposity limited to the face, neck and trunk; the round-shouldered and kyphotic attitude; the *lineae atrophicae* on abdomen and thighs; the plethoric dusky pallor; the vascular hypertension, nitrogen retention, indefinite back aches, polyphagia, polydypsia, polyuria, albuminuria, etc.,

* This circumstance, summers in the tropics and winters in almost Arctic temperature, was thought to have been a possible factor in bringing about severer arteriolar changes than those found in the majority of the reported cases of Cushing's Syndrome, assuming in the patient an abnormal vasomotor response to stimuli (cold and heat).

all fitted quite well in the picture of "Cushing's Syndrome" with a basophil adenoma of the adenohypophysis (pituitary basophilism) and this diagnosis was made. It offered, in spite of the obviously advanced vascular renal changes, gratifying hope of some improvement from roentgen therapy of the hypophysis.

X-ray examination of the skull (fig. 1) showed no abnormality of the sella turcica; the calvarium was very granular from marked osteoporosis; the thoracic vertebrae showed no abnormality.

We set out to improve the general condition of the patient by allowing a salt-free diet of 2,000 calories with 40 grams of protein and 65 percent of the total caloric intake in carbohydrates; absolute rest in bed was insisted upon, ferrous sulphate was given by mouth. Water was allowed *ad libitum.* After a few days (because of patient's appetite and extreme weakness) the diet was increased to 2,800 calories, the protein allowance left at 40 grams. His general condition improved and he gained strength. The systolic blood pressure went up to 145 mm. of mercury, the diastolic remaining at 90 mm. Roentgen therapy of the hypophysis was advised and in June, 1936, he left for the United States in the hope of finding improvement from that treatment.

During a brief sojourn at the Mayo Clinic, Rochester, Minn., where it was concluded he had "a chronic renal lesion", he was given one blood transfusion, ferric ammonium citrate, a diet of 1,500 calories with 40 grams of protein, luminal, plenty of fluids. By October 8, 1936, he had lost weight to 160 pounds; with the loss of this much weight he had lost strength to a state of severe asthenia; his blood pressure was then 185 mm. systolic, 110 mm. diastolic. Erythrocytes in the blood were 2.0 million per cubic millimeter, hemoglobin was 38 per cent. Blood transfusions (citrated) of 400, 480 and 500 cubic centimeters were given on October the 8th, 11th, and 15th, respectively, without untoward reactions and with but very fleeting subjective improvement, little if any hematologic betterment. On October 15, blood chemical analysis showed urea nitrogen of 99.0 mg., uric acid 6.6 mg., creatinine 6.0 mg. per 100 cc.

On October 17 he was readmitted in a condition of great restlessness, with distressing sense of suffocation, inability to swallow, non-productive cough, sleeplessness; he seemed

considerably worse. Cardiac action was very forcible at a rate of 80 beats per minute, regular; there was some congestion of both pulmonary bases; breath was somewhat uriniferous; the blood pressure was 180 systolic, 118 diastolic. Under small doses of digitalis, sedatives, rest, the pulmonary congestion disappeared, also the restlessness; the sense of suffocation and difficulty in swallowing persisted for 2 weeks and then gradually subsided. In spite of a satisfactory intake of food he was physically exhausted, small ecchymotic patches appeared here and there, especially on the abdominal wall. His body-aches became intense and he could not lie comfortably in bed. At a later date he had a small hydrarthrosis, with intense pain, of one ankle and the opposite knee. Severe tremors of hands made it impossible for him to feed himself; jerky involuntary movements of the extremities and the head made his waking hours more miserable and wakened him from sleep; there was acrocyanosis. We never thought there was "clinical" uremia at any time.

On October 27, 28, 29, 30, November 2, 6, 7, 11, 12, 13, the patient received roentgen therapy to the hypophysis through two portals (temporal) of 10 cm. square alternatingly, the central ray aimed at the pituitary fossa. The factors were 200 kilovolts, 4 milliamperes, 50 cm. focal skin distance, a filter of 0.5 mm. of copper plus 1 mm. of aluminum, 10 minutes. At 20 roentgen units per minute (15.16 in air), the patient received 200 roentgens per session and 1,000 roentgens per field or a total of 2,000 roentgens.

The analysis made by Freyberg, Barker, Newburgh and Collier * of the cases of pituitary basophilism in which roentgen therapy had been employed seems to indicate that these doses of roentgen rays may not have been sufficient, but the patient was very hopeful and thought he was improving; we also thought so, even if the improvement was only subjective; his spirits, at least, improved a great deal. On November 13 he complained of certain discomfort and anxiousness which he could not describe; later in the day he complained that he was impotent and had been for 2 weeks. Shortly before six the following morning he was found dead in bed; he had apparently been dead only a few minutes.

* Archives of Internal Medicine. 58: 187–212, Aug., 1936.

Necropsy was performed in accordance with the patient's own wishes.

Clinical diagnosis: Pituitary basophilism; essential hypertension; advanced renal nephrosclerosis; myocardial failure.

Autopsy

(*Autopsy No. 911.* Nov. 14, 1936. 4½ hours after death. Dr. E. Koppisch.)

Gross Description:

The body is that of a well developed white young man measuring 173 cm. in length. The face, trunk and abdomen are quite adipose, in contrast to the extremities, which are thin. The skin throughout the body is pale and, particularly in the face, distinctly tanned. Throughout the back is a skin eruption consisting of very minute papules and shallow ulcers not more than 2 or 3 mm. in diameter. There are no external bony abnormalities. The scalp hair is abundant, black and straight. There are no abnormalities in the distribution and amount of hair in the various hairy regions. The eyeballs are slightly prominent. The conjunctival and other visible mucous membranes are pale. The neck is rather short and thick. The chest is capacious, with a broad antero-posterior diameter and an obtuse costal angle. There is a slightly bluish area on the left side anteriorly, resembling a bruise. The abdomen is not very protuberant, but seems quite full. There are longitudinally placed, white striae at the flanks and lateral aspect of the upper third of the thighs. The penis presents no scars and is rather small for the size of the body. The extremities are not remarkable, save for being thin as compared with the trunk and face.

The subcutaneous abdominal fat measures 3.5 cm. in thickness, just above the umbilicus, and in the thorax measures 1.5 cm. over the center of the sternum. The musculature is pale pink, flabby and not very well developed. The connective tissue planes are somewhat edematous.

Peritoneal cavity: Contains approximately 200 cc. of clear, straw-colored fluid. The peritoneal surfaces are normal. The inferior edge of the liver extends 8 cm. below the xiphoid and 4 cm. below the costal margin in the right midclavicular line. The spleen is enlarged but does not present anteriorly. The various organs are normally disposed. The preperi-

toneal, mesenteric, perirenal and retroperitoneal fat is very abundant.

Thoracic cavity: No adhesions are found in either pleural cavity. On the left side is approximately 150 cc. of straw-colored, thin fluid, and some 200 cc. on the right. The pericardial sac contains a normal amount of unaltered fluid, but there are delicate organized fibrous bands to the antero-lateral surface of the heart near the apex. Thymic tissue can not be identified, there being abundant fat in its place.

Cranial cavity: The skull bones are rather thick but can be sawed through with great ease. However, nothing abnormal is seen upon examination of the line of cut and the surfaces. The dura mater and sinuses are normal. The middle ear and mastoid air cells are not diseased.

