POLYARTERITIS NODOSA *

Report of Case

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A patient who had been under observation at the Massachusetts General Hospital for asthma for 8½ years finally died of polyarteritis nodosa. The autopsy findings are considered sufficiently interesting and unusual to warrant reporting the case.

Report of Case

Clinical History: A 30 year old white stenographer entered the hospital for the fifth time with the complaints of fever, pain in the chest, abdomen and joints, and recurring asthmatic attacks. For the 8½ years previous to her final entry she had suffered from recurring attacks of typical asthma. Her four previous entries had all been for this reason, and on three occasions she had been in status asthmaticus. She had been treated by various means, including psychotherapy, without lasting results. There was nothing in the physical examination or laboratory findings inconsistent with the diagnosis of asthma. Her blood had shown an eosinophilia varying between 5 and 13 per cent.

One month before final entry she experienced some nausea and, for the first time, developed pain in the right lower chest and upper quadrant which radiated around to the back. During the next week the pain centered in the left lower chest posteriorly, and she began to have intermittent fever. She also had some stiffness in the shoulders. Three days before entry the elbows and wrists became red, swollen, stiff and painful. The following day painful red spots appeared beneath the nails of the fingers and toes. The evening before entry an asthmatic attack recurred in severe form and the elbows and wrists became very painful. She also had some nausea and vomiting, and had lost about 20 pounds in weight during the previous 4 months.

Physical Examination: This revealed a poorly developed and nourished woman in considerable respiratory distress. The lips and mucous membranes were pale and the nail beds were cyanotic. On the finger-tips and toes were many ham-colored lesions grouped together but not elevated. There were a few similar discrete lesions on the feet, and there were many petechiae beneath the fingernails and toenails and on the abdomen. A few, moist and sibilant râles were present in the lungs. No masses could be palpated in the abdomen, but there was diffuse tenderness and spasm in the epigastrium and right upper quadrant. The wrists were slightly stiff, tender, and painful with movement, and there was slight swelling on the dorsal aspects. Motion of the elbows was very painful so that they could not be fully extended. The blood

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pressure was 95/60, the pulse 120. the temperature 102° F., and the respirations 28.

Laboratory Examinations: The urine had a specific gravity of 1.022, contained 1+ albumin, and showed occasional red cells, white cells and granular and hyaline casts. The blood showed a red cell count of 4,000,000 with 75 per cent hemoglobin and a white cell count of 43,000, with 60 per cent polymorphonuclears, 18 per cent lymphocytes, 2 per cent monocytes and 20 per cent eosinophils. The platelet count was slightly below normal. The guaiac test on the vomitus was negative and on the stool 1+ positive. A blood Hinton test was positive, and a Wassermann test negative. The non-protein nitrogen of the blood was 24 mg. per cent, the protein was 61 per cent, and the chlorides were equivalent to 103 cc. of N/10 sodium chloride. Several blood cultures were negative.

An electrocardiogram showed moderate to marked left axis deviation and was interpreted as consistent with coronary heart disease.

A roentgenogram of the chest showed marked increase in the size of the heart, particularly on the right side in the region of the pulmonary conus. The hilar shadows were slightly increased in width and there was marked increase in the lung markings, particularly in the hilar regions and lower lung fields. Diffuse haziness was present above the diaphragm suggestive of a pneumonic process. Three weeks later another roentgenogram showed disappearance of the apparent pneumonic process with persistence of the other findings. A postmortem roentgenogram showed the hilar shadows to be smaller and the lung markings to be essentially unchanged. In the peripheral lung fields there appeared to be an early miliary process.

Course of Illness: During her stay in the hospital the white count varied between 25,000 and 45,000, the eosinophils rising from the initial 20 per cent to 40 and 50 per cent. The pulse remained elevated although the temperature fell to normal on the 11th day. The abdominal pain continued and spread into both flanks. Both the liver and spleen became easily palpable. She had transient blindness of the left eye lasting for 2 days. On the 36th hospital day she developed severe, migrating neuritic pains in the extremities which caused a great deal of distress. The course of illness was marked by progressive weakness and emaciation, and death occurred on the 45th hospital day. A clinical diagnosis of polyarteritis nodosa was made on the basis of the history of severe asthma, irregularly distributed pain in the joints and muscles, pain in the abdomen and chest, skin lesions, evidence of renal and cardiac damage, emaciation, and marked eosinophilia.

