POLYARTERITIS NODOSA *

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NOMENCLATURE

In 1865 Kussmaul and Maier [1] described an arteritis characterized by the formation of multiple circumscribed nodulations in the small arteries of various parts of the body. They named it periarteritis nodosa, a term that implies inflammatory changes in and around the adventitia of arteries with the production of nodules, and one that was intended as a précis of the morphological peculiarities of the condition. We now know that the inflammation is by no means confined to the adventitia, that the primary changes are probably in the media, and that the disease usually affects a large number of vessels. In recognition of these facts Dickson [2] suggested the name polyarteritis nodosa, which is a more accurate epitome of what we know of the condition, and which seems to us preferable to the older term.

INCIDENCE

Approximately 150 cases of polyarteritis nodosa have been reported, less than 20 of them in the American literature (although in this country a number of excellent summaries have appeared, notably those of Ophüls,[3] and Lamb [4]). The greater number of routine autopsies in European clinics partly explains the relative infrequency with which the disease is recognized in this country, for ante mortem diagnosis is made in not more than 20 per cent of cases. However, the lesion is rare even when histological studies are made in a large series of autopsies. In 2035 autopsies at the Peter Bent Brigham Hospital Bennett and Levine [5] found only 2 cases. At the Los Angeles County Hospital, during the past 15 years (1918–1933), there have been 10,000 autopsies, only 1 of which showed the classical pathological findings of polyarteritis nodosa.

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It is conceivable, of course, that there may be a mild or early form of the disease in which the arterial changes are so slight as to escape detection in the routine microscopic study of autopsy sections. Clinically there can be no doubt that many cases have been completely unsuspected or misinterpreted, for polyarteritis nodosa habitually masquerades as one of the commoner infectious diseases. It is generally believed to be almost uniformly fatal, usually in the course of a few weeks, but the high mortality and the low incidence may both be explained partly by the fact that with few exceptions only the fatal cases have been recognized. Some authors believe that the total number of recorded instances grossly underestimates the actual frequency of the malady, and that many mild cases have undergone spontaneous recovery.

Etiology

Of the many propounded theories of etiology none has been generally accepted. For some time there was a tendency to regard the disease as a sort of aberrant manifestation of syphilis or some other systemic infection. The present tendency is to regard polyarteritis nodosa as a disease in its own right, quite independent of any underlying condition, and incrimination of syphilis seems utterly without foundation.

The febrile course and other outstanding symptoms are those commonly associated with sepsis and there is every reason to suspect an infectious origin. The small blood vessels in other infections, such as the cerebral vessels in influenza and the skin capillaries in epidemic meningitis, may show comparable lesions, and Bennett and Levine [5] refer to the similarity between the pathological findings in polyarteritis nodosa and those of Rocky Mountain spotted fever and typhus fever, as discussed by Wolbach,[6] and Wolbach, Todd and Palfrey.[7]

Assuming that we are dealing with an infectious disease, we still have to decide whether there is a specific infective agent, or whether a variety of agents may produce the same striking vascular phenomena. Spiro [8] does not consider polyarteritis nodosa a disease *sui generis*; he thinks it merely one of the forms that may be taken by a mesarteritis due to a variety of infections. Gruber [9, 10] states: "We regard periarteritis nodosa as the expression of a con-

stant characteristic reactive process of the arterial system in the manner of an hyperergic phenomenon during the course of very different infectious-toxic diseases. This is hypothesis!" However, when we contrast the enormous number of infections with the rarity of the histological phenomena seen in polyarteritis nodosa, it is difficult to believe that the vessels are capable of such a constant specific response to non-specific excitants.

Evidence is accumulating in favor of the specific infectious nature of the disease. Harris and Friedrichs,[11, 12] though their experiments have not been widely accepted, believe they have produced the disease in animals. Other workers have observed in the lower animals (deer, calf, pig, dog) lesions almost identical with those we see in man. Altogether, the probabilities are that this peculiar and unmistakable lesion is induced by a specific infectious agent, probably a filterable virus with a predilection for the arterial system.