Heart: Weighs 625 gm. It is very distinctly enlarged. The anterior aspect of the wall of the left ventricle, including the apex, is very firm and distinctly lobulated. Dense organized bands of adhesions fix the parietal pericardium to this region. The remainder of the epicardial surface is quite smooth and glistening. The subepicardial fat is pale and abundant. The coronary arteries are somewhat tortuous. There is slight dilatation of the conus portion of the right ventricle, but the chamber as a whole is not particularly enlarged. The left atrium is distinctly larger than the right. The endocardium is whitish and diffusely thickened. The mitral valve is delicate and competent and the chordae tendineae not thickened. The cavity of the left ventricle is somewhat larger than normal and the trabeculae carneae and papillary muscles are distinctly hyperthrophied. The apex is rounded and at the very apex a dense plate of calcium measuring some 3 cm. in transverse diameter, and in places 0.5 cm. in thickness, has replaced the endocardium and most of the myocardium. What remains of the myocardium at the apex is distinctly fibrosed and the trabeculae carneae adjoining this area are covered by thick white endocardium. There are slight atheromatous deposits on the ventricular aspect of the aortic leaflet of the mitral valve. The anterior and right posterior aortic valve segments are adherent at the commissures and present in the area of adhesion a dense calcified mass 0.7 cm. in greatest diameter that projects from both sides of the affected valves. The sinuses of Valsalva are

deeper than normal. The coronary arteries are normally distributed and present numerous atheromatous and calcareous deposits which make the walls very rigid in places. The lumen of one of the branches of the anterior descending is pin-point due to eccentric thickening of the wall of the vessel, but complete obstruction is not found at any point. The myocardium is pale pink, firm and distinctly hypertrophied, especially in the wall of the left ventricle where several small areas of fibrosis are found in a tangential cut.
Measurements: T 12.5, P 6.3, A 6, M 9.8, LV 2, RV 0.6 cm.

Aorta: Yellow atheromatous deposits project from the beginning of the ascending aorta. Beginning at the arch there are very numerous greyish moderately elevated plaques, yellowish atheromatous deposits, and dense plaques of calcification with some superficial ulceration. The changes are most advanced in the abdominal portion. The elasticity of the organ is very markedly impaired.

Lungs: The right one weighs 545 and the left 520 gm. The parenchyma is crepitant and air-containing and on section is pinkish and exudes a small amount of frothy fluid on pressure. The larger blood vessels present only an occasional very small atheromatous deposit.

Spleen: Weighs 360 gm. and measures $14.5 \times 9.5 \times 5.6$ cm. The capsule is tense, smooth and glistening and the pulp shows purple through it. On section the pulp is firm and deep red with easily visible not enlarged corpuscles, and trabeculae of normal thickness.

Liver: Weighs 2,670 gm. and measures $30 \times 22 \times 8.5$ cm. The inferior margin is slightly rounded. The surface is smooth. On section the lobulations are easily visible and occasionally the central portion appears intensely congested. Most of the cut surface is pinkish brown and cloudy.

Gall bladder: The wall is thickened in places to 0.6 cm. and there is distinct edema of the outer fibrofatty layer. The mucosa, however, is velvety and there are no calculi. The extrahepatic bile ducts are free.

Suprarenal glands: Together weigh 20 gm. and seem normal in size. The cortex is pale yellow. The intermediate zone is broad and rounded. The medulla is normal.

Kidneys: The right one weighs 115 gm. and measures $10 \times 4.2 \times 2.8 \times 3.7$ cm. and the left weighs 105 gm. and measures $9.5 \times 4.5 \times 3.6 \times 4$ cm. They resemble each other. The capsule strips off easily. The organs are contracted, with a pale distinctly granular surface; between the granulations the blood vessels tend to be congested. On section the normal markings have to a great extent been obliterated and the separation between cortex and medulla is extremely blurred. The cut surface is very pale, the striations indistinct, and the glomeruli invisible. Many of the blood vessels stand out prominently because of their thickened walls and pin-point lumina. Many cysts are found throughout the cortex and medulla and vary in diameter from 1 or 2 mm. to 1.7 cm. The pelves and ureters are normal.

Pelvic organs: Normal.

Testes: Normal.

Gastro-intestinal tract: Esophagus, stomach, small intestine and colon: Normal. Appendix: The lumen is not obliterated but there is distinct constriction at a point some 2 cm. from the tip.

Neck organs: Larynx, trachea: Normal. Thyroid gland: Weighs 15.35 gm. The organ is not enlarged and on section presents no abnormalities.

Parathyroid glands: Four glands are removed. They are all very distinctly enlarged as follows:

Right upper, weighs 0.67 gm. and measures $1.7 \times 1 \times 0.8$ cm.
Right lower, weighs 1.02 gm. and measures $1.85 \times 1.5 \times 0.9$ cm.
Left upper, weighs 0.82 gm. and measures $2.5 \times 1 \times 0.6$ cm.
Left lower, weighs 0.97 gm. and measures $1.7 \times 1.4 \times 0.75$ cm.

They are of pale yellowish-brown color externally and on section reveal indefinite lobulations.

Pancreas: Normal.

Blood vessels: The splenic artery is extremely tortuous as it courses along the pancreas and feels very dense. It shows diffuse advanced calcification of its wall and frequent atheromatous deposits in its intima. The renal, superior and inferior mesenteric, iliac and hepatic arteries also show advanced arteriosclerotic changes but are only slightly tortuous.

Hypophysis: Measures: $1.6 \times 1 \times 0.7$ cm. It seems normal in size but is rather soft and in the region of the infun-

dibulum presents a slightly rounded depression. The gland is fixed in Müller's fluid.

Brain: Weighs 1,480 gm. (prior to fixation). The leptomeninges are delicate and normal. The convolutions seem slightly broadened and flattened, especially in the parietal lobes. The blood vessels at the base are slightly thickened and rigid. Multiple transections through brain and cerebellum reveal an entirely normal structure.

Parasitology report: Feces: Negative.

MICROSCOPIC DESCRIPTION:

Heart: A. The muscle fibers are uniformly hypertrophied, and the nuclei correspondingly enlarged, irregular and hyperchromatic. There is very little pigment. There is slight diffuse increase in stroma, but no large areas of fibrosis. The smaller coronary arteries are normal. No calcium is found.

B. The section includes epicardium and an incomplete segment of a large coronary artery, which shows a massive plaque of calcium underlying a fibrous thickening of the intima (fig. 2).

C. Apex of left ventricle: The endocardium over a large area is replaced by a deeply blue staining, calcified band which is surmounted over part of its extent by a thin layer of fibrous tissue. The plaque shows indications of a fibrillar structure which has become encrusted. The underlying tissue is very edematous, and contains abundant fibrin and poorly preserved fibroblasts and wandering cells (fig. 3).

Aorta: The intima is much thickened and densely fibrosed, with little lipoid deposit. A few vascular clefts are present. At one end of the section is a dense plaque of calcium. Media is normal; the adventitia shows fresh hemorrhage, possibly an artefact.

Superior mesenteric artery: There is extreme medial calcification of the Mönckeberg type. The calcified segments are interrupted by normal medial tissue (fig. 4).

Lung: The most interesting feature is the presence of numerous irregular calcified masses. They are surrounded by loose aggregations of histiocytes or young fibroblasts, and seem to be in what was originally the cavity of the alveolus or terminal bronchiole. Their shape and situation suggest

that they are derived from irregular masses of fibrin or protein coagulum which has become impregnated with calcium (fig. 5). In addition to these large solid clumps, there is occasionally seen a calcification of the basement membrane of the *ductuli alveolares*. In one duct there is an organizing blood clot and a few of the alveoli contain extravasated red cells.

Spleen: The follicles are large, irregular, without distinct germinal centers. The sinusoidal outlines are indistinct, the pulp congested with red cells, at the expense of the nucleated elements. Hemosiderin-laden phagocytes are numerous, both in the pulp, and about the arterioles.

Pancreas: Shows autolysis in the deeper portion of the block. Superficially, islands and acini are normal. There is no arteriolar sclerosis. Three hyalinized islands are found (fig. 6).

