CHRONIC GRANULOMA ASSOCIATED WITH PERIARTERITIS NODOSA

Report of a Case with Renal Failure *

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The original descriptions of periarteritis nodosa were made by Von Rokitansky[1] and Kussmaul and Maier.[2] Reviewing the literature prior to 1938, Harris, Lynch and O'Hare[3] found more than 300 cases recorded, and of these 101 were in English publications. From the nature of the case reports, it is evident that the disease is one of protean character. Its widespread manifestations can be explained by diffuse involvement of the arterial system with secondary changes in the tissues supplied by the altered blood vessels. The more common clinical features and the pathologic findings have been carefully studied and described.[3, 4] A consideration of the etiologic factors and a discussion of recent researches on the experimental production in rabbits of vascular lesions identical with those seen in the human form of the disease have been reported by Rich[5] and by Rich and Gregory.[6]

The tissue changes secondary to arterial lesions include ischemia, edema, atrophy, hemorrhage, inflammatory infiltration, infarction, necrosis and fibrosis.[7] There are, however, few descriptions in the literature of widespread granulomatous lesions associated with periarteritis nodosa. In 3 out of 4 cases studied, Neumann[8] described a peculiar granulomatous reaction containing eosinophils, multinucleated giant cells and zones of radiating necrosis. These lesions were present in the mediastinal tissues, the heart and the kidneys. One of the cases presented by Banowitch, Polayes and Charet[9] was that of a woman, 35 years old, who had an extensive granulomatous lesion involving the mediastinum, associated with granulomatous foci in many other organs. These lesions consisted of zones of necrosis, fibroblastic proliferation, multinucleated giant cells and cells resembling epithelioid cells.

Because of the nature of the granulomatous reaction which may occur in periarteritis nodosa, the latter should be considered in the differential diagnosis of any chronic granulomatous disease.

The present report concerns an unusual case of the granulomatous variety of periarteritis nodosa with extensive involvement of the kidney producing marked renal insufficiency and death.

Report of Case

Clinical History. A.H., no. U-67980, a married white woman, 67 years old, was first seen on December 27, 1940. One year before entry she had noted a painless depression on the bridge of her nose and since then had experienced marked crust-

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ing of the nasal mucous membrane and occasional slight epistaxis. She complained of progressive weakness and had lost 27 pounds in weight (56.8 to 44.5 kg.). On many occasions fever of 100° to 101° F. (37.8° to 38.3° C.) was noted. For the past 8 months she had complained of a slight cough with a moderate amount of sputum. Five months before entry she had had an attack of acute parotitis and swelling of the anterior cervical lymph nodes. Examination of one of the parotid glands by biopsy showed "no evidence of malignancy." Three months later the abdomen was explored under general anesthesia. The gallbladder and a small "congenital cyst" of the liver were removed. Histologic examination of the gallbladder revealed "chronic cholecystitis." Blood counts during the 5 months preceding entry showed a moderate leukocytosis and a gradually progressing hypochromic microcytic anemia, which did not respond to treatment with iron or liver. Numerous urinalyses were reported as normal. Roentgenograms of the nose demonstrated that the "saddle" deformity was caused by destruction of cartilage, the nasal bones remaining intact. Roentgenograms of the chest demonstrated very dense hilar shadows with some calcifications in the lymph nodes. Unusually prominent bronchial markings had suggested the presence of interstitial fibrosis.

Physical Examination. The patient was an alert, emaciated, white woman. Temperature, 97.6° F.; pulse, 84 per minute; blood pressure, 155/75 mm. of Hg; height, 166 cm.; weight, 99 lbs. (45 kg.). There was marked wasting of the musculature and subcutaneous tissues. The skin was pale and dry. The scalp was normal; the hair was thin and gray. There were a few small, shotty cervical lymph nodes. The pupils were equal and regular and reacted normally to light and in accommodation. Extra-ocular movements were normal. The retinal arterioles were diffusely narrowed and two small "cotton wool" patches were observed above the right optic disk. The ears and mouth were normal. There was a "saddle deformity" of the nose. The septum was intact, but depressed anteriorly. The nasal mucous membrane was thin and atrophic, and an adherent crusted discharge was present. The thyroid gland was not palpable. The breasts were small, flat and atrophic. The lungs were clear. The heart was not enlarged. An apical systolic murmur was present. The abdomen was scaphoid; none of the abdominal organs were palpably enlarged, and there was a healed right upper rectus scar. Examinations of the pelvis, rectum, nervous system, back and extremities revealed nothing abnormal.