Postmortem Examination

At autopsy no gross arterial lesions were discovered. The terminal ileum and colon showed numerous superficial areas of ulceration which were for the most part oval in shape, measuring up to 1.5 cm. in length, with long axes running transversely.

The heart weighed 325 gm. The right ventricle was somewhat dilated, and embedded beneath the endocardium of the left ventricle was a firm, dull gray nodule measuring 2 mm. in diameter.

Both lungs were similar in appearance. Scattered throughout the parenchyma, most marked in the right lung and least marked in the left upper lobe, were numerous grayish white nodules measuring 0.2 to 1 mm. in diameter, some of which were confluent. In the inferior edge of the left lower lobe was a triangular area of obvious infarction measuring 1.5 by 1 by 0.5 cm. No emboli were found.

In the left lobe of the liver and adjacent portion of the right lobe were large reddish areas of infarction.

The spleen weighed 825 gm. It was very soft and friable and the normal architecture was completely obliterated by almost confluent round areas of soft white tissue measuring up to 3 mm. in diameter with intervening areas of dark red hemorrhagic tissue. The splenic vein and artery were negative.

The adrenals and pancreas were grossly negative, but the kidneys showed a number of small areas of infarction measuring up to 3 mm. in diameter.

Several peripheral nerves and specimens of muscle appeared negative in gross.

The brain showed an area measuring 1.5 cm. in diameter of recently clotted blood in the posterior portion of the left lenticular nucleus.

Microscopic Examination

Microscopic lesions characteristic of polyarteritis nodosa were found in the heart, lungs, liver, pancreas, adrenals, kidneys, muscles, peripheral nerves and brain, but were not found in the ovary, aorta, lymph nodes, intestine or bone marrow. The size of the arteries affected varied considerably but none of them was larger than 1.5 mm. in diameter and few, if any, arterioles were involved. None of the affected vessels could be identified as veins. Although the colon showed extensive ulceration similar to that seen in tuberculosis, no microscopic arterial lesions could be demonstrated. Only ulceration and inflammation of an entirely nonspecific nature was seen. No gross or microscopic lesions were demonstrated in large vessels such as the coronary, mesenteric or renal arteries.

In this study four definite stages of the disease were found: (1) early acute stage; (2) advanced acute stage; (3) granulating stage; and (4) healed stage.

What appears to be the very earliest acute vascular lesion was limited to the vessels supplying the skeletal muscles. It consisted of apparent disintegration of the intima and innermost layers of the media of the arteries with infiltration of these areas by polymorphonuclear leukocytes, eosinophils and fibrin. In some blood vessels the internal elastic lamina remained intact, although it was usually partially destroyed. The middle and outer layers of the media were unaffected, and there was no periarterial thickening or inflammation. Many of the vessels were thrombosed.

Advanced acute lesions also occurred in the muscles, and in the pancreas, brain and nerve bundles. At this stage the intima and inner layers of the media were affected in all cases, and there were varying degrees of disintegration of the internal elastic lamina and muscular coats with loss of architecture and disappearance of many of the smooth muscle cells. The wall and often the adventitia were infiltrated by eosinophils and polymorphonuclear leukocytes. The mural disintegration did not always involve the entire circumference of the vessel. Frequently one-third or more of the circumference appeared perfectly normal with the muscle fibers and elastica preserved in their orderly arrangement. Often apparent aneurysmal dilatation of the affected segments of the vessels was seen, but there was no interstitial hemorrhage, probably because almost all these vessels were thrombosed. The lesions were characteristically segmental in their distribution. Longitudinal sections of the arteries showed involvement of as much as a millimeter of the wall without any damage to the adjoining segments on either side of the lesion.