Liver: There is a striking loss of liver cells in the central portion of each lobule, with thickening and condensation of the stroma—the picture of a fairly advanced cardiac cirrhosis. But in these areas are individual isolated cells, about the size of a liver cell, whose cytoplasm is filled with granular blue staining clumps, presumably of calcium (fig. 7). A few leucocytes or mononuclears may surround the calcified cells. What remains of nucleus is often fragmented and pycnotic. Better preserved liver cells often show a bluish clouding of the cytoplasm which may be the earlier stage of calcification. In addition there are many vacuoles containing spherical eosinophilic inclusions, but no filaments. Occasional Kupffer cells are filled with black pigment, probably malarial.

Gall bladder: The epithelium is exfoliated, and stains poorly. There is extreme subserous edema.

Suprarenal: The periadrenal fat is edematous. An occasional arteriole is hyalinized—most of them are unaltered (fig. 8). The cortex is broad and appears rich in lipoids. The medulla has lost the chromaffinity, but is otherwise normal. There is rather marked congestion of all the capillaries.

Kidney: The picture is that of an advanced chronic nephritis in which all the elements of the kidney are involved (fig. 9). A large proportion of the glomeruli are completely or partially transformed into hyalin, but there remain some

relatively normal ones of large size, showing only an increased cellularity, a slight thickening of the capillary membrane, and of the capsule. These contain little blood, even the best of them. There are occasional adhesions, but no crescents, and nothing to suggest a previous glomerulitis. The tubules are highly atypical—lined with low undifferentiated epithelium resting upon greatly thickened basement membranes. They are tortuous and often cystically distended. The stroma is everywhere in great excess, and contains irregular collections of lymphocytes and a few plasma cells. The large arteries are not abnormal, but the arterioles are for the most part hyalinized and stenotic, to a degree sufficient to explain the glomerular atrophy. A small portion of pelvis is lined with normal epithelium. Occasional small deposits of calcium are found (1) in the glomeruli, (2) beneath the endothelium of small arteries and (3) in the tubules. The amount of stainable calcium is however, surprisingly small.

Prostate: Normal.

Testis: Spermatogenesis is lost, the tubules containing no ripe spermatozoa. The basement membranes are thicker than normal, Leydig cells are fairly abundant.

Stomach: A beautiful picture of "metastatic" calcification in the mucosa. The calcium is concentrated in the middle third of the mucosa, where it incrusts the basement membrane of the tubules, or forms spherical globules of uniform size amongst the degenerating gastric epithelial cells. One has not the impression that these globules are formed within the cytoplasm; but rather precipitated upon their surface. The acid cells are often strikingly free from deposit (fig. 10).

Small and large intestines: Essentially normal, aside from postmortem loss of epithelium.

Thyroid: No changes of interest. Vesicles lined with flat epithelium and filled with dense colloid. No suggestion of "stimulation". The stroma is rather dense.

Parathyroids: Four glands have been sectioned. They all are of extreme size, and of compact and rather uniform solid glandular structure (fig. 11). The septa are delicate and there is no interstitial adipose tissue. The predominant cell type in all the glands is the chief cell which shows only

a slight tendency to differentiate into the clear cell type—such as is found in most cases of chronic nephritis. The nuclei are uniform, not obviously enlarged, and no mitoses are found. Oxyphile cells occur in large and small islands. One gland contains a rather large nodule which might almost be dignified as an adenoma. The glands show in many places a change in the character of the epithelium to a high columnar type, with formation of definite lumina or irregular cyst-like spaces. The spaces contain shreddy material and a few well preserved blood cells.

Lymph gland: The sinuses contain fibrinopurulent exudate, the gland evidently draining some infected focus. Hemosiderin is abundant in the pulp cords.

Hypophysis: Sections were cut at various levels, and stained with Mallory's aniline-blue-fuchsin, following the modifications of Crookes *(J. Path. and Bact. 1936, XLI, 339).* Only one half of gland was cut, the remaining portion having been mislaid. No adenomatous masses are found in the anterior lobe. The predominant cell is the eosinophile, and so far as can be determined without cell counts, the basophiles are reduced in number, rather than proportionally increased. Those present are concentrated largely near the ventral surface of the gland. The preparations are not very satisfactory for cytological detail. Hyalinization of the cytoplasm of the basophiles with degranulation, described by Crookes and Rasmussen, and regarded as a specific change in cases showing Cushing's Syndrome, cannot be demonstrated: The cells contain distinct granules. There are several small colloid cysts in the pars intermedia and a moderate invasion of the posterior lobe with basophile cells. These stain slightly more purplish than do the basophiles of the anterior lobe, and do not show distinct granulation. Their cytoplasm is filled with small vacuoles.

Bones: Calvarium: A cross section, about 8 mm. in thickness, shows the following alterations: The distinction between diploë and inner and outer tables is lost. The marrow is completely fibrous and devoid of hematopoietic elements. The trabeculae are very irregular and show punched-out defects in their surface, usually associated with the presence of numerous osteoclasts. About some of the trabeculae, are

rows of large vertically disposed osteoblasts, suggesting new appositional bone formation. In some trabeculae, the cement lines are conspicuous, giving a mosaic structure to the bone. The picture is that of a severe osteitis fibrosa (fig. 12).

Vertebrae: The changes are of the same character, but very much less intense. The trabeculae are eroded here and there by plugs of loose fibrous tissue, in which are a few osteoclasts (fig. 13). This lacunar absorption is sharply localized, most of the trabeculae having a normal appearance. There is no diffuse marrow fibrosis; and the marrow elements are present in normal proportions.

Rib: There are a few small areas of lacunar absorption, but the change is less striking than in the vertebrae.

Brain: Blocks from cortex, basal ganglia, cerebellum and medulla show no significant changes.

Anatomical Diagnosis: CUSHING'S PITUITARY SYNDROME, (clinical); adiposity of trunk and face; pigmentation of skin; essential hypertension (clinical); arteriolar nephrosclerosis, advanced; chronic passive congestion of liver; hypertrophy of parathyroid glands; osteitis fibrosa of skull, ribs and vertebrae; calcium deposits in lungs, liver, kidneys and stomach; generalized arteriosclerosis, advanced; coronary sclerosis; infarct of heart at apex, obsolete, with calcification; thrombosis of heart, left ventricle; fibrous pericardial adhesions; cardiac hypertrophy; ascites, slight; hydrothorax, bilateral; hyalinization of islands of Langerhans; cytoplasmic inclusions of liver cells; malarial pigmentation of liver; basophilic invasion of posterior lobe of pituitary.

DISCUSSION

Leaving aside the "pituitary" features—obesity with striae distensae and hyperglycemia, the case fits into a group which we may term provisionally "renal hyperparathyroidism". The evidence is accumulating that long-standing renal disease is accompanied regularly by enlargement of the parathyroids, and by increased functional activity of these glands. Bergstrand [1], Wilens and Pappenheimer [2] and Gilmour and Martin [3] have demonstrated that the weights of the parathyroids in a variety of chronic renal disorders,

exceeds the normal *. Experimental renal insufficiency produced in rats, is followed by pronounced enlargement of the parathyroids (Jarrett, Peters and Pappenheimer [4], Pappenheimer [5]). Recently, Highman and Hamilton [6] have demonstrated an increase in circulating parathormone in cases of chronic nephritis with uremia.

In certain cases, the parathyroid hyperplasia may be present to an unusual degree and lead to severe osteo-fibrotic lesions with calcium deposition in various tissues. We have summarized from the literature and the records of the Presbyterian Hospital a group of such cases (table I). The list is doubtless incomplete, and other cases regarded as primary hyperparathyroidism with diffuse or adenomatous enlargement of all or several parathyroid glands, might be included, (Albright, Bloomberg, Castleman and Churchill [7]). It has been suggested by Albright [8] that these cases are analogous to those which, occurring in childhood, are designated as renal rickets, the bone lesions being modified by the age of the patients. Indeed, such cases as that reported by Schelling and Remsen [9] in a boy of 17, are transitional between renal rickets and osteitis fibrosa of adults.