Laboratory Examination. Examination of the blood gave the following data: hemoglobin, 46 per cent (6.3 gm.); erythrocytes, 2.5 million per cmm.; packed cell volume, 20; platelets, 360,000 per cmm.; leukocytes, 13,400 per cmm.; neutrophils, 89 per cent (filamented, 72 per cent; nonfilamented, 17 per cent); eosinophils, 3 per cent; lymphocytes, 8 per cent; icterus index, 5; corrected sedimentation rate, 24 mm. per hour (Wintrobe). Differential cell counts of bone marrow pulp obtained by sternal puncture showed normal maturation of the myelopoietic series and slight suppression of activity of the erythropoietic series. Blood culture and cultures of urine obtained from each kidney showed no growth. Agglutination tests with *Bacillus typhosus, B. paratyphosus* A and B, *Brucella abortus* and *Bacillus tularensis* antigens were negative. Tuberculin (1:1000) skin test was negative. Chemical investigation of the blood showed: total serum proteins, 7.53 gm. per cent; albumin, 3.56 gm. per cent; globulin, 3.97 gm. per cent; serum calcium, 10.5 mg. per cent; serum phosphorus, 5.64 mg. per cent; plasma phosphatase, 8.12 mg. of phosphorus by method of Kay and Jenner [10] (normal, 4 to 7 mg.); plasma fibrinogen, 1.25 per cent; nonprotein nitrogen, 75 mg. per cent on January 5, 1941, 102 mg. per cent on January 18; creatinine, 2.7 mg. per cent on January 5, 2.91 mg. per cent on January 18. Blood indican and xanthoprotein reactions were negative. Kolmer and Kahn tests of the blood were negative. The urine was clear and yellow; pH, 5.0; specific gravity, 1.008; faint trace of albumin; sugar, none; occasional

granular casts. The Mosenthal test gave: total day urine, 835 cc.; total night urine, 580 cc.; maximum variation in specific gravity, 0.002. Esbach determination of albumin in the urine indicated 0.8 gm. per liter. With the phenolsulfonphthalein test there was 10 per cent excretion of the dye in 2 hours. An Addis count (12 hour test) gave: erythrocytes, 370,000; casts (all granular), 80,000; leukocytes and epithelial cells, 10,500,000. Roentgenograms of the chest revealed considerable calcification of the aorta. There was over-aeration and fibrosis of both lung fields. The cardiac silhouette was within normal limits.

Course. The temperature varied between 96.0° and 102.5° F. (36.4 to 39.2° C.), the pulse between 80 and 130 per minute and the blood pressure between 155/95 and 105/55. The course of the illness was short; the patient gradually lapsed into coma and expired on January 24, 1941, approximately 1 month after entry to the hospital. A clinical diagnosis of sarcoidosis was made.

Gross Examination

Autopsy was performed 30 minutes after death. Rigor mortis and post-mortem lividity had not appeared. A urinogenous odor was noted when the peritoneal cavity was opened. The latter was normal in appearance except for the presence of firm, fibrous adhesions in the right subhepatic region. The gallbladder was absent. The pleural cavities were normal. There were several firm, fibrous adhesive bands joining the pericardium to the apex and to the anterior left ventricular surface of the heart. The mediastinum was normal in all respects.

The heart weighed 245 gm. It was small and soft. The myocardium, endocardium, heart valves and coronary blood vessels were normal. The right lung weighed 400 gm., and the left, 380 gm. There was slight congestion of both lower lobes and a seropurulent exudate was present within the bronchioles of the right lung. The hilar and mediastinal lymph nodes appeared unaltered.

The liver weighed 1080 gm. There were adhesions on its under surface. The cut surface was normal. The common duct was dilated but not obstructed, and measured 8 mm. in diameter. The spleen weighed 140 gm.; the cut surface was light purple; it appeared moderately hyperplastic.