Classification

Obviously there can be no etiological classification. Histologically the lesions are readily grouped according to the stage of advancement of the inflammatory process. Clinically the victim's progress will depend upon the anatomical locations of the lesion and the severity of the arterial damage in these locations, so that we may attempt to divide polyarteritis nodosa into different types, according to predominant symptoms or the rapidity of its course. Sometimes the most battle-scarred areas may be mirrored in the clinical picture, but often the autopsy findings are the only reliable evidence upon which we may say that the disease is renal, cardiac, cerebral, abdominal, dermatological or neuromuscular in type.

Pathology

The affected vessels may often be recognized in the gross by the multiple small (peas-in-a-pod) nodules scattered along their course. These nodules may be inflammatory foci or actual aneurysms. Microscopically the periarterial connective tissue, the adventitia and the media show dense cellular infiltration consisting largely of polymorphonuclear leukocytes, and the media often shows extensive necrosis which may give rise to aneurysms. The intima shares the inflammatory process and, if the endothelium and internal elastic

lamina are destroyed, thrombosis results. Vascular occlusion with consequent infarction of the organs supplied by the affected vessels is the pathological key to the sudden critical clinical symptoms that may appear in the course of the disease. These vary according to the location and size of the occluded vessels.

The selection of the media rather than the adventitia as the primary site of attack (contrary to earlier conceptions) was demonstrated by Fishberg [13] in a patient who suffered from an acute form of the disease and died in a few days. The vessels affected are the small or medium sized muscular type arteries, while the elastic type escape. Arkin [14] says that the organs most frequently involved are the kidneys (80 per cent), heart (70 per cent), liver (65 per cent), gastro-intestinal tract (50 per cent), pancreas (25 per cent), mesenteric artery (30 per cent), muscles (30 per cent), and peripheral nerves (20 per cent). The central nervous system is attacked in 8 per cent of the cases. The disease may confine itself to one organ for considerable periods of time, and involvement of other organs is irregular and wholly unpredictable. Sometimes the characteristic nodules appear in the skin, and a diagnosis is then readily made by excision of one of these lesions.

In his illuminating analysis of the pathological findings Arkin divides the disease into four stages: (1) the alterative-degenerative or beginning stage; (2) the acute exudative inflammatory stage; (3) the granulation tissue stage; and (4) the healed end-stage, or scar tissue stage. Of course, these stages are no more sharply separable than those of any other inflammatory process. They may merge and vary enormously in each individual case, and sometimes may telescope into one short fulminating bout in which all the stages seem to occur almost simultaneously with terrifying despatch.

Clinical Syndrome

The victim of polyarteritis nodosa is usually a man (males predominate four to one) between 10 and 50 years of age (the youngest reported case was 3 months, the oldest 78 years of age). The typical onset is said to be acute, with a short septic course ending in death (often due to hemorrhage from a ruptured aneurysm) in a few weeks. However, more often than most textbooks quote, the onset is gradual and insidious, the course subtle, capricious and relatively pro-

longed. Arkin's case of histologically healed polyarteritis nodosa lived 4 years after his single attack of acute illness.