The question as to what constitutes "primary" or "secondary" hyperparathyroidism is obscured by the fact that long-continued hyperactivity of the parathyroids undoubtedly produces injury to the kidneys (Albright, Baird, Cope and Bloomberg [10]). This has been shown experimentally by Chown [11], who with repeated injections of parathormone, has produced in rats severe chronic nephritis. Whether this results from the precipitation of the calcium in the renal tissues, or is due to some other toxic effect of the parathormone upon the kidney remains to be determined. In any event, a vicious cycle is set up. The chronic nephritis induces hyperparathyroidism, and this in turn causes further damage to the kidney.

The exact chemical stimulus which provokes the parathyroid hyperplasia is not known to us. It has been suggested by Schelling and others [9], that the parathyroid functions ex-

* Unpublished data obtained since the publication of the paper of Pappenheimer and Wilens substantiate the earlier conclusions. The calculated average combined weight of the parathyroids in a series of 35 miscellaneous non-nephritic controls was 139 mgs.; in 44 cases of diffuse renal disease of various types, the combined parathyroid weight averaged 359 mgs.

CASES OF RENAL HYPERPARATHYROIDISM IN ADULTS

No.	Authors & References	Age	Sex	Duration of Renal Symptoms	Renal Lesions	Parathyroids	Bones	Metastatic Calcification	Remarks
1.	McCallum, W. G. & Bull, J., Bull. J. H. Hosp., 1905, XVI, 87.	26	M	Several years	Advanced chronic diffuse nephritis (histologic picture not given)	Right Lemmer adenoma–2cm. in diam.–2 other glands normal (no wts. or measurements)	Subsequent examinations showed osteitis fibrosa	Not recorded	
2.	Hubbard, R. S .& Wentworth, J. A., Proc. Soc. Exp. Biol. & Med., 1920–21, XVIII, 307	20	M	20 years	Interstitial nephritis with right hydronephrosis	2 large parathyroids, 2 cm. in diam. Micr. hyperplasia & small adenoma in 1	Osteitis fibrosa of skull, ribs & vertebrae	Peripheral arteries; large, irreg. Ca deposits about joints and in wall of auricle	Blood Ca 13.4; renal insufficiency; acidosis
3.	Barr, D. & Bulger, H., Am. J. Med. Sc., 1930, 179, 449, Case III	46	F	?	Cortex thin, many scarred areas, infiltrated with lymphocytes. Many tubules filled with hyaline casts. Ca deposits	3, the largest 1.1 x 0.5 cm. Micr. cells swollen and vacuolated	X-ray mottling of bones	Lungs, gastric mucosa & kidneys	Blood Ca 16.0; PO_4 37.0; renal insufficiency
4.	Gutman, A. B., Swenson, P. C., Parsons, W. B. Case IV, J. A. M. A., 1934, *103*, 87	60	F	+ 23 years	Polycystic kidneys		Osteitis fibrosa with cysts & spontaneous fractures	Ca in thyroid & kidneys	Blood Ca 9.7
5.	Schelling, D. H. & Remsem, D., Bull. J. H. Hosp., 1935, LVII, 157	17	M	Since early childhood	Extreme hydronephrotic atrophy	Marked diffuse hyperplasia (measurements given) with superimposed ac. inflammatory change	Osteitis fibrosa of calvarium, ribs & vertebrae	Calcification of arteries	Blood Ca–9.6 PO_4 8.9
6.	Castleman, B.&Mallory, T. B. (Case 23A 7119), Am. J. Path., 1935, XI, 1	25	F	Polyuria & polydypsia all her life	Chronic pyelonephritis	3 glands showed marked diffuse enlargement without adenomata (meas.)	Osteitis fibrosa with cysts	Calcification of arteries & subcut. tissue	"Diagnosis of renal rickets could not be ruled out"; Ca 8 mg. PO_4– 9 mg.

cessively to overcome the barrier to phosphate excretion offered by the damaged kidney. Assuming that the retained phosphate acts as a stimulus, Drake, Albright and Castleman [12] have recently reported the production of parathyroid hyperplasia in rabbits by injection of buffered phosphate solution over varying periods. The mean parathyroid weight in their injected animals was 20 mg. as compared with 13 mg. in the controls, and, microscopically, the glands exhibited a more compact structure.

Admitting that the excessive secretion of the parathyroids is deleterious to the kidneys, it is still clear that in many instances, the cycle is initiated by long-standing disease of the kidneys themselves. How otherwise can one explain the variety of kidney lesions which have been found in these cases? Chronic glomerulo-nephritis, arteriolar-sclerosis, hydronephrotic atrophy, chronic pyelo-nephritis, and even congenital cystic disease may all lead to parathyroid enlargement with or without osteofibrosis *.

If there are still many obscure points in this renal-parathyroid relationship, the complexity is deepened by the fact that our patient presented all the characteristic clinical features of the Cushing Syndrome. What can be said of a possible pituitary factor in this case? Since the classical paper of Cushing [13] in 1932, cases exhibiting the syndrome which has come to bear his name, have multiplied. The characteristic obesity of face and trunk, the striae distensae, hypertension, hyperglycemia and a decreased sugar tolerance, polyphagia, polydipsia, amenorrhoea or sexual impotence in the male, and a train of subsidiary and less constant symptoms, mark a disease picture that has become familiar to every clinician.

But although the clinical picture has become sharply defined and stabilized, the underlying anatomical changes have been the subject of much uncertainty. Not all the cases have shown basophile adenomata of the anterior pituitary at autopsy. At first it seemed as if the failure to demonstrate this lesion might have been due to the fact that the gland was not cut in series, or that special staining methods to bring out the basophile granulations, were not applied. But

* The entire subject of renal hyperparathyroidism has recently been ably reviewed by Park and Eliot in Brennemann's Practice of Pediatries, 1937, Vol. III, Chapter 29.

several cases have now been reported in which serial sections of the gland have failed to disclose an adenoma of the basophile type (Crooke [14], De Jongh [15]). Furthermore, cases are reported in which an adenoma was found, but in which it proved to be composed of chromophobe cells (Fuller and Russell [16]), of atypical cells in which no basophile granules could be demonstrated (Schmorl [17] and Molineus [17a], Zondek [18], Wieth-Pedersen [19], Bishop and Close [20], Raab [21], Lawrence and Zimmerman [22], Minciotti [23], Teachenor [24], Freyberg *et al.*[25]), or even of eosinophiles (Horneck [26], Konschegg [27]). That all the symptoms of the Cushing Syndrome may be found associated with large cortical adenomata or hyperplasia of the adrenal cortex is now well established.

The occurrence of basophile adenomata of the anterior lobe unaccompanied by symptoms of "pituitary basophilism" has been reported by a number of observers. We may cite in this connection the findings of Sussman [28], who examined 260 hypophyses at the Manchester Royal Infirmary. Eight basophile adenomata, up to 5 mm. in size, were discovered in this series. Costello [29] found 225 adenomata in 1,000 glands, and of these 72 or 27.2 per cent were composed of basophiles, and were not attended by clinical evidence of pituitary dysfunction. While not all adenomata are necessarily capable of functioning, the frequency of their occurrence in cases showing no symptoms should at least make one cautious in assuming a causal relationship.

The paper of Crooke in 1935 seemed to put the pathology of the Cushing Syndrome on a more secure basis. Careful study of the pituitary in 12 cases by a modified Mallory anilin-blue fuchsin stain disclosed cytological changes in the basophiles, which seemed to be pathognomonic, inasmuch as a study of 350 control glands (300 cut serially) showed similar changes in only 9, and these to but a slight degree. The essential lesion described by Crooke is a progressive degranulation of the cytoplasm, with hyalinization, and it was found in every case of Cushing's Syndrome, even in those associated with adenomata of the adrenal. In those cases in which a basophile adenoma was present, the tumor cells did not show this hyaline change.