The right kidney weighed 175 gm. and the left, 180 gm. They presented essentially the same appearance. The capsule was firm, white, fibrous and measured 1.5 mm. in thickness. The capsule was not adherent to the perirenal fat and could be easily stripped from the cortical surface of the kidney (Fig. 1). The surface of the kidney was smooth and showed only a few depressions which appeared to be the remains of fetal lobulations. The cut surface showed a clear differentiation between the cortex and medulla (Fig. 2). The average thickness of the cortex was 0.5 cm. It was extremely firm, fibrous and light yellow. The pyramids were of normal size and light pink, but were poorly striated.

There were no scars, infarcts, hemorrhages, or nodules present. The renal pelves, blood vessels, ureters and bladder were grossly normal.

The gastro-enteric tract presented no abnormalities. The internal genitalia were atrophic. The aorta was atherosclerotic and partially calcified. The vena cava and iliac vessels were not altered.

The thyroid gland was normal in appearance. The adrenal glands were small, the right weighing 4.2 gm. and the left, 2.8 gm. The pituitary gland was normal in size, but contained in its anterior lobe a cyst (filled with clear yellow fluid) which measured 0.5 cm. in diameter. The only lymph nodes of note were a group lying adjacent to the celiac axis. They measured approximately 1.5 by 1.0 by 0.5 cm.; the cut surfaces were normal. The brain weighed 1300 gm. and was normal except for minimal atherosclerotic changes in those vessels comprising the circle of Willis.

Microscopic Examination

Only those tissues involved in the granulomatous process will be described in detail. Other findings of note included bilateral pulmonary congestion, and bronchopneumonia of the right lower lobe. There was atherosclerosis of the aorta, coronary arteries, and mitral and aortic valves.

The most striking alterations were seen in the kidneys. The markedly thickened capsule was composed of dense, hyalinized fibrous tissue, which, with the perirenal fat, was moderately infiltrated with lymphocytes and a few plasma cells, usually arranged around blood vessels (Fig. 3). Practically the entire renal cortical structure, including glomeruli and tubules, was replaced by moderately cellular fibrous tissue, which was densely infiltrated with plasma cells, lymphocytes, and neutrophilic and eosinophilic leukocytes (Fig. 4). The fibrous connective tissue was more abundant in and around the glomeruli.

Few glomeruli were normal; many were entirely replaced by hyalinized fibrous tissue with obliteration of the glomerular space. A few retained small centrally placed glomerular tufts or vascular channels, while others either contained a small central collection of neutrophilic leukocytes or were extensively infiltrated with these cells. Some glomeruli contained small masses of hyaline fibrin, either deposited in glomerular tufts or between the glomerular capsule and the capsular epithelium. Other glomeruli were altered by shrinkage, partial hyalinization or pericapsular fibrosis.

The few tubules remaining in the fibrotic cortical zone occurred singly or in scattered groups. The convoluted tubules were dilated and hypertrophied, and showed cloudy swelling and minimal fatty degeneration of their lining cells. The solitary tubules were lined by flattened

atrophic epithelium and contained colloid, purulent material, or a combination of the two. The tubules became more numerous toward the medullary portion of the kidney; the collecting tubules in the renal pyramids were normal, although the interstitial fibrous tissue in this region was abundant, hyalinized and slightly infiltrated with lymphocytes, neutrophilic leukocytes and plasma cells. Toward the pelvis, the inflammatory reaction was minimal.

The altered renal cortex was quite avascular. The few small arteries and arterioles present appeared normal. The larger arteries (arciform) of the corticomedullary region presented a subintimal proliferation of fibrous tissue with secondary hyaline degeneration. There was thickening, irregularity and reduplication of the internal elastic membrane. The external elastic membrane was thick and well defined. Evidences of active arteritis were absent.

The epidermal layer of the nasal mucous membrane was atrophic. The submucosa was fibrotic, almost avascular and densely infiltrated with neutrophilic leukocytes, lymphocytes, macrophages and plasma cells. In the deeper layer of the submucosa was a large artery having a thick, almost acellular, hyalinized fibrous tissue wall (Fig. 5). The lumen was represented by a narrow, endothelium-lined cleft which was surrounded by a folded, hyalinized, fragmented, elastic tissue membrane. Inflammatory cells were present at the periphery but not within the wall of the vessel.

The entire posterior lobe and part of the intermediate and anterior lobes of the pituitary gland were involved in a granulomatous process composed of fibrous tissue, densely infiltrated with the same varieties of inflammatory cells as were present in the kidneys (Fig. 6). The neutrophilic leukocytes were grouped in small, rounded foci. In the less involved portions of the posterior lobe and in the capsule, the inflammatory cells were distributed in a perivascular arrangement. The majority of the blood vessels were not altered. A few presented mild edema of the media.

