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PERIARTERITIS NODOSA.*

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Up to the present the literature contains the reports of fifty-two cases described as periarteritis nodosa. In addition to these there are probably a number of others which, having been encountered in the early or late process of development, were not recognized as belonging to this peculiar disease of the arteries. On the other hand, some confusion has developed in the use of the term periarteritis or polyarteritis in that a number of authors, not clearly recognizing the individuality of the lesion, described cases of clearly syphilitic origin as types of this condition. We have to-day come to appreciate clearly enough the peculiar clinical and pathological picture in the true forms of periarteritis nodosa to exclude the specific syphilitic nodular arteritis from this group. Hence we are bound to reduce the above number of reported cases to forty-three by omitting the syphilitic cases of Wilks, Pellizari, Baumgarten, Gilbert and Lion, Bruce and Raymond. There can be no hesitation in dropping these cases from discussion, even though the authors define them under the term periarteritis nodosa. Rokitansky's case was the first to be observed, but a clear description of the disease and its pathology was first offered by Kussmaul and Maier in 1866. Their case was clear cut and with it subsequent findings were easily compared. Taking the character of the

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disease as described by Kussmaul and Maier (Case I.) as our guide and dealing only with such in which the diagnosis was fully established by autopsy or microscopical section, there remain forty cases. It is possible that Case II. of Kussmaul and Maier as well as those of Benedict and Sabin may have been of this nature, but as the cases were only clinically observed and the diagnosis rested upon a study of the excised skin nodules, some doubt still remains as to the exact nature of the process.

The mortality as indicated in the study of the forty undoubted cases is one hundred per cent, not including the case reported by Schmorl, dying after an interval of two years of portal thrombosis. This is rather astounding, particularly in view of the fact that the disease has no prominent symptomotology and the apparent progress of the clinical events does not indicate that we are dealing with virulent infection. This high mortality is rather to be viewed in the light that only the fatal cases are properly diagnosed and reported. As the typical lesions are found upon the vessels of internal organs, the skin being involved in only a few cases, no opportunity is given the clinician to analyze the lesions. The clinical diagnosis was made in four cases, one of which died and was verified at autopsy (Schmorl). This rather grave outlook for the proper recognition of periarteritis nodosa must also be viewed from another angle, which is this: Periarteritis nodosa is not a disease entity, but is only a complication of lesions present in an infection which has many other manifestations. As one reviews the well-studied cases there are many points of similarity strongly suggesting a common bacterial infection which, be it through chance or because of a previous preparation of the soil, has led to a localization in and around the arteries. Undoubtedly in many instances a similar localization and infection of milder character involves various systems of the arteries, but in the absence of marked clinical signs or serious pathological change, the cases proceed to recovery without our attention being called to the characteristic lesion. It would appear to us, as we will point out later, that the condition is,

in its mild form, not so uncommon during rheumatic fever and rheumatoid affections.

The term acute nodose periarteritis has been well selected to describe the pathological picture of the cases coming to autopsy. It must be remembered, however, that where recovery takes place and the lesion is examined at a later period the nodose lesion is a fibrous one devoid of all evidence of acute inflammation. The process is one essentially affecting the small arteries, more particularly of the kidney, stomach, mesentery, liver, and heart, occasionally of skin, thyroid, lung, brain, and spleen. The aorta and its main branches show no involvement, in as far as a naked eye recognition of inflammation and degeneration is concerned. Clinically the symptoms vary so greatly that no characteristic picture can be drawn. The most characteristic features are the presence of rheumatoid pains in the muscles and joints, occasional sore throat, some temperature, indefinite colicky pains of the abdomen leucocytosis and an albuminuria. At times this clinical picture is overshadowed by the presence of cardiac lesions, endocardial, myocardial, or pericardial. For a review of the reported cases up to 1914, I would refer the reader to an excellent article by Lamb. Prior to this, two thorough analyses of the clinical and pathological findings were made by Dickson and Longcope (1908). These previous studies have well outlined the pathological findings, showing a remarkable similarity in the reports based upon the observations of different authors. It might be said that the description of the lesions as found in man has been completely detailed and requires little further addition. It is, however, equally patent that the different attitude of the various observers has led them to place varying importance upon factors and processes so that the final interpretations and conclusions are not in thorough agreement. The part played by syphilis is still debated, while the question of the localization of the initial insult, whether in intima, media, or adventitia, has also led to considerable polemic. More important than these, and yet having received meager attention, is the question why particular

groups or systems of arteries have been picked out by the materies morbi for localization.

We have been interested in diseases of the arteries and have for a long time been on the lookout for a case of periarteritis nodosa. In a series of over three thousand autopsies no case came under our observation until recently when, within four weeks of each other, two came to autopsy. Every advantage was taken of the material and, as neither case had been diagnosed during life, further information was sought for the clinical history to cast as much light as possible upon this indefinite condition. In each instance the patient sought the hospital for aid in conditions not suggesting acute vascular or circulatory disturbances. One would expect that the information obtained from a study of the clinical and pathological findings of the first case would have been an assistance in establishing a proper diagnosis for the second. This, however, was not the case even in the face of the fact that the arteries mainly involved in each were almost identical and that the cause of death, arterial rupture into the peritoneum, was the same. The one striking feature of difference, however, was that there were some subcutaneous nodules in the second case which were not present in the first. The detailed history and findings in those two cases are as follows:

Case I. — E. S. (under the service of Dr. J. I. Johnston), an unmarried woman of 33 years, employed as a music teacher, was admitted to the Mercy Hospital on November 8, 1916, complaining of pain over the abdomen, radiating to the anterior and posterior chest wall. *Past history:* There was nothing important in the history of the family, all of whom are living and well. As a child she had measles, chicken-pox, diphtheria, mumps, and whooping-cough. She has had two attacks of pneumonia, at the ages of 18 and 24, respectively. At the age of 27 she had an attack of typhoid fever. On several different occasions she suffered severe attacks of tonsilitis. In her work as a music teacher, she has had many pupils who at times made her very nervous. Her menstrual history is unimportant. For many years she has suffered constipation. *Present illness:* Three weeks prior to admission she became chilled while out in cold weather and developed severe pain in the back

and loins. With the application of heat, the pain was relieved. A few days later she was again exposed to a rain-storm, so that she was wet from head to foot. On the following day she suffered severe pains in muscles and joints as well as in the region of the stomach. The pains were of a piercing nature. The pains of the abdomen were cramp-like, and of great severity. She was unable to retain food in the stomach and she would have periods of vomiting, unassociated with the taking of food or medicine. The pain in the loins reappeared with greater severity than at the first attack. *Physical examination:* The patient was quite restless as she lay in bed. Examination of the eyes, ears, and nose was negative. The teeth were only in fair condition, showing some pyorrhea. The fauces and throat were quite injected and swollen. There was no glandular enlargement of the neck. Examination of the heart and lungs showed nothing abnormal. The abdomen was rather pendulous; the tissues being well supplied with fat. Tenderness was elicited in the right upper quadrant, and particularly in the region of the gall-bladder. It was thought that a soft mass could be palpated in this area. There was also some tenderness in each flank. The liver and spleen did not appear enlarged.