Evidences of sepsis are the rule — fever, high leukocytosis (and in our case eosinophilia), anemia, prostration and sometimes splenic tumor. Concomitant with these there are other more variable signs and symptoms that reflect the hidden vascular insults. The cardiac type behaves like a case of coronary sclerosis and there is apt to be an anginoid syndrome with manifestations of myocardial insufficiency. When the kidney is chiefly involved the course is often indistinguishable from essential hypertension with nephrosclerosis. There may be hypertension, visual disturbances and renal insufficiency, and if infarction occurs there is likely to be sudden hematuria. When the mesenteric vessels are occluded the symptoms may simulate those of an acute abdominal condition, and differential diagnosis is extremely difficult when the surgeon is confronted with a patient who has abdominal pain, fever, leukocytosis, nausea and vomiting. Neuromuscular symptoms of pain and tenderness along the peripheral nerves and in the muscles occur to some degree in most forms of the disease. It has been supposed that the neuritis was always secondary to changes in the arteries accompanying the nerves, but Carr's case [15] seems to confirm the work of other investigators (*e.g.*, Wohlwill,[16]) who believe that there may be severe parenchymal nerve degeneration with or without arterial damage. Fletcher,[17] Dickson,[2] and Bennett and Levine [5] reported cases of the cerebral type of polyarteritis nodosa, and Bennett and Levine's second patient developed a meningitis, during the active stage of which there was an increased number of polymorphonuclear leukocytes in the cerebrospinal fluid, though no organisms could be detected.

Differential Diagnoses

Small wonder that with such bizarre manifestations polyarteritis nodosa with monotonous regularity should pass wholly unsuspected (in about 88 per cent of cases probably) before autopsy. In our case, as in many others, even autopsy failed to reveal the condition until tissue sections were seen under the microscope.

During life the disease is usually mistaken for neuritis, myositis, trichinosis, vascular nephritis, typhoid fever, miliary tuberculosis, gastro-enteritis, pyemia, purpura hemorrhagica, hemorrhagic ne-

phritis, endocarditis, or acute abdominal conditions. It would be academic to point out features that might distinguish polyarteritis nodosa from each of these conditions. Indeed, it is seldom necessary or possible to make a careful differentiation. The diagnosis is usually unprovable but the possibility of a common vascular cause should be considered whenever a patient with sepsis exhibits a wide variety of symptoms, not peculiar to a specific disease. When an obscure sepsis cannot be fitted into one of the commoner infectious groups, the internist should consider polyarteritis nodosa as a possible diagnosis.

The following case is reported because it presents some peculiar features of a rare condition.

Report of Case

Clinical History: A male negro, aged 49 years, was admitted to the Los Angeles County Hospital Jan. 15, 1932, with a diagnosis of influenza. He complained of headache, pain in the shoulders and neck, chills, fever and cough. His temperature was 104, pulse rate 100.

In childhood the patient had had measles, mumps, chickenpox and pertussis. He remembered no other illness until Nov. 21, 1931, when he was ill with what he thought was the "flu." He recovered and went to work for a while but in January had similar complaints. He denied venereal disease. By occupation he was a carpenter. He had never used alcohol or tobacco. His father, mother, brother and three sisters were living and well.

Examination revealed a well nourished and well developed negro with a blood pressure of 135/90. There were no significant findings except several carious teeth, tenderness and pain on pressure along the course of the left spinal accessory nerve, and a temperature that fluctuated between 99 and 102 F. The pulse was from 88 to 100.

Blood and spinal fluid Wassermanns were negative. The white blood count was 11,300, polymorphonuclear leukocytes 82 per cent. Urine negative.

The patient left the hospital Feb. 11, 1932, with a diagnosis of left spinal accessory neuritis, radiculitis and pharyngitis.

On May 18, 1932, the patient returned to the hospital complaining of pain in the shoulders, neck, and arms. He said that he had been feeling somewhat better until Feb. 16, 1932, when in trying to stop a gun fight, he fell unconscious and remained so for 16 hours. When he recovered consciousness he found his right arm and right leg were paralyzed. In 3 days he was able to walk with a cane, but the full use of his right extremities did not return.

Physical examination at this time revealed paresis of the right leg and arm with occasional fine tremors. There was marked tenderness on attempting to palpate the right kidney. The legs and ankles were edematous. The blood pressure was 118/80, temperature 99 to 104, pulse 88 to 100.