Re-examination of the specimen of the parotid gland obtained 5 months before death showed diffuse replacement of the glandular tissue and interlobular fat by cellular fibrous tissue, infiltrated with plasma cells, lymphocytes, and smaller numbers of neutrophilic and eosinophilic leukocytes (Fig. 7). Some of the ducts and acini showed epithelial degeneration and desquamation and contained a few inflammatory cells. Minimal hyaline thickening was the only alteration noted in the few blood vessels present.

Microscopic examination of the liver at autopsy showed it to be essentially normal. The portions removed surgically 2 months before death contained a longitudinal segment of a large vascular channel. Be-

cause of its large diameter and location at the anterior edge of the liver, this structure undoubtedly represented a small aneurysm. The vessel was partially lined by a layer of low cuboidal endothelial cells; one segment was completely occluded by dense hyalinized connective tissue and presented a folded, dense, eosinophilic wall. An adjacent portion was partially occluded by loosely arranged, newly formed, cellular fibrous tissue containing many inflammatory cells, including lipoid-filled macrophages. The vessel wall consisted of a thick layer of hyalinized fibrous tissue which contained the remaining irregular fragments of the elastic membrane, and a mild infiltration of lymphocytes and neutrophilic leukocytes. The vasa vasorum were partially or completely occluded by connective tissue and had perivascular collars of lymphocytes and neutrophilic leukocytes. A large blood vessel in the adjacent parenchyma was the site of an active inflammatory process with a diffuse infiltration of the vessel wall by lymphocytes, plasma cells, and neutrophilic and eosinophilic leukocytes (Fig. 8). The lumen was represented by a small, endothelium-lined cleft surrounded by large, young fibroblasts, acute inflammatory cells and small masses of fibrin.

All tissues involved in the granulomatous process were stained with the Glynn modification of the Gram stain, Ziehl-Neelsen carbolfuchsin and the Levaditi stains. No acid-fast organisms or spirochetes were found in any of the sections. Thorough search was made for *Histoplasma capsulatum* with negative results. In the submucosa of the nasal mucous membrane there were numerous gram-positive cocci in groups and in short chains, and a few short gram-negative bacilli. Bacteria were not observed elsewhere.

Summary

The case presented is that of a woman, 67 years old, who had suffered for almost a year from weakness, fever, anemia, weight loss, cough, sputum, and crusting of the nasal mucous membranes, and whose death was due to renal insufficiency. During the course of her illness she developed transient swelling of the parotid glands and anterior cervical lymph nodes. She was found to have atrophic rhinitis with a "saddle" deformity of the nose. The retinal arterioles were narrowed and several small patches of "cotton wool" exudate were observed. The blood pressure was not elevated and no symptoms of renal insufficiency were present until uremia supervened late in the course of the disease. However, tests of renal function during the last month of the patient's illness showed azotemia, hyposthenuria, slight albuminuria and marked impairment of excretory function. The Addis count showed only a

slight increase in granular casts, leukocytes and epithelial cells, and the xanthoprotein and indican reactions curiously were negative. At autopsy there was found a chronic granulomatous inflammatory process, which had practically replaced all of the functional renal cortical parenchyma and had likewise involved the nasal cartilage and septum, the posterior lobe of the pituitary gland, the parotid gland and a small portion of the liver. Numerous vascular lesions corresponding to periarteritis nodosa were found, the majority of which were histologically healed. The renal vessels, a nasal artery and most of the glomeruli showed evidences of a healed process. In a few glomeruli there was active glomerulitis. Active arteritis with aneurysm formation was demonstrated in tissue taken for biopsy from the liver 2 months before death.