November 8, 1916: The heart sounds were weak, but no murmurs were found and there was no increase in size. The lungs were negative, the liver not enlarged upward, the spleen not palpable. There was no fluid in the abdomen and the patient was tender all over, but particularly in the right upper quadrant. There had been a history of vomiting and upper abdominal pain.

November 9, 1916: The leucocytic count was 12,000 with 76 per cent polymorphonuclear cells. The patient's scleræ showed slight icterus. There was no further vomiting and the tenderness over the abdomen was more localized in the right upper quadrant, the distention of the abdomen having been relieved by enema.

November 10, 1916: On this day the abdomen was soft and all tenderness except over the gall-bladder was gone. A diagnosis of cholecystitis with acute exacerbation and possibly empyema of that organ was made. The liver dulness extended to the fourth rib and down to the costal margin.

November 12, 1916: All signs pointed to empyema of the gall-bladder, and the opinion of a surgeon was advised. The gall-bladder was palpable and tender; and the patient, while feeling much better and asking for food, showed slightly increased icterus about the scleræ.

November 13, 1916: The patient developed pain and tenderness of a severe type in the right elbow, accompanied by sore throat, but by no apparent swelling. The whole picture, including throat, gall-bladder, and joint, was looked upon as a Streptococcus viridans infection. The proposed consultation with surgeon was then postponed.

November 14, 1916: The patient was improved on this date and little complaint was made of the elbow. No consultation with the surgeon was then held. About 5 P.M. on this date the patient, with very slight complaint of additional pain, went into collapse and died from shock in about fifteen or twenty minutes.

During the period in which the patient was in the Hospital, the temperature was continuously high, ranging from 100° to 103° F. There were no remissions in this temperature, and it never had a septic character.

The urine was repeatedly examined and found to have a high specific gravity, 1,030; was acid, had a moderate amount of albumin and showed the presence of pus cells and granular casts.

The clinical diagnosis was given as acute cholecystitis.

A blood culture taken at the time of death was negative.

Autopsy. — Dr. D. G. Richey (four hours after death): The body was that of a middle-aged, white female, measuring 162 centimeters in length. The body was well developed, slightly jaundiced, and very obese. The scleræ were yellow, the pupils were equal, dilated, and measured 7 millimeters in diameter. There was a slight amount of pyorrhea alveolaris. There was no rigor mortis, and only a slight amount of lividity could be seen over the dependent parts. The thorax was well formed. The abdomen possessed a slight rotundity and was dull on percussion. The external genitalia were normal in appearance. There was no edema of the extremities or scars upon the body.

Thorax: There was no excess fluid in either pleural cavity. Numerous tough fibrous bands of adhesions occurred along the lateral and diaphragmatic surfaces of both lungs. The pericardial sac was quite thin and contained about 20 cubic centimeters of clear straw-colored fluid. On the right side the upper border of the liver extended to the fourth interspace, while the heart had rotated somewhat on its transverse axis and its upper border lay under the second rib in the left parasternal line.

Lungs: The left weighed 340 grams. The surface of the lung was for the most part smooth, except for the fibrous tags of adhesions on the lower lateral and diaphragmatic surfaces. It was of a bluish-gray color and the posterior portion showed some lividity. The lymph nodes at the hilus of the lung were slightly enlarged, but were quite soft and moist and showed no areas of caseation or fibrosis. The lung was fairly anthracotic and crepitated throughout, though in the posterior portion it was somewhat congested. All sections floated in water. The bronchi were reddened and showed a small quantity of frothy yellowish mucus covering the mucosa. The vessels were clear. No evidence of tuberculosis was noted in the organ. The right weighed 225 grams. This organ resembled its fellow in all respects.

Heart: Weight 208 grams. The pericardial surface contained large, irregular masses of fat and the coronary vessels were well marked. The heart muscle was rather flabby and soft. It was dark in color and quite glassy in appearance. The ventricles were empty. The chambers were not dilated. Some fatty plaques could be seen on the aortic and mitral valves. The coronary arteries also showed this condition. Otherwise the heart valves were clear. The F. O. was closed. The A. O. measured 6.8 centimeters, M. O. 8.7, T. O. 9.2, P. O. 6.2, L. V. 2.2 centimeters.

Aorta: The aortic wall was of moderate thickness and quite elastic, and showed a large quantity of fatty streaking of the intima which extended throughout its whole length, greatly predominating along the posterior wall. On the external wall of the aorta, and particularly in the vicinity of the arch and the first part of the descending thoracic, were found a number of small petechial hemorrhages lying in the adventitia and to some extent infiltrating the connective tissue of the vicinity. These hemorrhages formed small blotches, varying from a pinhead to .75 centimeter in diameter. A similar hemorrhagic blotch was also seen at the main stem of the celiac axis. The adventitia of the abdominal aorta was free from this process.

Abdomen: The abdominal wall was very thick, due to a panniculus adiposus measuring 9 centimeters. On exposing the peritoneum, large, irregular, blotchy areas could be seen beneath it. On opening the peritoneum, which was quite thin, the cavity was found virtually filled with dark red blood forming large gummy clots between the intestinal coils. The lower border of the liver was pushed upwards under the ninth rib in the R. N. L. The small intestine was quite flat and there was no sign of peritoneal irritation throughout the abdomen, all surfaces being smooth, moist, and glistening. The great omentum was spread over the greater part of the coils of the intestine. It was very fatty. No enlarged lymph glands could be found in the very adipose mesentery. The diaphragm arched to the second rib on the right side and the third rib on the left side. Over the right lobe and upper surface of the liver, one could see a large oval dark red area, simulating a sub-capsular hemorrhage, which extended to the extreme border of the right lobe. The capsule over the area of hemorrhage was very friable and could be ruptured with ease. No adhesions could be found in the abdomen, except some recent blood clot between the upper surface of the liver and diaphragm.