On June 2nd a consultant noticed extreme tenderness in the right costovertebral angle and thought it significant of a pyelitis. On July 25th there was ten-

derness on palpation in both lumbar regions. The next day the patient complained of sudden, severe abdominal pain for which no cause could be detected. On Oct. 3rd he was suddenly stricken with agonizing precordial pain which radiated down the left arm. Morphine was administered and the pain was relieved in about half an hour. The next day there was still residual precordial pain, but not nearly so severe as on the previous day.

Laboratory Findings: Wassermann negative; urine 30 pus cells per field, few casts; basal metabolic rate +6; blood smears negative.

The blood counts were as follows:

May 18, 1932, red blood cells 4,250,000, hemoglobin 75 per cent, white blood cells 7000, polymorphonuclears 60 per cent, eosinophiles 27 per cent, mononuclears 5 per cent, basophiles 3 per cent.

July 26, 1932, red blood cells 3,220,000, hemoglobin 47 per cent, white blood cells 12,500, polymorphonuclears 64 per cent, eosinophiles 15 per cent, lymphocytes 16 per cent, mononuclears 5 per cent.

Aug. 23, 1932, white blood cells 16,700, polymorphonuclears 38 per cent, eosinophiles 33 per cent, lymphocytes 27 per cent, mononuclears 2 per cent.

X-ray examination on Aug. 22, 1932 showed no parenchymal pathology in either lung. Moderate enlargement of the left ventricle consistent with hypertensive heart disease was present.

On May 24, 1932, kidney, ureters and bladder studies were not significant of any renal lesion.

On Oct. 8, 1932, the patient left the hospital against his physician's advice. At least twelve special consultants had examined him but no satisfactory diagnosis could be agreed upon. Suggestions included coronary sclerosis, subdiaphragmatic abscess, echinococcic liver cyst, tuberculosis, coccidioidal granuloma, pyelonephritis, Malta fever. Practically all of these possibilities were ruled out conclusively while the patient was hospitalized.

On Nov. 23, 1932, the patient was readmitted for the third time and was brought to the hospital in a comatose condition. He was emaciated, extremely dyspneic and his heart tones were barely audible. He died 1 hour after admission.

Summary of Autopsy

About the base of the cerebellum and around the brain stem the leptomeninges were greatly thickened. The affected area had a greenish gray color that gave it the appearance of being an acute process superimposed upon a more chronic lesion. The entire area was limited to the base of the brain and was thus quite similar to a tuberculous meningitis, but careful search revealed no miliary tubercles.

A few pleural adhesions were found at the left apex but no tuberculosis was in evidence. There was marked edema of the lungs.

A recent fibrinous pericarditis involved the entire pericardial sac and considerable serosanguinous fluid was present. The heart weighed 460 gm., the increase in size being due to left ventricular

hypertrophy. The myocardium was light brown in color and no areas of fibrosis were found. The aortic cusp of the mitral valve had a soft vegetation 5 mm. in diameter attached to the line of contact. The coronary arteries were quite markedly sclerotic but not occluded.

A small infarct was found in the spleen.

The kidneys presented a striking appearance. Each weighed 290 gm., and on section showed a diffusely granular appearance. The capsule was adherent and when stripped left a granular surface. The cortex was thicker than usual.

The adrenals, pancreas, gastro-intestinal tract, bladder and prostate presented no evidence of gross pathology.

A smear taken from the meninges showed numerous pneumococci.

Microscopic Examination

Meninges: There is a marked acute purulent meningitis which overshadows any other pathological condition that might be present.

Heart: The pericardial surface is greatly thickened and infiltrated with large numbers of polymorphonuclear leukocytes, plasma cells and eosinophiles. A small amount of fibrin is present. The small branches of the coronary arteries show a striking change. There is considerable periarterial cellular infiltration of leukocytes, including eosinophiles and plasma cells, which in many instances takes a peculiar bipolar arrangement seen in the photomicrographs. Even more striking is the marked medial and intimal thickening with almost total occlusion of the vessel lumen. The myocardial fibers show surprisingly little evidence of degeneration.