REFERENCES

1. Von Rokitansky, C. Über einige der wichtigsten Erkrankungen der Arterien. *Denkschr. d. k. Akad. d. Wissensch.*, 1852, **4**, 49–121.
2. Kussmaul, A., and Maier, R. Über eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht. *Deutsches Arch. f. klin. Med.*, 1866, **1**, 484–518.
3. Harris, A. W., Lynch, G. W., and O'Hare, J. P. Periarteritis nodosa. *Arch. Int. Med.*, 1939, **63**, 1163–1182.
4. Arkin, A. A clinical and pathological study of periarteritis nodosa. A report of five cases, one histologically healed. *Am. J. Path.*, 1930, **6**, 401–426.
5. Rich, A. R. The role of hypersensitivity in periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 1942, **71**, 123–140.
6. Rich, A. R., and Gregory, J. E. The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. *Bull. Johns Hopkins Hosp.*, 1943, **72**, 65–88.
7. Jones, G. M., Jr. Periarteritis nodosa: with case reports. *Ann. Int. Med.*, 1942, **16**, 920–940.
8. Neumann, R. Eigenartige Riesenzellgranulome mit Strahlennekrosen bei Periarteriitis nodosa. *Virchows Arch. f. path. Anat.*, 1940, **306**, 389–403.
9. Banowitch, M. M., Polayes, S. H., and Charet, R. Periarteritis nodosa: report of five cases. *Ann. Int. Med.*, 1942, **16**, 1149–1179.
10. Jenner, H. D., and Kay, H. D. Plasma phosphatase. III. A clinical method for the determination of plasma phosphatase. *Brit. J. Exper. Path.*, 1932, **13**, 22–27.

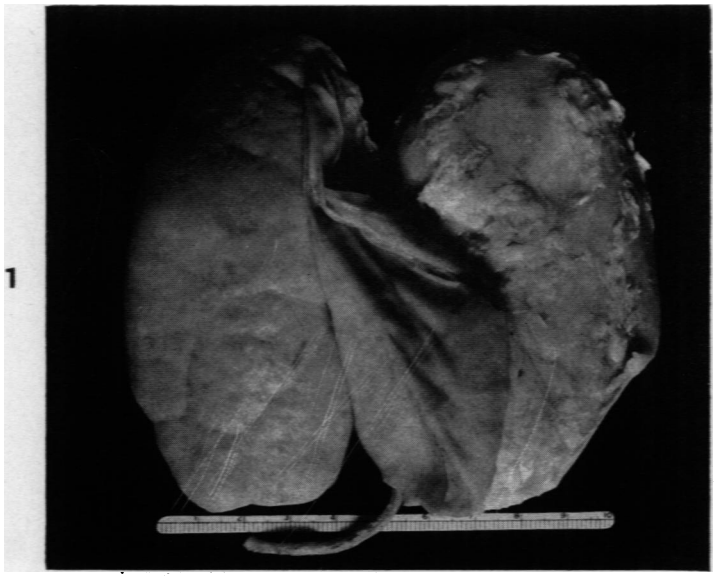
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 193

FIG. 1. External surface of left kidney demonstrating the thickened capsule and the smooth cortical surface after stripping. × 3/5.

FIG. 2. Cut surface of left kidney showing pallor of cortex with well preserved corticomedullary differentiation. × 3/5.



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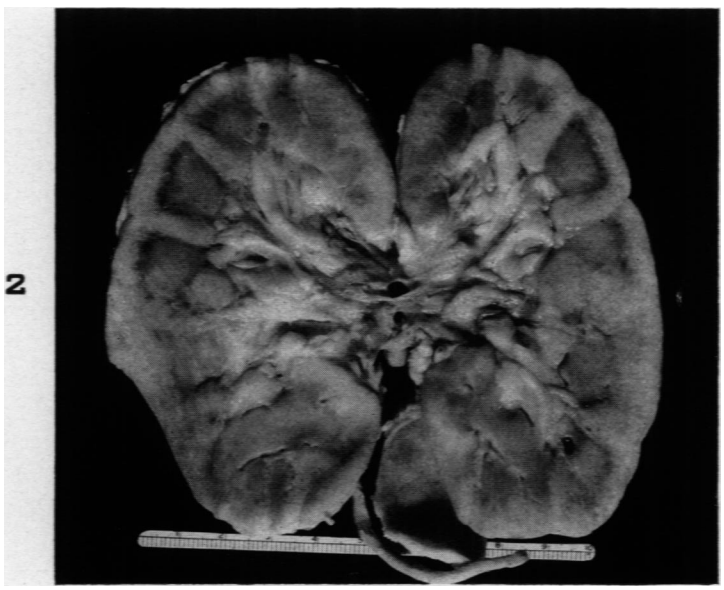