Stomach: The stomach was not enlarged. The serosal surface was quite smooth and free from adhesions. When opened, the stomach contained a fair amount of thin fluid, which was free from bile. The gastric wall was of normal appearance. The mucosa was fairly thick, indistinctly mammillated and pale. There were no ulcers. The pylorus was healthy.

Intestines: The duodenum, in all its portions, was free from any demonstrable lesion. The bile papilla was rather prominent and presented a slightly reddened appearance. A probe could be easily passed through it, far into the lumen of the common bile duct. The rest of the small intestine showed nothing of particular note. The mucosa was smooth, pale, and pinkish in color. No hyperplasia of Peyer's patches was present. No ulcerations could be made out. The appendix presented a smooth surface and was free from adhesions. It measured 7.8 centimeters in length. The large bowel was similarly healthy throughout its length. The mesentery of the small intestine was very fatty, but showed no change in its vessels or lymphatic structures.

Liver: Weight 2,130 grams; measured 29 x 20 x 8.6 centimeters. The liver was enlarged and felt very soft. On looking down upon the liver in its normal position there was a diffuse red hemorrhagic area under the capsule extending from the costal margin to the diaphragm on its right lateral aspect. The surface of this portion of the liver was irregular and lumpy from coagulated blood. On examination the finger easily passed through the capsule into a mass of blood clot which appeared to lie directly between the capsule and the liver substance. There was no evidence in this hemorrhage of any purulent exudate. The remainder of the superior surface of the liver was smooth, excepting that here and there, particularly in the left lobe, slight, white, fibrous thickenings of the capsule were observed. These fibroses were particularly well marked on the under surface of the left lobe. In places they appeared almost like ridged scarrings. Along the inferior margin of the left lobe there were one or two small fusiform bulgings. These, on section, showed small discrete globular thromboses varying in size from a pea to a bean. The blood in them was clotted and appeared to lie within a vessel wall. In some of these areas there was also some extravasation of blood into the surrounding tissue. The inferior margin of the liver was a little rounded. On removing the liver it was seen that the capsule over the hemorrhagic area on the right lateral surface showed a large tear, from which blood could be expressed. This tear was about 8 centimeters in length. The capsule over this area of hemorrhage could be very easily lifted up and removed. It had been completely separated over almost half of the right lobe by this sub-capsular hemorrhage. The capsule itself was not thickened. The sub-capsular blood clot in places was 1.5 centimeters in thickness. The liver substance appeared intact, showing no evidence of rupture save at one point on the right lateral surface, where the blood clot seemed to be closely adherent and run directly into the liver substance. At this point it appeared that the liver substance was replaced by a mass of blood communicating with the surface. On section into the liver substance at this point, the hemorrhagic area was seen to be pyramidal in shape and extended into the hepatic tissue obliquely in an upward direction. On removal of the gummy blood clot, the wall of the cavity was

dark red, quite friable, and consisted of denuded liver tissue. On section through the liver the tissue had a dull, rather yellow, soft, somewhat mushy character. The general markings of the liver, particularly the lobules, were indistinct. The liver tissue was very easily pitted with the finger. Throughout the liver there were numerous small localized hemorrhages. Some of these hemorrhages were irregular in outline, while others appeared round, and on closer examination were seen to be enclosed in thin vascular walls. Numerous thrombosed vessels were observed. These thromboses were made up of fairly recent red blood clot, but many of them also showed on the side adjacent to the vessel wall a white, partially organized material, which was adherent to the wall. Furthermore, most of the thromboses lay in aneurysmal dilatations of the vessel. In some sacs the wall was very thin and undoubtedly some of the hemorrhage, which appeared devoid of a vascular connection, represented a rupture of these aneurysmal dilatations. The type of structure in which these dilatations occurred was not at first clear. They appeared to be associated with Glisson's capsule. The portal vein was clear in its main stem as well as its branches. The bile ducts also did not show evidence of inflammation. Occasionally, a connection between the hepatic artery and one of the aneurysmal dilatations could be followed out. Some of these dilatations were almost as large as a hazel-nut 1.5 centimeters in diameter. The majority, however, were pea-sized, being 4 to 5 millimeters in diameter. The portal vein at the base of the liver was clear. The main hepatic artery showed a peculiar ridging along its intima, which was firm and had the appearance of an organized exudate. Section of the vessel showed considerable thickening of its wall, made up chiefly of an organizing exudate upon the intima. The common bile duct at the base of the liver was clear. The portal systems throughout the liver substance showed a very prominent Glisson's capsule, and on a little pressure a yellowish bile could be expressed from the duct. Even the smaller hepatic vessels appeared to have thicker walls than normal. There was no bile pigmentation of the liver substance. The left lobe of the liver on account of the prominent Glisson's capsule of the portal system had a moderately fibrosed appearance. There was no bile-staining of the connective tissue, but the portal systems appeared a little glassy and swollen. On numerous sections through the liver it was seen that these aneurysmal sacs filled with blood clot were widely distributed and abundant. There were twenty-eight such dilated sacs of the hepatic artery found in the liver substance.

The gall-bladder was enlarged and presented a fairly smooth surface, with some fine fibrous adhesions bridging between it and the liver. The peritoneal surface was of a dull reddish hue and at one place on the right side in the middle third could be seen a small oval projection which had a blue center with a red areola. This projection felt very firm. On

opening the gall-bladder it was seen to contain about 15 cubic centimeters of a yellow bile. The lining of the gall-bladder was smooth and brown in color. The gall-bladder was thickened by edema, most of which seemed to be in the serosa. The firm mass just described was seen to be a large thrombus which extended from the tip of the gall-bladder to the base. At this point it had been cut across on removing the gall-bladder. The thrombus was red in color, firm, and showed evidence of organization about its edges. It lay in a much dilated vascular channel (cystic artery), which showed a very thin wall. In appearance this vascular channel had exactly the same characters as the aneurysmal sacs seen in the liver. A probe could be passed from one end of the vessel through the open cut end at the base of the gall-bladder. At the tip of the gall-bladder the end of this large dilated channel was seen as a very thick-walled artery, much larger than is usually seen in this situation. At the opposite end, where it had been cut across, the vessel was 2 centimeters in circumference. The cystic duct and the hepatic and common bile ducts appeared healthy. The portal vein showed no thrombosis.