Granulating lesions were seen in the lungs, adrenals and kidneys. There was ingrowth of fibroblasts into the affected portions of the wall and adventitia with decrease in the numbers of eosinophils and polymorphonuclear leukocytes, and increase in lymphocytes, plasma cells and large mononuclear cells. In this stage the adventitia was almost invariably involved in the process. In the more advanced granulating lesions the necrotic tissue of the acute stage was entirely replaced by cellular fibrous tissue which extended into the adventitia. The areas of the wall unaffected in the acute stage remained normal in appearance. There was also marked thickening of the intima by moderately cellular fibrous tissue, often with complete occlusion. It is difficult to say whether

the appearance was due to organization of a preexisting thrombus with or without recanalization or to intimal proliferation in a vessel that was not thrombosed. In at least a few of the more acute lesions the occluding acute thrombi showed very definite beginning organization, indicating that this process was responsible for some of the luminal occlusion seen in the later stages. An artery in the adrenal showed infiltration of the entire media with densely packed, blue staining, fibrin-like material. The rest of the lesion showed an advanced stage of granulation.

Healed lesions were seen in the liver and heart. In the liver the granulation tissue was replaced by dense, relatively acellular fibrous tissue containing a few pigment-bearing mononuclear cells and occasional foreign body type giant cells. In some of the lesions part of the media of the blood vessels could be identified with the underlying elastica intact. The lumen was almost invariably occluded and recanalized. In the heart all the lesions were healed, and only a few of the smallest arteries were affected. These, however, showed no definite involvement of the muscular layer. Marked fibrous thickening of the intima with partial or complete occlusion, or occlusion followed by recanalization was present. In some, the internal elastic lamina was partially destroyed but in the majority it was intact.

The histological appearance of the spleen was most unusual. With the exception of a few very small follicles around persisting trabeculae, the normal architecture was almost completely obliterated. There was massive infiltration of the parenchyma by large numbers of monocytes and red cells with a few lymphocytes and moderate amounts of fibrin. In some areas the fibrin was arranged concentrically around collections of cells giving a follicle-like appearance. There were no areas of necrosis, no fibrosis, and no suggestion of tubercle formation. Sections stained for tubercle bacilli showed no acid-fast organisms, and material inoculated into guinea pigs failed to produce tuberculosis. Very extensive degeneration of the walls of many of the arterioles was present, but no infiltration by eosinophils or polymorphonuclear leukocytes and no periarteriolar thickening was seen. Many arterioles were almost unrecognizable. Some of them were thrombosed and only a few were normal in appearance. However, no definite specific lesions such as occurred in other organs could be identified. Some

of the small arteries showed infiltration of the adventitia by lymphocytes and plasma cells, and in many of the veins there were small subendothelial collections of mononuclear cells elevating the endothelium and encroaching upon the lumen.

In the lungs were widespread miliary foci of organizing pneumonia involving areas which would normally be occupied by one to ten alveoli, although some of them were considerably larger. These foci consisted of interlacing fibrous tissue with a few mononuclear cells and eosinophils, occasional small foreign body type giant cells, and small amounts of fibrin. No areas of caseation necrosis were present, and no acid-fast organisms could be identified in sections stained for tubercle bacilli. In many of the larger branches of the bronchial arteries measuring 0.5 to 1.5 mm. in diameter were specific lesions in the advanced stage of granulation, most of which were located near the hili. In some of the pulmonary arteries were lesions that appeared to be organized mural thrombi. They were suggestive of specific lesions, but without destruction of the arterial walls or infiltration by inflammatory cells they could not definitely be considered as such.

Varying stages of ischemic necrosis were present in the heart, liver, kidneys, adrenals and pancreas. However, the stages of infarction did not necessarily correspond with the apparent age of the corresponding arterial lesions. In the heart where the arterial lesions were healed were a few areas of acute necrosis of the muscle bundles, although there were present also numerous small areas of healed infarction. In the liver all the infarction was early; whereas the majority of the arterial lesions were healed. In the kidneys areas of early infarction and also areas where the tubules were degenerated without damage to the glomeruli or interstitial tissue were present. The adrenals showed several areas in the cortex where the cortical cells were completely replaced by macrophages filled with fat. A few small areas of early ischemic necrosis were seen in the pancreas.

Comment

In all the arterial lesions observed there was some degree of damage, with or without repair, of the intima and almost invariably of the inner layers of the media. Aside from the evidence already offered this would indicate that in this case the primary lesion

occurred in the intima and progressed outward through the wall to the adventitia.