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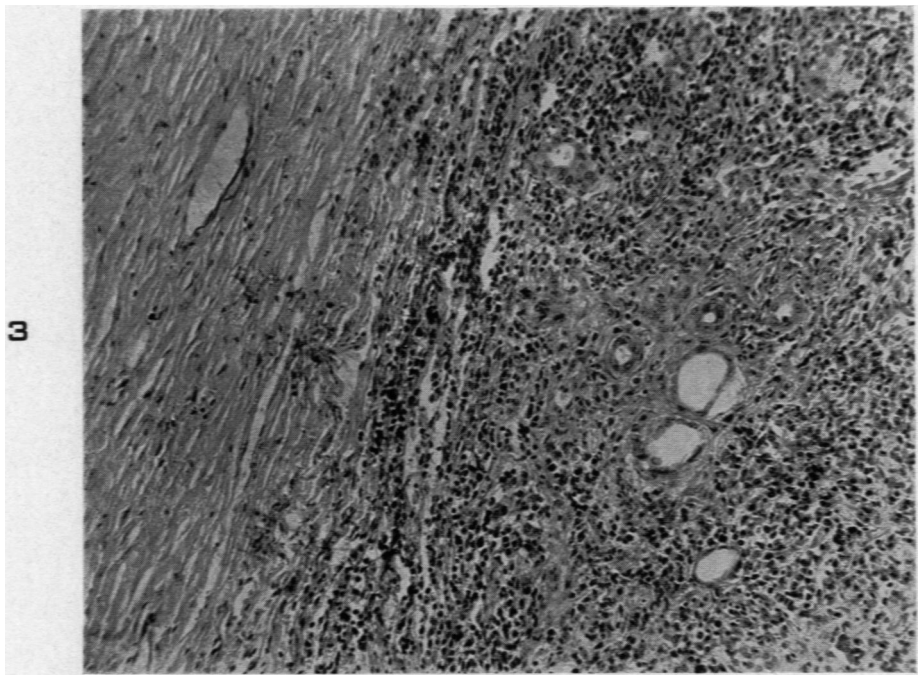
PLATE 194

FIG. 3. Thickened renal capsule with adjacent cortex. Hematoxylin and eosin stain. × 120.

FIG. 4. Renal cortex, demonstrating replacement of glomeruli and tubules by the chronic granulomatous reaction. Hematoxylin and eosin stain. × 120.



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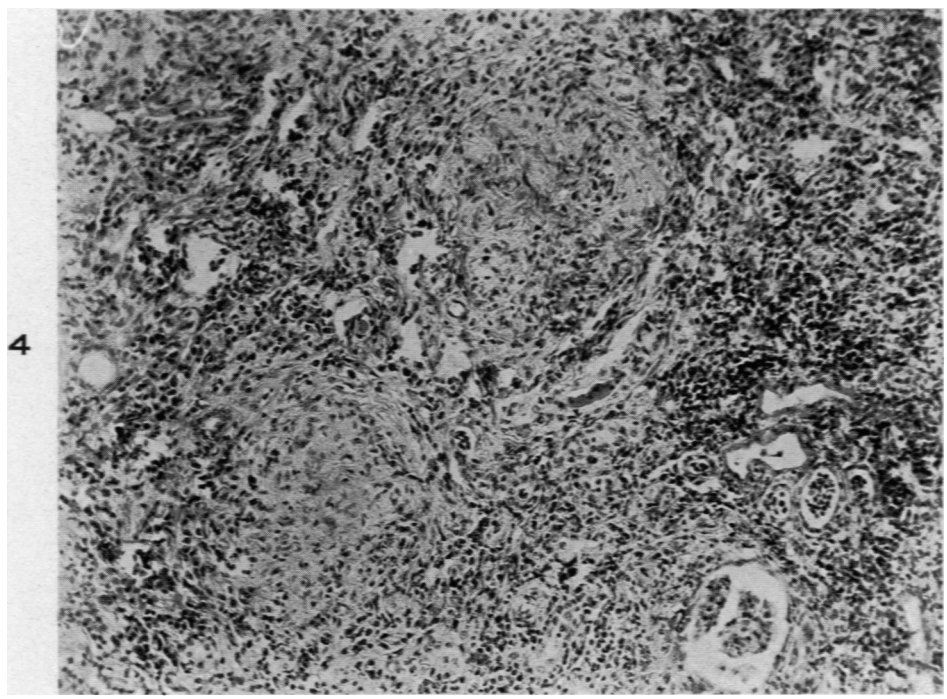