Crooke's observations have been confirmed by Rasmussen [30] in three further cases, and Severinghaus has found

identical lesions in 4 cases of Cushing's Syndrome, two of which were associated with large adrenal cortical neoplasms (personal communication).

In view of these findings, it was disappointing that our own case showed neither a basophile adenoma, nor hyalinization of the normal basophile elements. On the contrary, the basophiles contained numerous well-stained granules. Although the greater part of the gland was sectioned, we cannot state with certainty that a small adenoma may not have been present.

The rather massive ingrowth of cells into the posterior lobe, forming a fairly compact block of tissue, is of interest in connection with the view advanced by Cushing that such invasion is correlated with hypertension. A number of authors, Shubrizewski [31], Kraus and Traube [32], Berblinger [33] and others, have attempted to correlate an increase in anterior lobe basophiles, and a supposed migration of these cells, with hypertension and chronic nephritis. The recent study of Hawking [34], who made differential cell counts by Rasmussen's method on 12 cases of essential hypertension, and found no significant increase in basophiles, casts doubt on the less accurately controlled observations of Kraus, Berblinger and Cushing. A recent paper of Scribe [35], in which the degree of posterior lobe invasion is recorded in 346 hypophyses, showed no correlation with essential hypertension or chronic nephritis. Spark [36] carefully studied 70 cases of hypertension, and 108 controls with normal blood pressure; he found no significant difference in the degree of posterior lobe invasion in the two groups. This confirms previous similar conclusions of Marcano [37] and others. The weight of evidence at present is against a significant correlation between either basophile increase in the anterior lobe or posterior lobe invasion, and hypertension and renal disease. We are not inclined therefore to stress the finding in our case of basophile cell masses in the *pars nervosa* as a possible factor in the production of the hypertension or other symptoms.

It would carry us too far afield to enter into the still controversial question as to the identity of these posterior lobe cells with the basophiles of the anterior lobe. It is of interest to note, that in our case they could be sharply differentiated in their staining reactions, in that they contained no

blue-staining granules. McCallum, Dutcher, Duff and Ellsworth [38] have recently reported a case of Cushing Syndrome in which they found a small adenoma derived from the pars intermedia, the cells of which could be definitely distinguished by special staining methods from the basophiles of the anterior lobe. They suggest that some of the other so-called basophile adenomata in the recorded cases of Cushing Syndrome may in reality have been derived from cells of the *pars intermedia.* Rasmussen [39] also regards the posterior lobe cells as distinct from the anterior lobe basophiles, but criticises McCallum's technical methods and conclusions.

One other question arises in the discussion of this case, and that is the possible rôle of the pituitary in stimulating the parathyroid to unusual growth and activity. It was suggested by Cushing that the osteoporotic changes which characterize most of the reported cases of Cushing Syndrome may be the result of excessive parathyroid function. The existence of a parathyrotropic hormone in extracts of the anterior lobe has been made probable by the experiments of Hertz and Kranes [40], and Anselmino and Hoffmann [41, 42], and if these should be confirmed by further work, one might reasonably inquire as to whether the parathyroid hyperplasia were not initiated by the excessive production of this pituitary hormone.

An analysis of the reported cases of Cushing's Syndrome lends little support for this view *. In autopsies upon cases of "pituitary basophilism" the parathyroids are described as normal (Anderson [43], Zondek [18], Craig and Cran [44], Russell Evans and Crooke — 2 cases [45], Swan and Stevenson [46], Wright [47]) or as showing fat infiltration (Raab-Kraus [21], Rutishauser — 2 cases [48], Horneck [26], Konschegg [27], Kalbfleisch [49], Lawrence and Zimmerman [22], Freyburg et al.[25]), or as being fibrotic (Mooser [50]). One small gland in the case of Lawrence and Zimmerman contained a microscopic adenoma.

However, in the case reported by Schmorl [17] and in greater detail by Molineus [17a] the parathyroids were much enlarged. Although the clinical history is incomplete, the patient having

* See also discussion by Albright in Case Records of Mass. Gen. Hosp., No. 23011, reported in N. Eng. J. of Med., 1937, *216*, 23.

been under observation only a short time, sufficient data are given to identify it, as Cushing has done, as one of "pituitary basophilism". The patient, a woman of 47, showed the characteristic obesity of face and trunk, hypertrichosis and had had amenorrhoea since the age of 20. There is no mention of renal insufficiency or hypertension, but contracted kidneys were found at autopsy. There was a very large "basophile" adenoma (no special stains or demonstration of granules) of the anterior pituitary lobe. The four parathyroids were greatly enlarged, and the bones were affected by an advanced osteo-fibrosis, with multiple brown tumors. Minciotti [23] has also described a case which seems to combine the features of Cushing Syndrome with those of renal hyperparathyroidism. A woman, aged 38, had the following symptoms and signs: obesity of the trunk, striae, amenorrhoea, hirsutism, hypertension, polycythemia, hyperglycemia. The bones radiographically showed extreme porosis. The blood calcium was elevated (13.5 mg. %). The autopsy disclosed an adenoma of the anterior pituitary lobe, cortical hyperplasia of the adrenals, intense glandular hyperplasia of the parathyroids (no weights or measurements), chronic nephritis with severe glomerular lesions. The bones showed lacunar resorption and "proliferation of the type of osteitis fibrosa" especially in the subperiosteal zones.

A clinical case combining the features of the Cushing Syndrome with hypercalcemia and X-ray changes in the bones suggestive of osteitis fibrosa, is reported by Pero [51]. Unfortunately there was no autopsy.

With the exception of the above two cases, the bones have on microscopic study been found to be normal (Russell, Evans and Crooke [45], or to show simple osteoporosis without osteoclasts, lacunar resorption or marrow fibrosis (Rutishauser [48], Horneck [26], Konschegg [27], Kalbfleisch [49], Teachenor [24], Lawrence and Zimmerman [22]).

Since, therefore, hyperplasia of the parathyroids and bone lesions characteristic of hyperparathyroidism are not characteristically associated with the Cushing Syndrome, we incline to the view that the parathyroid enlargement and osteofibrosis of the bones in our case has resulted from the chronic renal

disease, rather than from some obscure pituitary stimulation. Further experimental studies, however, are needed to define more clearly the interrelation of pituitary, parathyroids and kidneys.

Summary

A case is reported, which combined the classical features of the Cushing Syndrome with those of renal hyperparathyroidism. The literature bearing on the subject is reviewed and discussed.

Acknowledgments: We wish to express our thanks to Professor Enrique Koppisch, for permission to include his autopsy record, and to Professor Severinghaus for reviewing our findings on the histological study of the pituitary.

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Fig. 1. Lateral X-ray film of skull showing osteoporosis, normal sella.