Arkin [1] has classified the lesions in four stages. The first is an alterative degenerative stage. The elastica interna and innermost layers of the media become edematous and infiltrated by a thready fibrinous exudate, and part of the muscle layer of the entire wall undergoes a coagulation necrosis with beginning infiltration by leukocytes. This stage corresponds roughly with the early acute stage described in this case but differs from it in that the lesion is not confined to the innermost layers of the artery. Arkin's acute inflammatory, granulation and healed stages correspond to the three later stages described in this case.

In any inflammatory process progression from the acute to the healed stage occurs, and the lesion of polyarteritis nodosa is no exception to this. The effect of the toxic agent is limited by the inflammatory response, and greater or less damage is done depending on the various factors operative in each individual instance. The extent of the healed lesion depends directly on the amount of damage done in the acute stage.

An unusual feature of this case was the coincident existence of all stages of the arterial lesions. In many of the cases reported [2-8] with detailed descriptions of the histological findings, the lesions showed some variation in their stage of development, but in this case variation from the earliest acute to the healed stage was observed. However, with one exception this marked variation did not occur in the individual organs. Except in the liver, all the arterial lesions of each individual organ were roughly in the same stage. Only acute lesions were seen in the pancreas, brain, muscles and nerve bundles; only granulating lesions were seen in the lungs, adrenals and kidneys; and only healed lesions were seen in the heart. The majority of the lesions in the liver were healed, but a few were acute. This restriction of lesions to one stage in the individual organs cannot be readily explained. From a purely speculative point of view it may possibly have some bearing on the pathogenesis of the disease. Although the lesions are widely distributed throughout the body with the primary damage to the arteries, each individual organ as a whole may have a specific reactivity or resistance which determines its response to the toxic agent.

The lungs in our case showed an unusual X-ray appearance similar to findings in the case reported by von Conta [9] (quoted by Spiegel [10]), and in the case reported by Herrman [11] and Wiener.[4] Von Conta described shadows ranging in size from "a lentil to a cherry" located near the hilus with specific lesions of the pulmonary arteries at autopsy. Herrman and Wiener described a diffuse perivascular infiltration spreading out uniformly and equally from both hilar regions with specific lesions of the bronchial and pulmonary arteries. In this case the hilar shadows were slightly increased in width with marked increase in the lung markings, particularly in the hilar regions and lower lung fields. A postmortem film showed a generalized early miliary process. At autopsy there were numerous specific lesions of the bronchial arteries near the hili with miliary foci of organizing pneumonia throughout the parenchyma. The pulmonary arteries and peripheral branches of the bronchial arteries showed very little involvement. This appearance by roentgen examination of perivascular infiltration spreading out from the hilar regions may be helpful in establishing the diagnosis in a suspected case of polyarteritis nodosa. It cannot, of course, be considered diagnostic.

The gross appearance of the spleen was the most striking feature of the case at autopsy. It was enlarged to more than four times its normal size and showed lesions suggestive of very extensive tuberculosis of an unusual variety. Microscopically the entire organ was involved by a hemorrhagic, apparently inflammatory process, which had no resemblance to tuberculosis or any other specific disease.

The gross autopsy findings as a whole simulated tuberculosis more closely than any other condition. The miliary process in the lungs, the splenic lesions, the small infarcts in the kidneys, and the ulceration of the colon gave a combined picture which could well have been produced by widespread tuberculosis. The infarcts of the liver, the cerebral hemorrhage and the absence of any primary focus of tuberculous infection were, of course, incompatible with the diagnosis.

A note may be appended about nomenclature. Many of the older writers, including Lamb,[12] believed the lesion to be primarily periarterial. More recent evidence presented by numerous writers and the findings embodied in this report make it reasonably cer-

tain that the lesions are not primarily periarterial. In 1907 Dickson [13] suggested that the name polyarteritis nodosa be adopted. Periarteritis nodosa is, without much question, a misnomer and for that reason should be dropped. Polyarteritis nodosa would be a suitable substitute.

SUMMARY

A case of polyarteritis nodosa is reported with clinical findings which made possible an accurate clinical diagnosis. The outstanding symptoms and signs were a history of severe asthma, irregularly distributed pain in the joints, muscles, abdomen and chest, skin lesions, evidence of renal and cardiac damage, emaciation and marked eosinophilia.