In following the hepatic artery from the hilus into the liver a very remarkable appearance was found. Not only was the vessel of irregular external outline with occasional saccular enlargements involving its whole circumference, but on looking at the inner surface of the vessel the intima appeared curiously scarred and corrugated, frequently showing pits and longitudinal depressions, so that at first sight one was reminded of some of the characteristics of lues. As the vessel extended into the liver occasional stretches of intima were found to be fairly smooth, but then again in the midst of a fairly healthy looking surface would be found an outward pit like a little mouth entering a sac lying outside of the vessel. The appearance of some of these sacs suggested the development of false aneurysms in some situations. Some of these sacs when viewed from the outside had the appearance of a bright red berry attached to the structure of Glisson's capsule. The amount of reaction around the course of the hepatic artery and about the saccular dilatations varied greatly. In some places there was a certain amount of diffuse, pearly, fibrous tissue apparently of recent origin as observed in its succulent character.

Pancreas: Weight 75 grams. The pancreas was 18 cubic centimeters in length. It was of good size and was removed with the duodenum. It had a normal lobulated appearance. On section through the pancreas, the tissue in all portions was yellowish gray, quite firm and healthy. Its ducts and arteries were patent and clear.

Spleen: Weight 130 grams; measured 13.3 x 7.2 x 2.8 centimeters. The organ was of a dark red color and showed several small notches along its convex border. The surface was smooth, finely wrinkled, and glistening to the touch. The splenic substance was soft and mushy.

The cut-surface was moist and the stroma indistinct. The cut edge everted slightly. The Malpighian tufts were recognizable. On scraping the surface large quantities of pulp could be removed. On pressure the structure broke readily, being quite friable.

Left kidney: Weight 141 grams; measured 11.8 x 6.8 x 3.1 centimeters. The capsule peeled quite readily and the surface was left smooth and intact. The surface was a pale pinkish gray in color and showed some slight fissuring. Minute red points could be seen on close examination to stud the renal surface. A few slightly congested blood vessels were noted. On section, the cortex and medulla were well defined. The intermediary zone was slightly darker than either. The cortex was of good thickness, pale pink in color, and many very small red capillaries could be seen arranged in a radial manner. Here, also, the glomeruli appeared as small red pin-point projections. The medulla was pale and presented no striking peculiarities. A large quantity of fat surrounded the renal pelvis.

Right kidney: Weight 135 grams; measured 11.2 x 6.8 x 3 centimeters. The organ was very much like its fellow in every respect.

Adrenals: Weight, 15 grams. The organs were flat and firm. On section the medulla was rather thin. The cortex likewise was thin and showed numerous opaque, yellow, fatty areas. The organs presented a healthy appearance.

Bladder: The bladder was smooth-walled and pale. The mucosa was quite healthy in appearance, though somewhat trabeculated. The openings of the ureters were patent and healthy.

Genitalia: The vagina was small and quite normal. The cervix was of the nulliparous type, being quite small, of normal contour and free from erosions. The uterus was noticeably small in size, measuring 4 x 3 x 1.4 centimeters. The walls were quite thin and the uterine cavity showed nothing of note. The adnexa showed normal structures, save for a few follicular cysts in both ovaries. One hemorrhagic cyst was also noted in each ovary.

Microscopical.

Lung: In some portions the alveolar walls were intensely congested; in other places, the congestion was lacking. Otherwise the tissue was quite healthy looking. The pulmonary vessels showed no evidence of inflammatory change. The adventitial tissues of the vessels showed no evidence of infiltration.

Heart: The muscle fibers appeared fairly healthy. There was some evidence of a granular deposit as found in cloudy swelling, and the nuclear staining was not very distinct. The interstitial tissue, and particularly that in the vicinity of the nutrient vessels, was loose and

somewhat edematous. In a few places this edema was accompanied by a slight amount of lymphocytic infiltration.

Aorta: The general character of the aorta was well preserved. The intima was slightly thickened. The thickening in places had the appearance of an edema with relatively little proliferation, while in other places this loose thickening was accompanied by the presence of a considerable number of large, round cells having endothelial characters. These cells contained fats and lipoids. For the most part these cells lay quite superficially in the loose meshwork of the sub-endothelial layer. Some hyperplasia of the fixed tissues was also evident in the thickened areas, but it was not possible to distinguish a muscular thickening in any coat. Occasionally the intimal reaction was accompanied by an infiltration of lymphocytes which appeared to be making their way from the surface inwards. The media of the aorta was virtually without change. Along the inner surface it was slightly involved in an edema and slight hyaline degeneration In the adventitia the small blood vessels were distinctly outlined by a perivascular infiltration surrounding the vasa vasorum, so that these small nutrient vessels were clearly outlined from the surrounding loose tissue. This inflammatory response was more prominent in some portions of the aorta than in others. It was particularly marked in a section taken from the abdominal aorta close to the celiac axis. The inflammatory reaction was entirely periarterial, and was found to follow the vasa for short distances into the outer portion of the media. The infiltrating cells were almost entirely composed of lymphocytes, a few plasma cells, and only rarely polymorphonuclear leucocytes. The aortic wall in the vicinity of the vasa showed evidence of injury in the destruction of neighboring elastic fibers.

Liver: The parenchymatous tissue of the liver was altered, but the changes were not uniform throughout the organ. In a number of places necroses were found which involved the greater part of a lobule or several lobules. Some of these necroses showed an infiltration by lymphocytes with very polymorphonuclear leucocytes In other portions of the liver the lobules were quite distinct, though everywhere the liver cells showed an atrophy and degeneration so that the sinuses were more prominent. There was more or less infiltration by lymphocytes in the liver substance. In certain regions the liver lobules were decidedly jumbled as if severely disturbed by nutritional or other change. In these areas the sinuses appeared large, and lymphocytes and blood cells were not uncommonly seen lying between the walls of the sinuses and the liver cells. Various grades of degeneration could be observed in the liver cells. In a portion of liver tissue taken from the area of sub-capsular hemorrhage it was found that the liver tissue was in a much disorganized state, the structure having the appearance of a severe but early necrosis, and the whole being flooded with blood.