Lám. I. *Radiografía lateral del cráneo, donde se destaca la osteoporosis de la bóveda, con la silla turca de contorno y dimensión normales.*

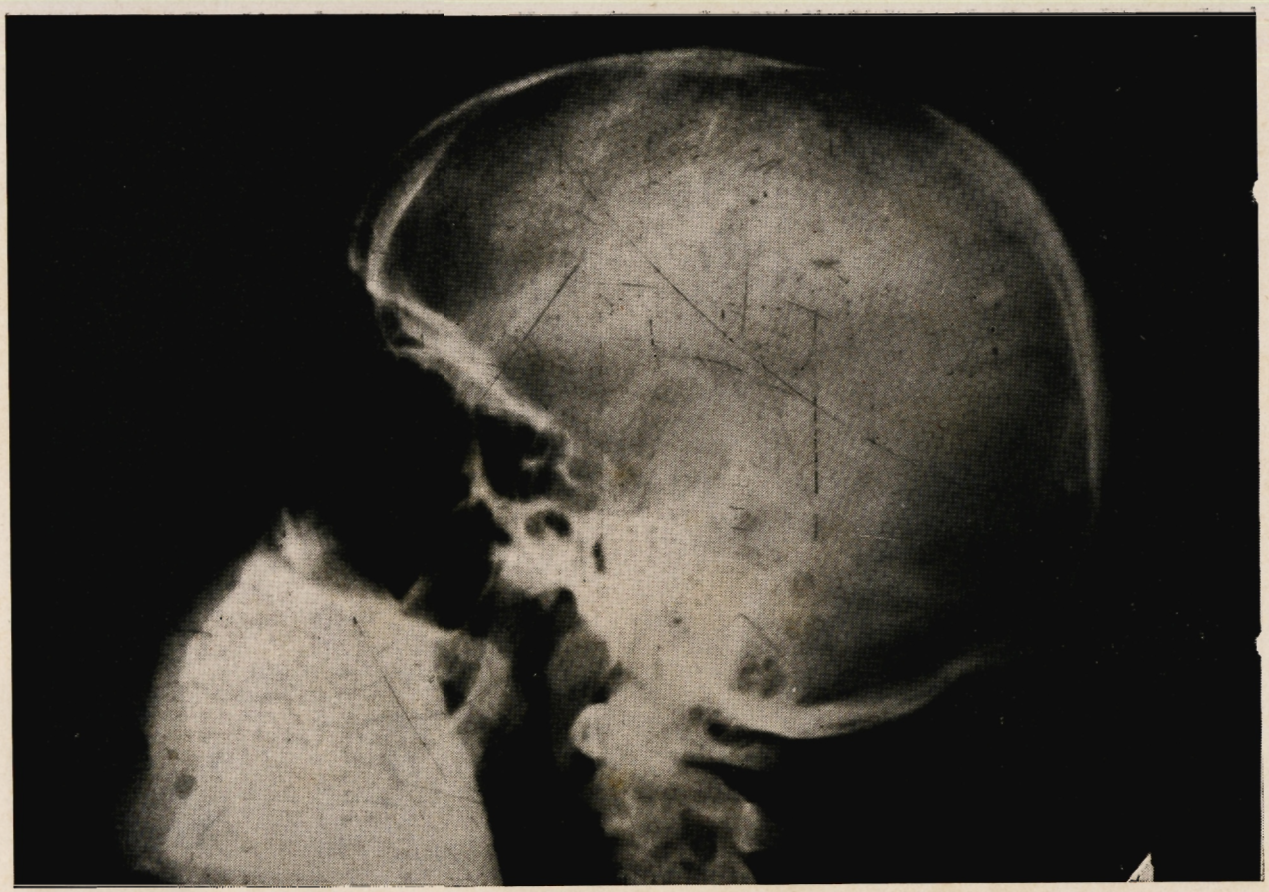

FIG. 1

FIG. 2. Coronary artery: large calcified plaque in intima.

FIG. 3. Apex of left ventricle: calcified band in endocardium.

LÁM. 2. *Arteria coronaria: gran placa calcificada en la íntima.*

LÁM. 3. *Vértice del ventrículo izquierdo: banda calcificada en el endocardio.*

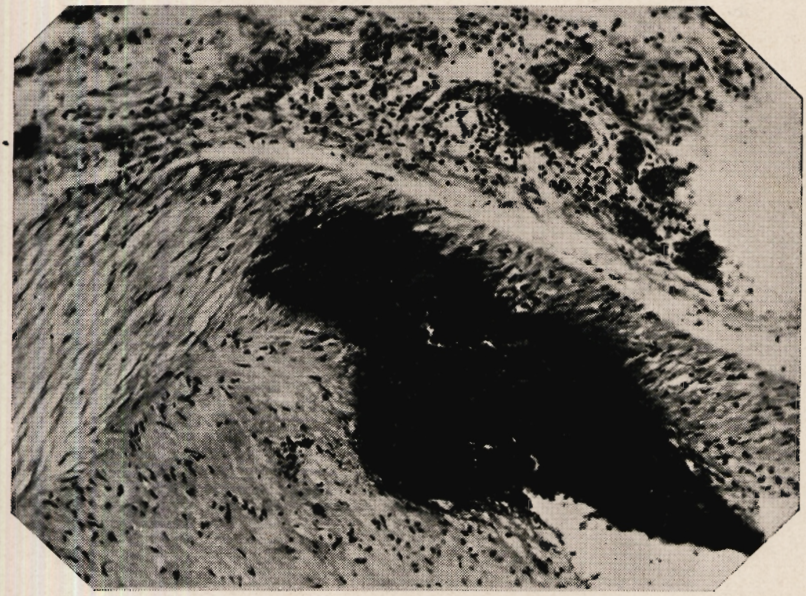

FIG. 2

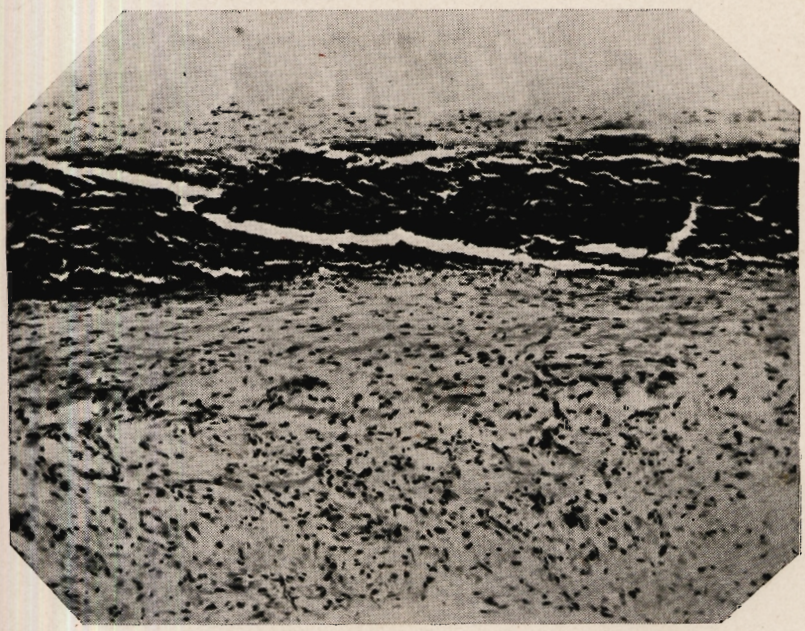

FIG. 3

FIG. 4. Superior mesenteric artery: medial calcification.

FIG. 5. Lung: calcified deposits surrounded by fibroblasts.