A detailed description of the gross and microscopic autopsy findings is given with comments on a number of unusual features of the case. These unusual features are: (1) Evidence that the primary lesion occurred in the intima and inner layers of the media and progressed outward through the wall to the adventitia; (2) occurrence of all stages of arteritis from the earliest acute to the healed, but restriction of the lesions in each individual organ to roughly one stage; (3) remarkable parenchymatous lesions of the lungs and spleen; and (4) resemblance of the gross autopsy findings to widespread tuberculosis.

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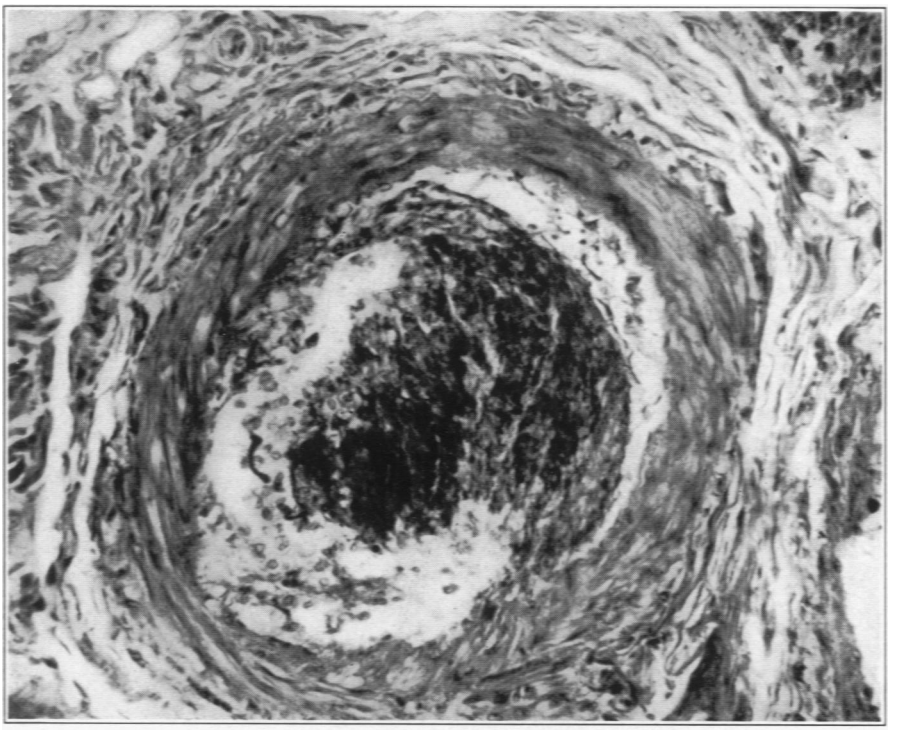
DESCRIPTION OF PLATES

PLATE 18

FIG. 1. An early acute lesion in a small artery of the biceps muscle. The intima and inner layers of the media are disintegrated and the lumen is occupied by a recent thrombus. There is no degeneration or cellular infiltration of the outer layers of the media, and no periarterial inflammation. Phloxine-methylene blue stain.

FIG. 2. A somewhat more advanced acute lesion of an artery 1 mm. in diameter in a nerve bundle. In the upper part the destruction of the wall is almost complete and there is beginning periarterial inflammation. Phloxine-methylene blue stain.



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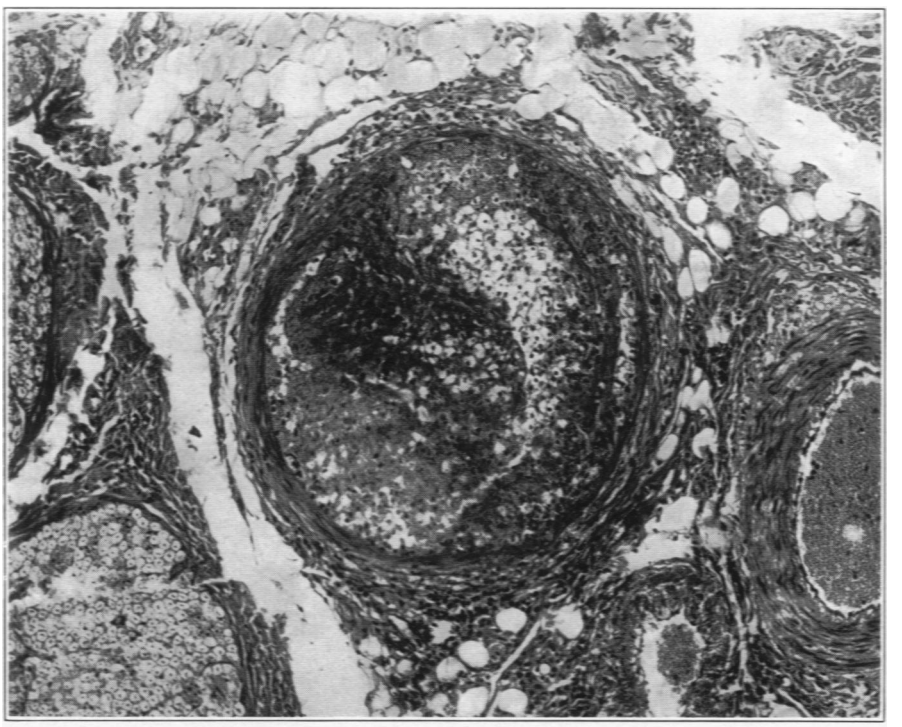