The most remarkable change within the liver was found in the portal systems. In these regions all gradations of a non-suppurative inflammation could be found. This inflammatory response often occupied the whole of the portal system so that the artery, vein, and duct were each surrounded by this acute reaction. With this, however, it was remarkable that the duct did not appear to suffer from the presence of the inflammation. In the majority of instances the inflammation was more particularly distributed about the hepatic artery, but the portal vein was not always devoid of a perivascular reaction. Where the inflammation was in its early stages the exudate occupied the adventitial tissues of the hepatic artery, forming a zone or crown of shells in the periphery of the arterial wall. Under these conditions, little change other than an edema was noted. Not uncommonly, however, these milder reactions were also accompanied by a proliferation of fibroblasts which, along with the surrounding edema, gave a very loose appearance to the tissues around the hepatic artery in the portal system. The more severe inflammatory reactions led to a greater non-suppurative inflammatory exudate which encroached more closely upon the muscular portion of the arterial wall. Under these conditions marked degeneration was evident in the muscular wall. In this tissue and without the advance of the inflammatory exudate into the muscle wall itself there was a complete degeneration, whereby the musculature was changed to a hyaline material. This type of degeneration was very striking. Under these conditions the vessel was seen to lie in the center of a non-suppurative inflammation, its muscular walls showing little or no cellular infiltration, and yet giving evidence of extensive damage of the nature of a hyaline or bland necrosis of the muscle. From this stage onward all degrees of distortion and further involvement of the arterial wall was found. Frequently the vessel wall became stretched and thinner. The hyaline band which originally replaced the normal thickening of the arterial coat was stretched and thinned in an irregular manner. The degree to which these small intrahepatic arteries could be stretched without bursting was astounding. All of the arteries were not equally fortunate, rupture having taken place, leading to local hemorrhage and destruction of liver tissue. Although these pouches and dilatations of the hepatic artery were a type of aneurysm, they represented a very acute process in which but little of the arterial coat remained to act as a boundary to the vascular channels.

Where the process of hyaline degeneration was advanced, and particularly in those instances in which the arterial wall had suffered great dilatation, there was an accompanying thrombosis. At times the process led to a complete occlusion of the channel, but more often an opening was still available in the blood clot. The thrombus was of a hyaline type closely adherent to the vessel wall and having irregular patches of

leucocytes and lymphocytes scattered in its substance. The hyaline nature of the thrombus was to a great extent the result of a degeneration of the blood elements within it. The hyaline portion of the thrombus was not rich in fibrin. At times the portal vein was also involved in a perivascular reaction similar to that about the hepatic artery. Processes of degeneration and occasional thrombosis were also seen, but the results of the inflammatory reaction did not bring about the serious consequences with dilatation and rupture that were found in the hepatic artery. In a study of the elastic tissues it was found that the degenerative process accompanying the periarteritis involved not only the musculature, but also these fibers. In the early stages the fibers were found split into several laminæ and frequent interruptions in their course were seen. In the later stages a complete dissolution, in as far at least as the absence of a staining reaction indicated, occurred. Thus the severe involvement of the hepatic artery left no trace of the internal or external system of elastic fibers. In these arteries with advanced degeneration it was difficult to distinguish the line of demarcation between the hyaline thrombi and the hyaline degeneration of the arterial wall. In examining the artery in other sections it was found that during the early stages of the inflammatory process about its wall a reaction of considerable extent involved the media and intima. In some instances the reaction in the intima was unique in that it was out of proportion to the response observed in the media. Under these conditions inflammatory exudate was present in marked quantity in peripheral portions of the artery as well as beneath the endothelium of the intima. In this respect the reaction simulated much that described by McMeans in arteritis occurring in meningitis. The endothelial layer was lifted from its normal position, forming a large bleb containing lymphocytes and some leucocytes as well as evidence of fluid. Between this reaction in the intima and the periarterial inflammatory responses lay the media in which only a few wandering cells were observed. It is true that the degenerative changes occurring in the media were commonly quite out of proportion to the amount of cellular exudate present. In fact it was not uncommonly observed that extensive dissolution of the media of the nature of hyaline degeneration was present in the absence of a definite cellular response. Where the medial degeneration became more advanced there was an exfoliation of the inner loosened intima, laying bare the underlying diseased tissue. It was upon such a denuded area where fibrin thrombosis was prone to develop. The fibrin deposit not only occupied the surface of these tissues, but the threads were found to interlace the meshes of the degenerated media. Associated with these marked reactions of degeneration and inflammation the internal elastic lamina was found to become involved and show tinctorial change. Splitting of this band was common while a change of its composition became apparent in that it no longer

gave the reactions for elastin. Thus the entire vessel wall was involved in grave changes which though commonly beginning in a particular portion of its structure advanced rapidly to include all of its layers. In viewing the gradations of the changes in the vascular wall, one is not surprised that the blood pressure could be properly maintained within the channels. Irregular dilatations were the outcome, the dilatations occurring at the points most severely attacked and least able to contain the internal pressure.

Gall-bladder: Sections were made of the gall-bladder in the vicinity of the thrombosed cystic artery. In the tissue surrounding the gall-bladder there was a considerable edema along with a non-suppurative inflammation localized for the most part about the arteries. Along with the infiltration by lymphocytes there were also many plasma cells and some leucocytes. A proliferation of fibroblasts was also present. In these arteries with the perivascular exudate could be seen a degeneration of the muscular walls similar to that described in the liver. Here also was found a proliferative reaction in the intima accompanied by a lymphocytic infiltration. In the most severely damaged arteries thrombosis was present. The wall of the gall-bladder was in itself but little changed. Small collections of lymphocytes were seen between the muscle bundles. The mucosal surface did not show an acute inflammatory reaction, but the epithelial lining had desquamated.

Pancreas: The tissue was quite normal in appearance. There was no evidence of an inflammatory reaction. The small arteries were free from change. The islands were numerous and appeared healthy.

Spleen: The lymph follicles were very diffuse, so that they were not clearly defined. The pulp substance was much congested. There was no evidence of endothelial proliferation. Some of the blood vessels showed hyaline change of the intima, but there was no evidence of a perivascular inflammation.

Kidney: The tubules of the cortex appeared somewhat irregular on account of degeneration of the lining epithelium and the development of enlarged lamina. The tubular cells were somewhat eroded and there was some débris within the lumen. Some of the epithelial cells had lost their nuclear staining. The glomeruli were large and without evidence of fibrosis. Many of the glomeruli appeared quite cellular, but no definite infiltration by wandering cells was evident. The lining of the capsules and the glomeruli showed some proliferation. The glomeruli were quite compact. The vessels within the kidney were without change.