LÁM. 4. *Arteria mesentérica superior: calcificación de la media.*

LÁM. 5. *Pulmón: depósitos calcáreos rodeados por fibroblastos.*

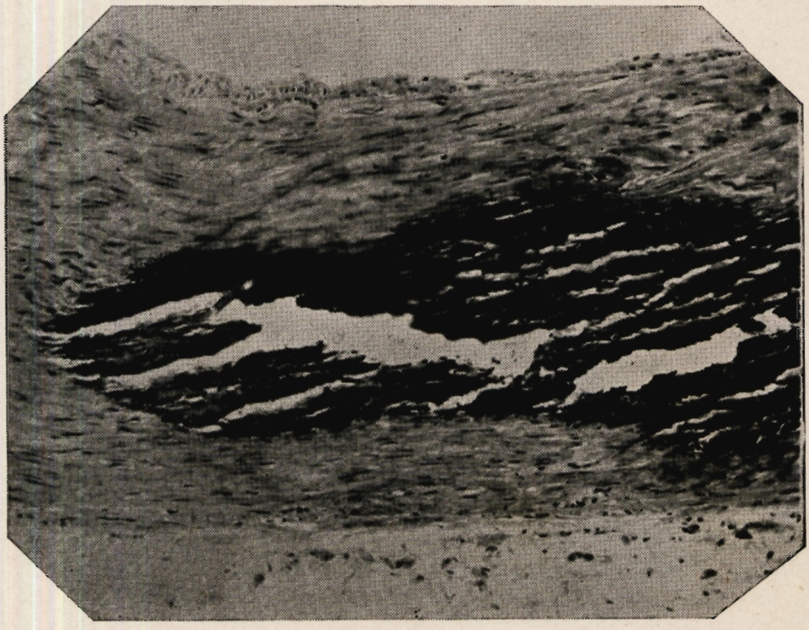

FIG. 4

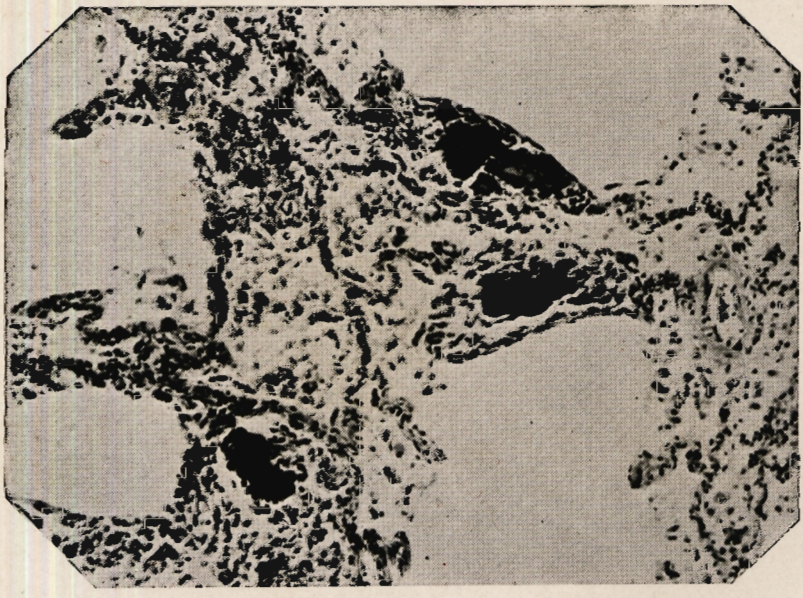

FIG. 5

PONS AND PAPPENHEIMER

RENAL HYPERPARATHYROIDISM
WITH
CUSHING'S SYNDROME

FIG. 6. Pancreas: Island of Langerhans showing hyalinization.

FIG. 7. Liver: central necrosis and calcification of liver cells.