Kidneys: The process in the kidneys is similar to that in the heart but much more pronounced, so that the entire interstitial structure is infiltrated with numerous polymorphonuclear leukocytes, eosinophiles, and fewer plasma cells. The glomeruli and tubules show little change. The arterioles of all sizes are involved and there is more periarterial infiltration than was seen in the heart. Another feature not seen in previous sections is the presence of numerous giant cells around the vessels. These are small in size and contain six to eight relatively large nuclei. The destruction and separation of the various layers of the media are especially well demonstrated in this section.

Liver: Only a few of the larger arterioles show characteristic changes.

Spleen: A typical anemic infarct is found. There is no evidence of polyarteritis.

Pancreas: In the section studied there is one small artery showing changes similar to those noted in the heart and kidney.

Pathological Diagnosis: From the microscopic examination, which, unfortunately, is somewhat incomplete (due to the diagnosis not being suspected at autopsy so that only routine tissue blocks were saved for microscopic examination), this is a case of polyarteritis nodosa affecting chiefly the kidneys and the heart.

Discussion

In this case our failure to make a correct diagnosis of the condition present is instructive enough to deserve some emphasis. Here was a man dramatically ill over a period of nearly 1 year, during most of this period surrounded with competent medical talent, and with all desirable facilities. Yet, as far as we know, polyarteritis nodosa was not once mentioned as a possible explanation of his illness. Even if it had been considered it is doubtful if the diagnosis would have been verified ante mortem, or if the course of the disease could have been altered by its recognition. But this does not justify our failure to consider the possibility of polyarteritis nodosa. It is true that the disease is rare and the clinical symptoms vary, so that we cannot expect positive ante mortem diagnoses in a large percentage of cases. However, as we learn more of its behavior we should come to include it more frequently in our differential consideration of obscure sepses.

Even at autopsy the condition was not suspected. This was due to the fact that in this case only the very small arteries were involved, so that the characteristic nodulations were not noticeable in the gross. Only on microscopic examination of tissue blocks was the positive diagnosis revealed.

Arkin lists the important symptoms observed in his 5 cases as accelerated regular pulse in 5 instances, edema of the legs in 5, septic type of temperature in 4, pain in the extremities, polyneuritis in 4, hematuria in 4, cardiac insufficiency in 3, melena in 3, cerebral symptoms in 2, onset with acute angina in 2, abdominal pain in 2,

and changes in the fundus oculi in 1 case. The clinical findings in our case correspond quite closely with this list, *viz.*, accelerated regular pulse, edema of the legs, septic temperature, pain in the extremities, an acute anginoid syndrome, abdominal pain, a hemiplegic attack, costovertebral pain and tenderness, secondary type of anemia, leukocytosis with eosinophilia, and progressive emaciation.

In all probability the hemiplegic attack that occurred in February, 1932, was due to cerebral arteriopathy, which our histological investigations were not thorough enough to discover. Meningitis has been observed in polyarteritis nodosa, but in this case the meningitis was probably a terminal acute pneumococcic invasion entirely unrelated to the arteritis.

The most striking laboratory finding was the eosinophilia noted in repeated blood examinations. Eosinophilia, however, has not been stressed by other writers and probably is by no means a criterion of the disease.

Polyarteritis nodosa is generally regarded as a progressive and incurable disease. This view is supported by the rapidly fatal termination of most of the reported cases, nearly all of which reveal histological evidences of acute inflammation as well as chronic reparative changes. In spite of this dubious prognosis, there can be no doubt that occasionally the process comes to a halt. Arkin [14] described 1 case of complete histological healing. This patient suffered only one acute illness and then lived 4 symptom-free years before death.