Mesentery: The sections of the mesentery showed a fairly fatty tissue through which were scattered a fair number of plasma cells and lymphocytes. The tissue appeared loose and edematous. There was no evidence of serious arterial involvement by inflammation. In a few nstances small arterioles were seen around which scattered mononuclear cells were found.

Retroperitoneal gland: The follicles were rather diffuse and appeared loose. The sinuses were dilated and contained many endothelial cells. The appearance of the gland suggested an edema. A fair number of lymphocytes and plasma cells were seen in the stroma surrounding the gland as well as about the vascular channels at the hilus. The blood vessels were not particularly involved.

Right renal artery: The media of the artery showed some fibrosis. The intima was slightly thickened and the elastic lamina reduplicated. In the thickened intima were found some endothelial cells with fat.

Celiac axis: The intima and media of this vessel were healthy looking. In the adventitia there were some scattered lymphocytes and occasional leucocytes. These, however, were not present in large numbers. Occasionally some of the small arteries of the adventitia showed a slight perivascular infiltration. This, too, was not extensive.

Bacteriology: Cultures of the heart's blood showed no growth. Cultures of bile showed Streptococcus mitis and B. proteus vulgaris.

Anatomical diagnosis: Periarteritis nodosa with hemoperitoneum; periarteritis of hepatic artery and artery of gall-bladder with multiple aneurysms; thromboses of hepatic and cystic arteries; rupture of aneurysmal sacs; hemorrhage into liver and peritoneum; jaundice; fatty plaques of mitral valve; fatty change of aortic intima; cloudy swelling of heart and liver; acute splenitis with enlargement; pyorrhea alveolaris.

Notanda: Death resulted from peritoneal hemorrhages arising as a sub-capsular extravasation of blood over the liver. This hemorrhage and others in the liver substance followed rupture of various aneurysms occurring throughout the liver, along the course of the hepatic artery.

Case II. — W. A. W. (under the service of Dr. J. A. Lichty), a man of 53, who was admitted to Mercy Hospital on November 8, 1916, complaining of general weakness and nycturia. For the last year and a half he has not been feeling well, complaining of dyspnea on slight exertion. About two months ago he was exposed to rain and contracted a cold from which he was slow in recovering. *Past history:* At the age of 12 years patient had diphtheria; at 16 he was drawn through a shaft in a mill, having his scalp lacerated over the longitudinal sinus, his chest crushed, and left arm crushed. At the age of 38 he had an attack of typhoid fever (seven weeks); at 39 he had another attack of (?) typhoid fever (six weeks). About nineteen years ago he had a sprained left hip. About eight years ago he had rectal fissures and hemorrhoids. Five years ago he was operated upon for hemorrhoids; he also had his second toe on the right foot removed at the same time (hammer toe). Three years ago patient had an attack of acute rheumatic fever, for which he was in bed three weeks. Right knee is still swollen. *Family history:* Father died of old age, paralytic stroke. Mother died of old age, paralytic

stroke. One brother living and well. One brother died of diphtheria. One brother was killed. Six sisters living and well. *Personal history:* Mail carrier for the last sixteen years. Worked in a steel mill for four years. Traveling salesman for two years. Clerked in a dry goods store for five years. Married. Wife died fourteen years ago of "gastric fever" (?). Two children living and well. Three died at childbirth. Several miscarriages. Patient drinks beer and whiskey, but does not drink enough to become intoxicated. Patient has been a hard and active worker. Exposed to all kinds of weather. Patient smokes. Had gonorrhea. Denies lues.

November 9, 1916: Present condition: Patient lies comfortably in bed. Skin in exposed parts is quite dark in color. There is some cyanosis of the face and particularly of the lips. The small veins of the mucous membranes of the mouth are distinct. The scleræ are slightly yellow. The skin is moist. There are a number of small papillomata in the axilla. There is a large scar just under the right knee, an injury received when a boy. Front of shins shows fine brownish scarring. There are prominent varicose veins on the left side; no edema. Pupils equal and react normally. Tongue shows very marked tremor and is cyanosed and coated; upper teeth are false, lower not very good and show pyorrhea; a good deal of cyanosis of gums.

Lymphatic system: There are no glandular enlargements.

Chest: Expansion fair and equal, tactile and vocal fremitus normal. Chest is resonant in front and in axilla. Posteriorly at both bases a few moist râles were heard, but the lungs were resonant throughout.

Heart: Pulse full, regular, of high tension; some sclerosis of radial artery. Pulsations were visible in neck and along the course of the radial artery. The apex beat was not visible nor palpable. The upper border of the heart lay at the third rib; transverse diameter was 16 centimeters. The left border lay 1.2 centimeters external to the nipple line. Heart sounds well heard. The apex beat was regular. There were no murmurs. At the base the sounds were somewhat distant. Aortic second not accentuated.

Abdomen: Liver extends from the fifth rib to 5 centimeters below costal margin in nipple line. It is palpable and appears smooth. The spleen is not palpable. The abdomen is somewhat prominent, but shows no tenderness or mass.

Muscular system: The left arm is shorter and smaller than the right. This followed an accident when 15 years old. At the present time has perfect movement of shoulder. Right knee shows good movement, but definite creaking can be felt.

Nervous system: There is considerable tremor of body in general. Knee jerks are present.

Urine 1,030, acid, some albumin, leucocytes, and casts. Red blood cells 2,910,000; white blood cells 7,400.

November 20, 1916: Patient has had a slight rise in temperature in the last three days, also increase in pulse rate. Complained of sore throat at the onset. Yesterday bluish raised mottled areas were noted over the legs, thighs, and on the chest wall. These were firm, some were small and nodular, but not very painful. On the anterior surface of the legs they formed large irregular blotches. The general condition remains about the same; cyanosis is not so marked. Red blood cells 2,530,000; white blood cells 13,600.