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PLATE 19

FIG. 3. A granulating lesion of an artery 1 mm. in diameter in the kidney. There is almost complete destruction of the media except for a small area on the right where a segment of persistent media can be made out between the elastic lamellae. Verhoeff's elastic tissue stain.

FIG. 4. An advanced granulating lesion of a bronchial artery 1 mm. in diameter. Most of the inflammatory cells have disappeared and many small vessels have developed, partly in the granulation tissue which has replaced the media, and partly as recanalizing vessels in the thrombus. Verhoeff's elastic tissue stain.

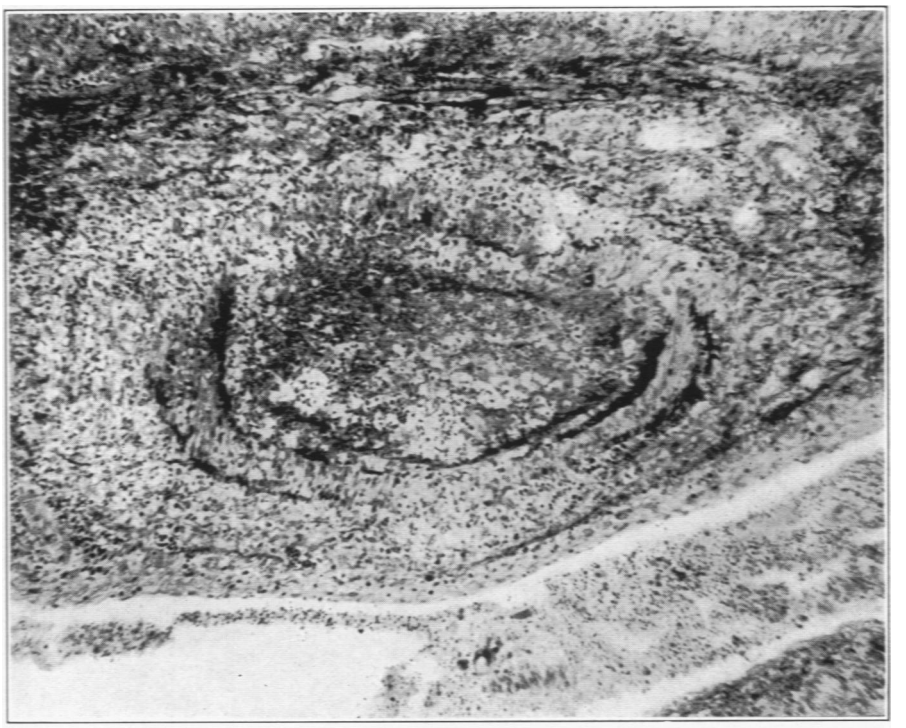

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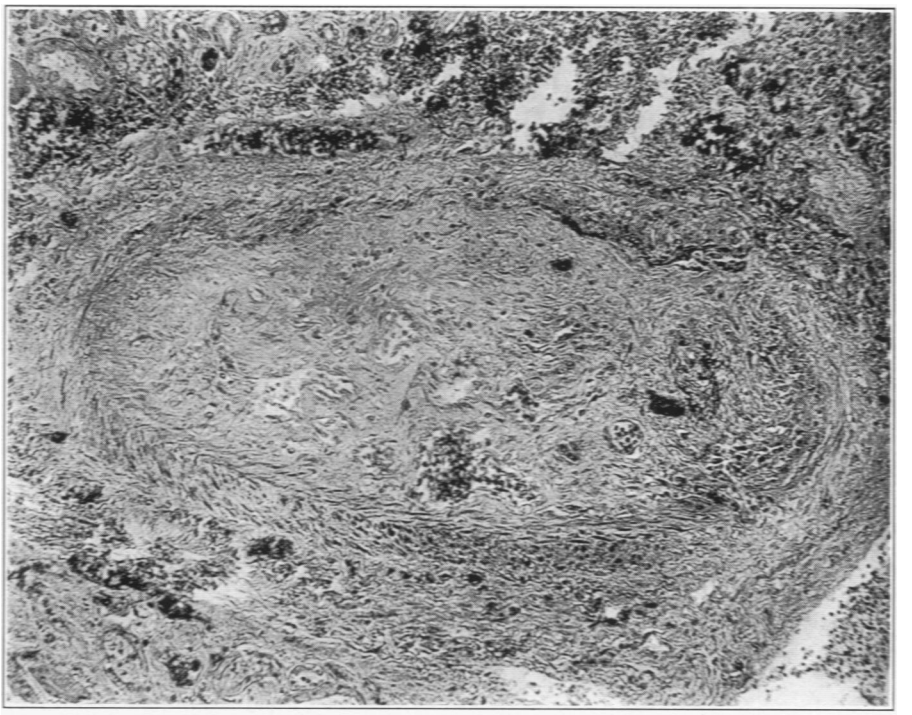
PLATE 20

FIG. 5. An advanced granulating lesion of an artery 1 mm. in diameter in the kidney. Most but not quite all the inflammatory cells have disappeared. Some of the smooth muscle of the media is preserved. Phosphotungstic acid hematoxylin stain.

FIG. 6. An almost healed lesion of an artery 1.5 mm. in diameter in the liver. Several foreign body giant cells are seen in the wall. Hematoxylin-eosin stain.



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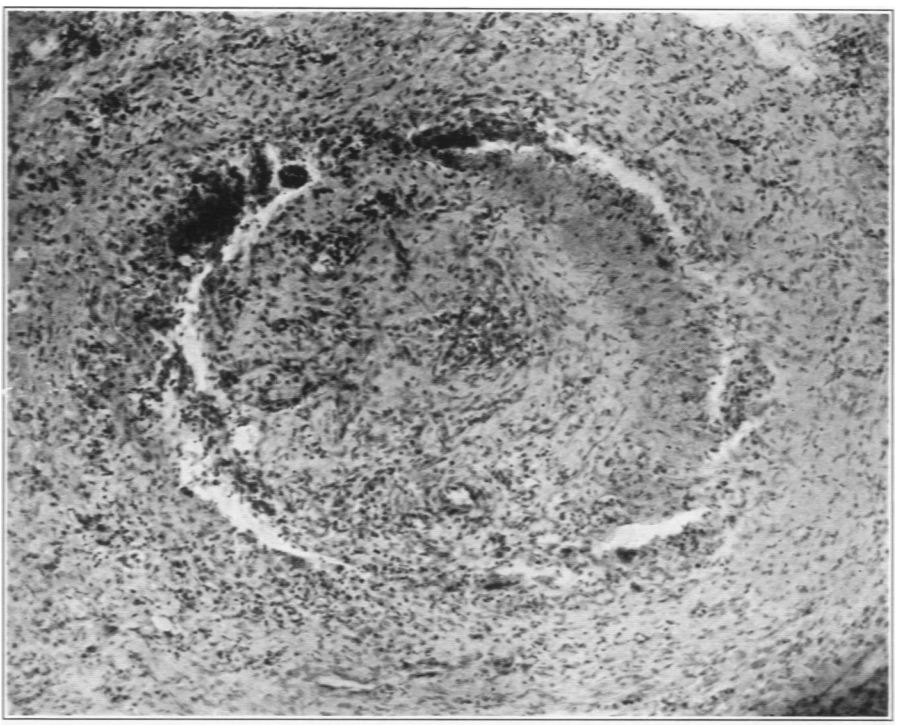

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