At present it is impossible to judge if any form of therapy can retard the inflammatory changes or assist the healing processes. However, Carling and Hicks [18] used arsenical preparations intravenously and observed consequent remission of symptoms, and this was strikingly confirmed in a recent report by Schottstaedt.[19]

Summary and Conclusions

The term "periarteritis nodosa" does not accurately connote the morphological realities of the disease as we now know them. Dickson suggested "polyarteritis nodosa" as a name for this condition, which seems a more descriptive term, free of misleading implications.

A specific filterable virus with a selective affinity for the small

and medium sized muscular type arteries of the body is probably the cause of polyarteritis nodosa. Any organ or combination of organs may be affected at any time in the course of the disease, and the resulting clinical manifestations may be bizarre in the extreme. The visceral arteries are involved more frequently than those of the extremities, and the organs most commonly affected are the kidneys, heart, gastro-intestinal tract, pancreas, muscles, peripheral nerves, liver, spleen, and cerebrum.

Pathologically the inflammatory changes are not confined to the adventitia and periarterial connective tissue, as originally supposed. All the vascular coats are eventually involved and the primary changes take place in the media. Destruction of the media may give rise to aneurysm formation. Involvement of the intima with rupture of the elastic membrane may produce thrombosis. The process as a rule is progressive and in practically all of the reported cases there has been evidence of acute inflammatory changes superimposed upon the chronic reparative efforts. However, Arkin has described 1 case of histological healing and he believes that in rare instances the process may come to a complete standstill.

Polyarteritis nodosa is seldom diagnosed or even suspected before autopsy, and even at autopsy there may be no gross indications of its presence. The internist should be familiar with the cardinal symptoms of the disease and its notoriously capricious behavior. Then, when the commoner possibilities have been carefully ruled out in a patient with septic manifestations and varied symptomatology, polyarteritis nodosa should be given consideration.

Carling and Hicks, and recently Schottstaedt have reported cases in which remission of symptoms seemed to follow the intravenous administration of arsenicals.

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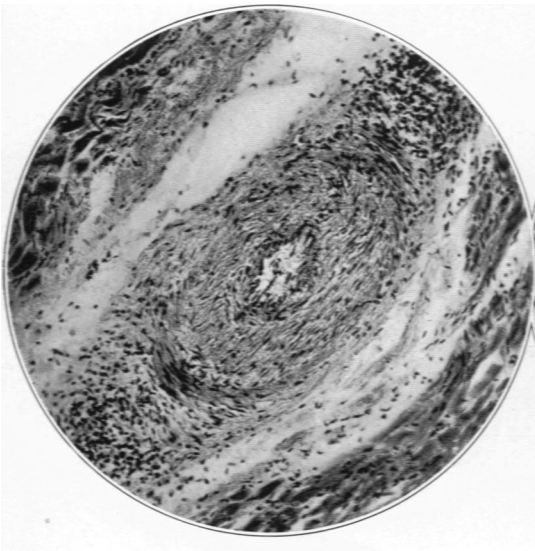
DESCRIPTION OF PLATES

PLATE 95

FIG. 1. Section from heart showing peculiar bipolar distribution of periarterial exudate. × 130.

FIG. 2. Arteriole of kidney showing intense cellular infiltration with separation of muscle layers. × 130.

FIG. 3. Arteriole of kidney showing marked thickening of the wall and giant cell formation. × 130.



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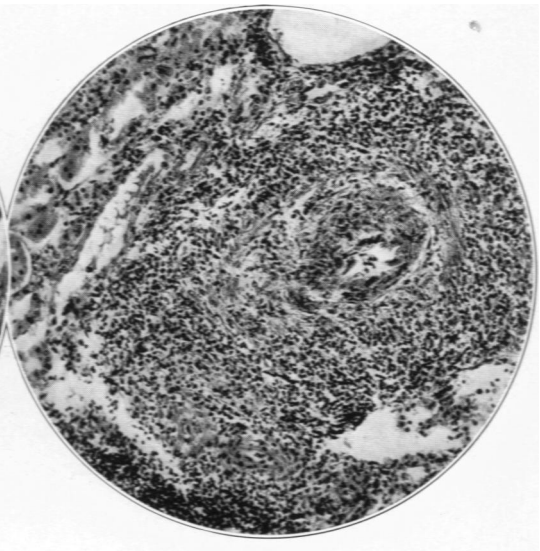