December 11, 1916: Since the onset of his tonsilitis he has been running a moderate temperature. The nodular, reddish, purpuric areas in the skin still appear about the same. Some have disappeared, leaving only a dull, bluish-brown mottling in the skin with just a suggestion of some induration; other new ones have appeared. These nodules have never been very painful, a point of difference from the usual course seen in rheumatic erythema nodosa. One nodule in the right upper arm became fluctuating and was opened. A thick, gelatinous, brownish material escaped. Cultures from this were negative. He further developed a very husky voice, at times almost imperceptible, was partially conscious most of the time, and showed very marked tremor. The mental condition, in association with cirrhosis of the liver, is somewhat suggestive of Wilson's disease, a degeneration of lenticular nucleus. For the past week the patient has been about the same. The skin condition is not so marked as it was last week or even earlier. White blood cells 21,000. Wassermann reaction ++++ both with lipoid and cholesterin antigen. Blood culture negative.

Temperature: During his stay in the hospital the patient had a variable temperature through the whole course of his illness. This temperature varied between 100° and 103° F. The temperature was of an irregular character, but was never of a septic type.

Death occurred on December 11, 1916.

A blood culture taken at the time of death was negative.

Autopsy: Drs. Maclachlan and Richey (seven hours after death): The body was that of an adult male, past middle life, well developed, but somewhat poorly nourished. There was slight post-mortem rigidity and dependent lividity. The skin, particularly of the face, lips, and mucous membranes, was cyanotic. The lower lips were covered with herpetic eruptions. The pupils were of normal size and equal. A very slight trace of yellow was present in the conjunctivæ. On the chest, anus, abdomen, and thigh were many faint, brown areas of variable size, the remains of the nodular eruptions noticed during life. These pigmented areas were no longer nodular, but still, in some of them, slight induration could be made out, localizing them from the surrounding subcutaneous tissue. On the right upper arm, the scar of a small incision 1 centimeter in length was all that remained of a nodule which in

life was the size of a very large walnut. A number of other nodules of almost equal size were now only represented by faint, brown, flat, pigmented areas in the skin. Over the right chest, at the level of the third and fourth spaces between the nipple and right sternal border, were two nodular areas which on palpation felt about the size of hazel-nuts, but whose skin surfaces showed no change in color. On the left upper arm a very large, bluish, soft nodule, distinctly fluctuating and about the size of a tangerine orange was noted. On section these nodules were found to consist of yellow circumscribed areas of necrosis with central softening. The centers contained a thick, brownish yellow, gelatinous, necrotic material. Running throughout the yellowish necrotic substance of those nodules was much red blood clot. The whole mass presented a soft, friable character, and gave the impression of local necrosis rather than abscess. The section of the skin at a point showing the bluish discoloration presented only a brown, pigmented layer in the superficial, subcutaneous tissue, like the remains of blood effusion. There was no capsule to the nodular area of necrosis, although its outline was quite distinct. The chest was well formed. The abdomen was a little prominent. No scars were present on the penis. A small external hemorrhoid was seen.

Head: The skull cap was thick. The dura was moderately adherent over most of the skull cap. The longitudinal sinus was clear, but it showed very prominent Pacchionian granulations projecting into it. The convolutions of the cortex had a normal appearance. There was no softening to be palpated. A considerable amount of sub-pial edema was present. On section through the brain a very normal looking gray and white matter was observed. The nuclei at the base of the brain showed no degeneration nor hemorrhage. The cerebellum, mid-brain, and medulla presented quite healthy surfaces. The vessels at the base of the brain were not sclerosed to any appreciable degree. The sinuses at the base of the brain were free. The hypophysts were normal and there was no pus in the middle ear.

Thorax: The left pleural sac contained about 200 cubic centimeters of an amber clear fluid. There were no adhesions on either side. The right chest was free from fluid. The pericardial sac contained 100 cubic centimeters of a clear amber fluid. A small milk spot was present over the right auricle.

Lungs: The left weighed 550 grams. The surface of the lung was smooth. The lung was soft and crepitated throughout. On section the cut-surface of the lower lobe was of a reddish-gray color, a little moist, but smooth and glistening. No evidence of consolidation was present. There were no hemorrhages. The bronchi showed congestion of the mucous membranes and considerable thick mucopurulent exudate in the lumen. The peribronchial glands were anthracotic, but there was no sign

of tuberculosis. The right lung weighed 935 grams. It had characters similar to the left lung.

Heart: Weighed 495 grams. The heart was of good size and firm. It contained clotted blood. The chambers were somewhat dilated and the walls were thickened. The myocardium was a little pale, showing a fine yellowish change and in places was almost of the "tabby cat" appearance. The muscle, however, was of firm consistency. The valves at the mitral, pulmonary, and aortic orifices showed slight fibrous thickening along the free margin. The orifices were all relatively enlarged. The F. O. was closed. The coronary arteries showed fatty intimal change with small areas of beginning atheroma in one or two places. There was no narrowing of the lumen of these vessels, in fact many appeared much larger than usual. The A. V. measured 9 centimeters, P. V. 8.5, M. V. 11, T. V. 13, L. V. 2.8, R. V. .9 centimeters.

Aorta: The aorta was thin and elastic throughout its extent; in fact it was somewhat thinner than is usually found. Some small areas of early atheroma were scattered in the descending thoracic and abdominal aorta. The abdominal aorta appeared somewhat wider than usual. In the arch, the aorta was 6.5 centimeters, in the descending thoracic 6 centimeters, and in the abdominal portion 4.5 centimeters in circumference. The iliac arteries were also thin and quite wide. In the abdominal portion there was a single area of calcification. Small areas of pitting with calcification were seen in the right iliac.

Abdomen: The abdominal wall showed a thick fatty layer, and well developed recti muscles. On opening the abdominal cavity about 2 liters of fluid blood escaped. In the upper quadrants of the abdomen about the liver and spleen large masses of recent blood clot could be shelled out. One of these masses, the largest, weighed 450 grams. In the pelvis only fluid blood was present, and this appeared to be mixed with some ascitic fluid, as it was not quite the consistency of pure blood. The great omentum was fatty and had much recent blood clot attached to it in its upper part. It covered most of the coils of the small intestine, which was of normal appearance. The mesentery was intact. No thromboses nor thickenings of mesenteric veins or arteries were made out. The appendix was long, free from adhesions and normal looking. The mesenteric lymph nodes were not enlarged. In the upper abdomen some adhesions of the omentum, fibrous in type, were found attached to the gall-bladder. About the spleen and in the region of the pancreas, in the lesser sac, and retroperitoneally there was a massive and diffuse recent blood clot and hemorrhage. It was impossible to find the ruptured vessel in these tissues. The pancreas could be separated from this mass of hemorrhage only partially and with difficulty. This retroperitoneal hemorrhage extended down to the kidney tissues on both sides.