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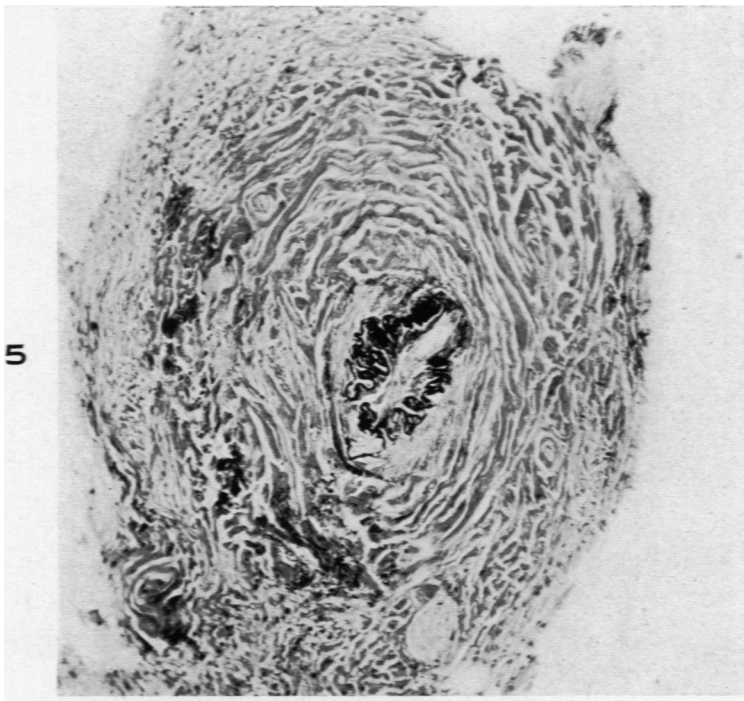
PLATE 195

FIG. 5. Thickened artery in the submucosa of the anterior nasal cavity. The internal elastic membrane is present. Weigert's elastic tissue and van Gieson's stains. × 120.

FIG. 6. Posterior lobe of pituitary gland, with replacement of the normal glial structure by chronic inflammatory tissue. Hematoxylin and eosin stain. × 300.



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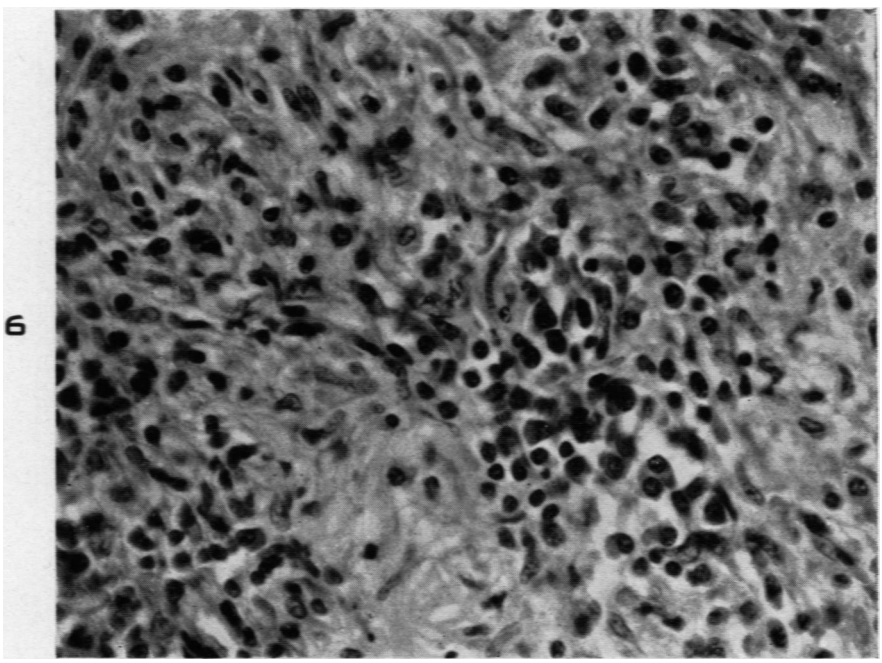