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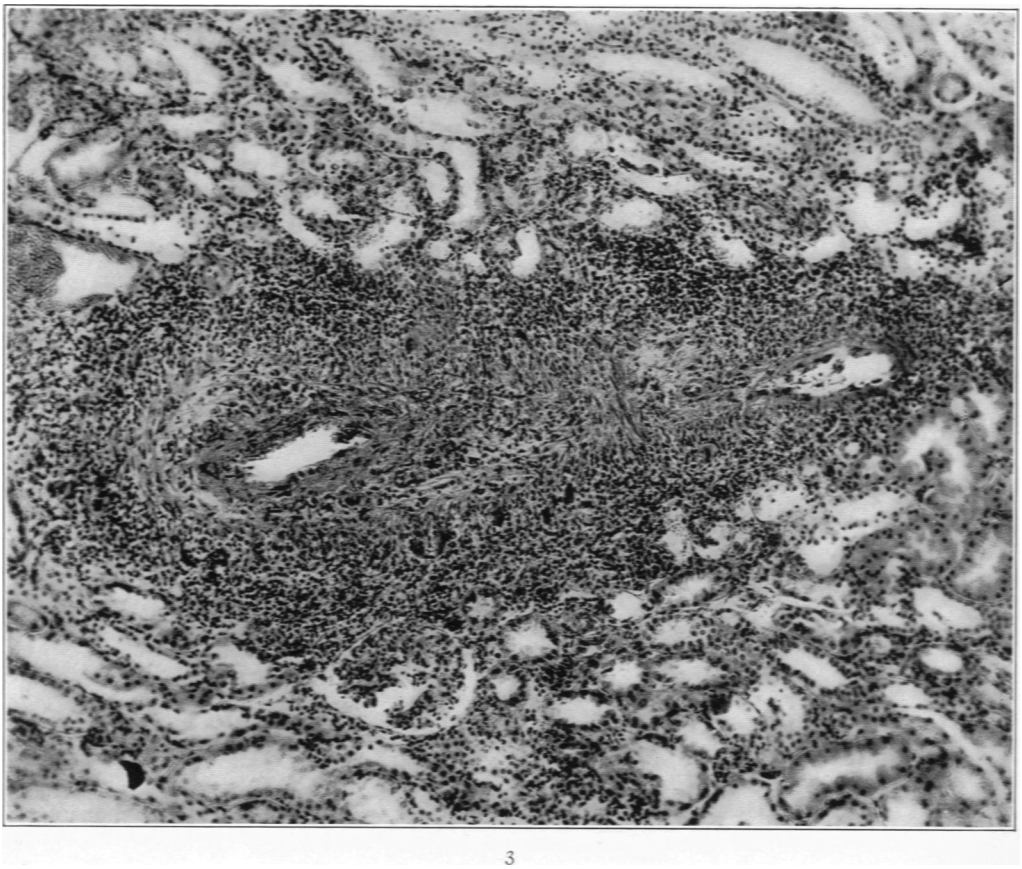