LÁM. 6. *Páncreas: hialinización incipiente de un islote de Langerhans.*

LÁM. 7. *Hígado: necrosis central y calcificación de las células hepáticas.*

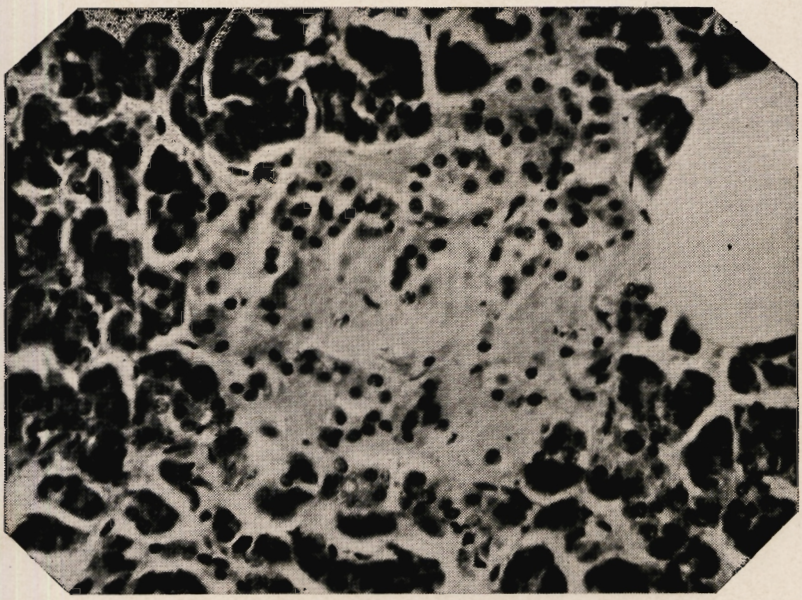

FIG. 6

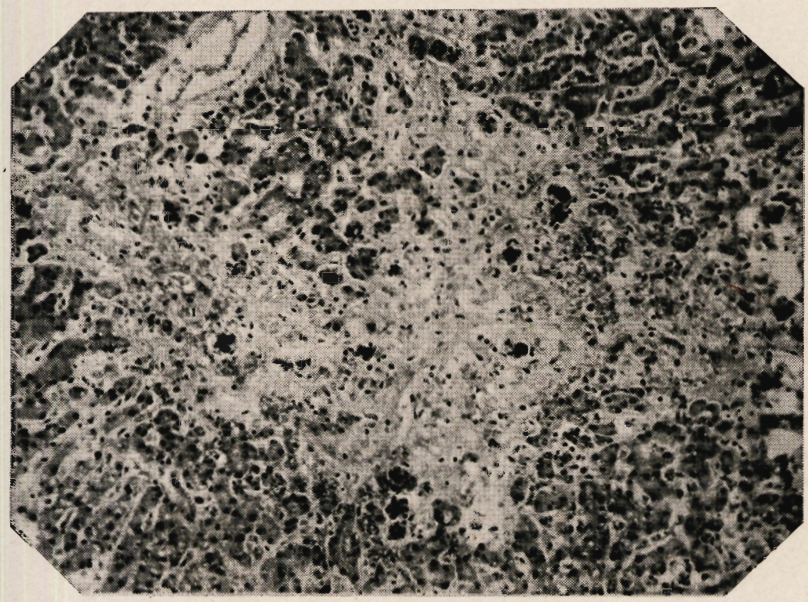

FIG. 7

PONS AND PAPPENHEIMER

RENAL HYPERPARATHYROIDISM
WITH
CUSHING'S SYNDROME

FIG. 8. Adrenal: **hyaline arteriole in periadrenal tissue.**

FIG. 9. Kidney: **advanced arteriolar nephrosclerosis.**

LÁM. 8. *Glándula suprarrenal: arteriola hialina en tejido periadrenal.*

LÁM. 9. *Riñón: nefroesclerosis arteriolar avanzada.*

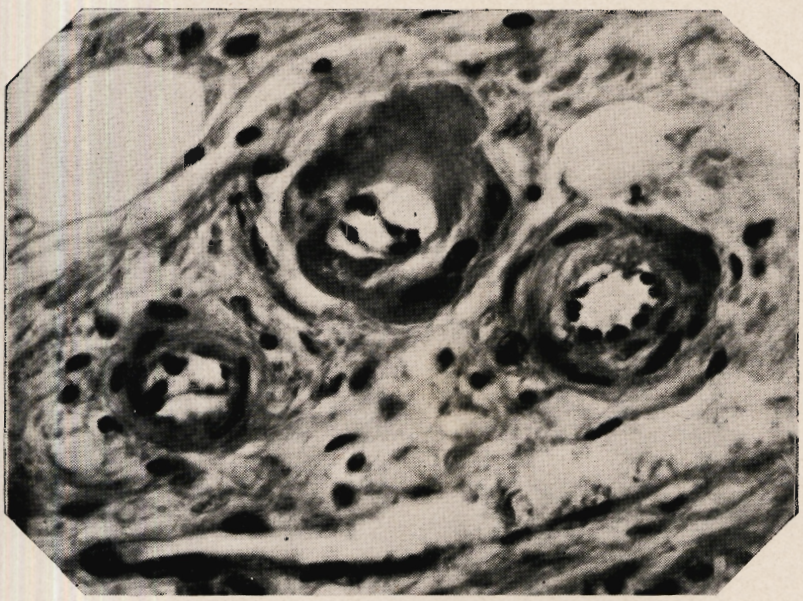

FIG. 8

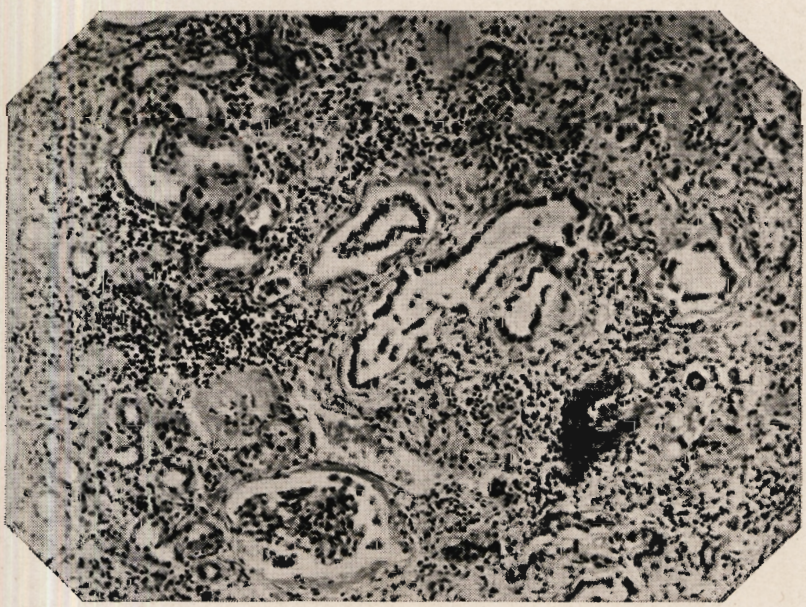

FIG. 9

PONS AND PAPPENHEIMER

RENAL HYPERPARATHYROIDISM
WITH
CUSHING'S SYNDROME

FIG. 10. Stomach: calcium deposits in mucosa.

FIG. 11. Parathyroid: diffuse hyperplasia.

LÁM. 10. *Estómago: precipitaciones cálcicas en la mucosa.*

LÁM. 11. *Paratiroide: hiperplasia difusa.*

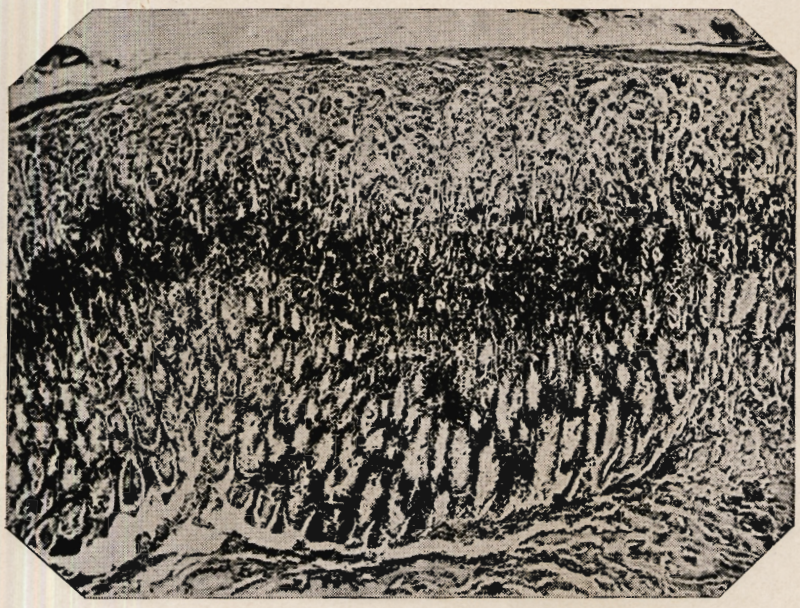

FIG. 10

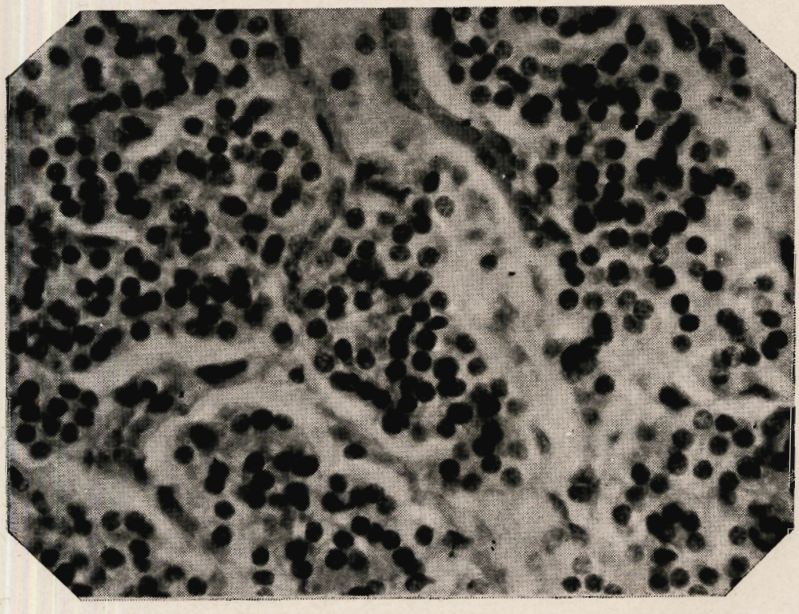

FIG. 11

PONS AND PAPPENHEIMER

RENAL HYPERPARATHYROIDISM
WITH
CUSHING'S SYNDROME

FIG. 12. Calvarium: marrow fibrosis, lacunar resorption with osteoclasts.

FIG. 13. Vertebra: similar changes to those in calvarium.

LÁM. 12. *Bóveda craneal: fibrosis de la zona medular, reabsorción lagunar con osteoclastos.*

LÁM. 13. *Vértebra: alteraciones óseas semejantes a las de la bóveda del cráneo.*

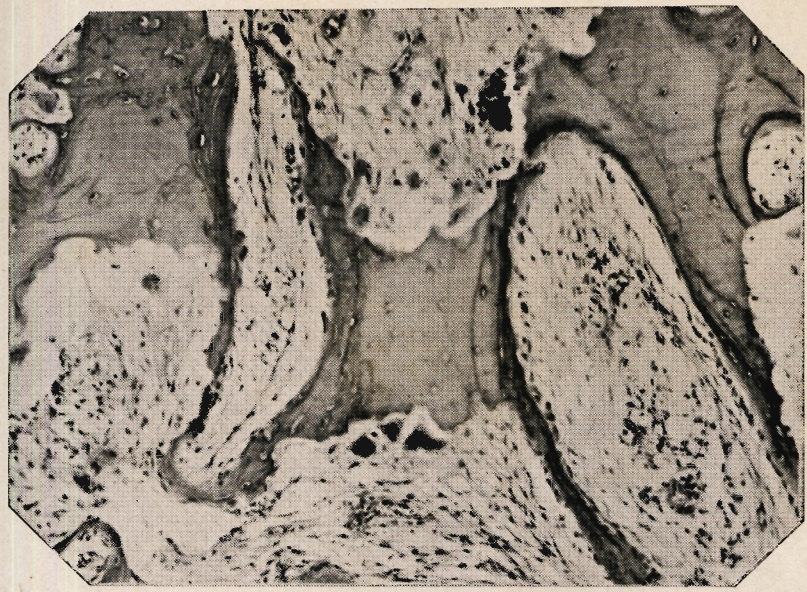

FIG. 12

FIG. 13

PONS AND PAPPENHEIMER

RENAL HYPERPARATHYROIDISM
WITH
CUSHING'S SYNDROME