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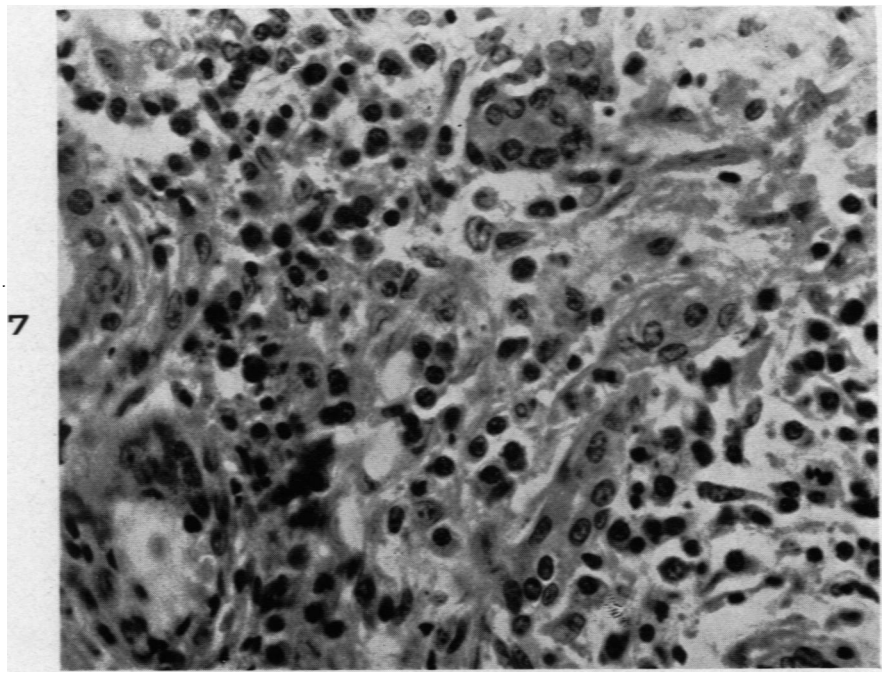
PLATE 196

FIG. 7. Parotid gland, showing replacement of most of the glandular tissue by fibrous tissue and inflammatory cells. Hematoxylin and eosin stain. × 300.

FIG. 8. Section of an hepatic artery near the small aneurysm, showing destruction of the vessel wall and replacement by connective tissue and inflammatory cells. Hematoxylin and eosin stain. × 120.



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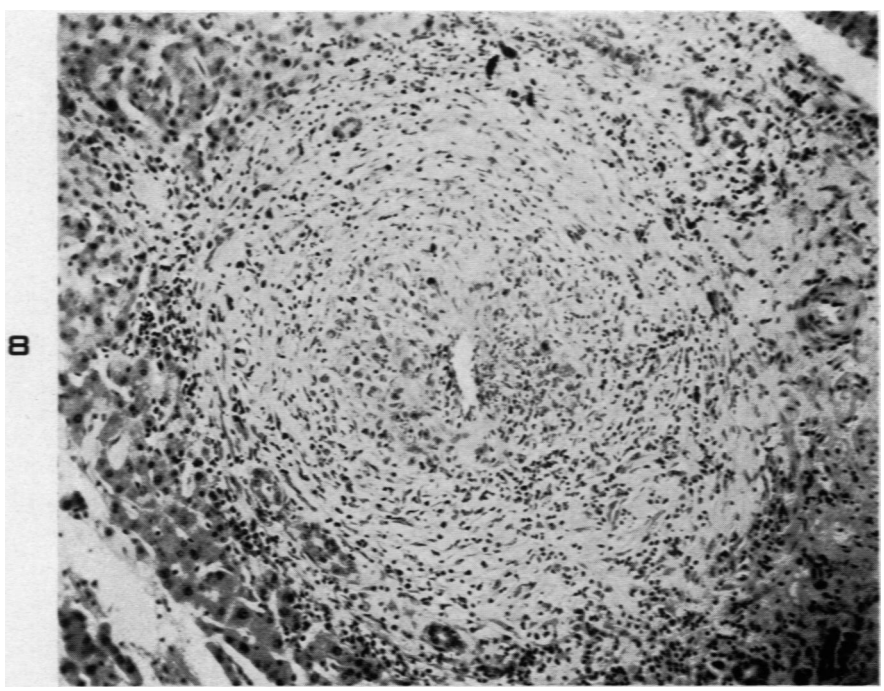

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