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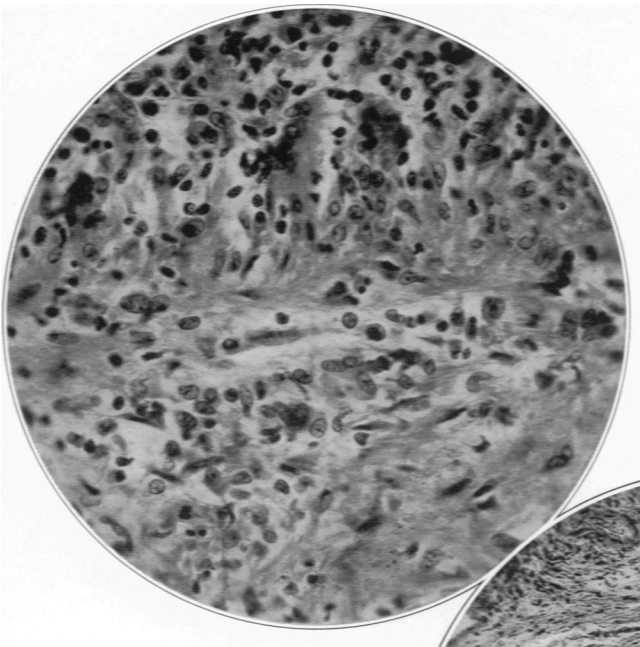
PLATE 96

FIG. 4. High power view of giant cells seen in Fig. 3. × 250.

FIG. 5. Small artery in pancreas showing extreme intimal thickening. × 130.

FIG. 6. Arteriole of liver showing extreme intimal thickening. × 130.



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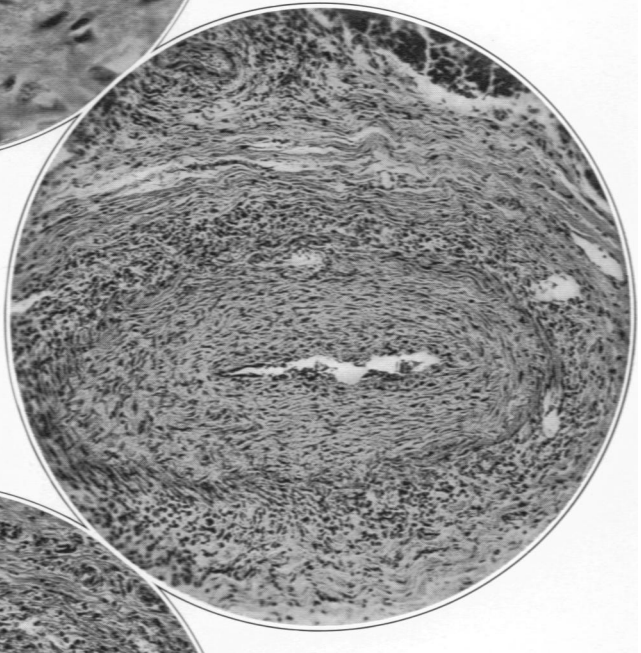

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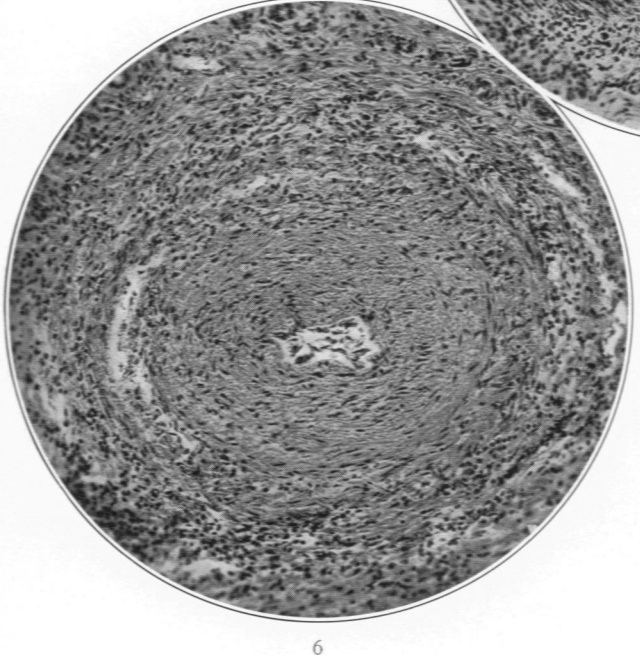

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