The diaphragm arched to the third rib on the right and the fifth on the left. The liver did not reach to the costal margin.

Stomach: The stomach was of moderate size. Its lining was smooth and glassy. There were numerous petechial hemorrhages in the mucosa. The lower end of the esophagus did not show prominent veins. The wall of the stomach was not thickened. The pylorus was normal. No perforation nor ulcers were present. The vessels appeared normal.

Intestines: The duodenum showed nothing unusual. There was no blood in this portion of the bowel. The mucous membrane was pale and smooth. In the rest of the S. I. nothing remarkable was noted except two or three small raised areas lying in the sub-mucosa and not eroding the overlying mucosa. They were the size of split peas. They were firm and on section showed a soft yellow tissue with a central mass of blood clot looking like thrombosis of some duration. These bore a resemblance to the nodules of the skin. There was no evidence of inflammatory reaction of the mucosa over them or of the tissue around them. The large bowel throughout its course presented a normal lining and showed no change in its walls.

Liver: Weight 2,700 grams; measured 32 x 22 x 10 centimeters. The organ was very large and well pushed up under the ribs. The organ was surrounded by fluid and clotted blood. The inferior margin was slightly rounded. The capsule was not thickened except the posterior surface of the left lobe, where it was raised into several white arborescent ridges. On section, through these ridges, a bead of yellowish purulent material could be expressed from a central lumen which was surrounded by a thick fibrous wall resembling a vascular channel. In one or two other places similar structures lying in the same relation showed a like purulent fluid. These possibly represented lymph channels, as they were definitely in the capsule. The surface of the liver had a mottled white and yellow appearance. The liver was quite flabby. On section through the liver the tissue cut with increased resistance, and the liver substance felt tough and fibrous. It was pale yellowish gray in color, slightly tinged with bile. There was a diffuse increase in fibrous tissue which involved all parts of the liver equally. The lobules were isolated in round or oval areas by the diffuse glassy connective tissue. No heavy bands of fibrous tissue were seen. The portal channels did not show up prominently, and there was no evidence of special increase of connective tissue about them nor any sign of an acute inflammatory reaction. The portal and hepatic veins appeared quite clear. On several sections through the liver a number of localized round or oval thrombi in vascular channels were noted. In one place the thrombus was clearly seen to be in Glisson's capsule, and the hepatic artery was traced directly to it, showing that it was in the arterial system. These thromboses lay in aneurysmal pouches of the artery and in many the wall of the vessel could be clearly seen. The

thrombi were red and laminated, but some of them showed white peripheries as if early organization were going on. These were firmly attached to the vessel wall. In no part of the liver did we find any evidence of rupture with hemorrhage into the liver tissue. Where the round ligament of the liver entered the liver substance there were marked thrombi, but the round ligament itself was quite normal looking and did not show an involved vessel. In the gastro-hepatic omentum the artery, vein, and duct appear clear. No sign of inflammation of the bile duct could be seen. One thrombus in the liver was traced by section for about 7 centimeters. Its connection with the hepatic artery was demonstrated. The gall-bladder was a little enlarged. It contained about 75 cubic centimeters of a thin yellow bile. The surface of the gall-bladder showed a number of fibrous adhesions which attached it to the omentum. There were also numerous localized nodules in different parts of the gall-bladder which looked, from the outside, like fibrous thickening. The mucosa was smooth and healthy looking. On section through many of these nodules in the wall of the gall-bladder, dilated and thrombosed vessels were found to form the greater part of them. These were quite similar in appearance to the thromboses of the liver and also like those seen in the bowel. Some of the nodules in the gall-bladder wall were larger than others, the largest being the size of a pea. They appeared to lie chiefly in the serosal tissue. No reaction whatever was present in the mucosa. Some of these thickened arteries were traced as they coursed over the surface of the gall-bladder. It was found that these arteries formed chains like a string of beads wherein their walls showed irregular and periodic nodular or fusiform dilatations. The main artery of the gall-bladder formed an irregular mass down one border and it was found that its lumen was obliterated throughout its length by an adherent clot. This thrombus was gray in its periphery and red in the center. The second vertical branch of the cystic artery was not so extensively involved, but was beaded in its outline. In this vessel the dilated sacs alone were thrombosed. At the hilus of the liver, just above the cystic duct and where the hepatic artery breaks up into its several branches, was found an aggregation of dilated and thrombosed vessels. These vessels were ramifying into various directions in the liver. The thromboses had not completely occluded their lumina, but there remained small channels more or less centrally placed. The main hepatic artery lying outside of the liver was not involved in the process. Its inner lining was smooth and there were no sacculations or thromboses. Just as soon, however, as the vessel and its branches became imbedded in the liver substance and in the wall of the gall-bladder, its walls showed inflammatory thickening accompanied by degeneration. No naked eye changes could be observed in the portal and hepatic veins nor in the inferior vena cava as it passed behind the liver.

Pancreas: The organ was enlarged and densely matted down by hemorrhagic fatty tissue which first made its outlines difficult to see. On separating the pancreas, the head was much enlarged, measuring 6 x 4 centimeters. This gradually tapered off toward the tail, which was 5 x 3 centimeters. Under the peritoneal covering the pancreatic tissue looked very pink and there was much diffuse hemorrhage in the pancreatic tissue at the duodenal end. The organ felt firm, but a little softer than the normal pancreas. On section through the head of the pancreas a large dilated aneurysmal pouch the size of a hazel-nut, containing some clotted and fluid blood, was noted. This thrombosed aneurysm was followed and was found to communicate with a small artery lying in the pancreatic tissue at the upper border of the head. This artery appeared to be a branch of the pancreatico-duodenalis. The splenic artery running along the upper border of the pancreas was clear. The greater part of the head of the pancreas had lost its normal appearance. The tissue was dull yellow and necrotic looking with recent hemorrhage perfusing its structure. This necrotic tissue was most evident adjacent to the thrombosed aneurysm. The body and tail of the pancreas were of a pink color and, although none of it was normal looking, appeared glassy, swollen, and degenerated. The lobules were not clear in outline. The whole pancreatic tissue was soft. A few yellow interstitial areas of fat necrosis were also observed in this portion of the pancreas. The head of the pancreas in its necrotic portion had an appearance similar to the large necrotic nodules seen in the skin. The fatty tissue immediately surrounding the pancreas and particularly along its lower border showed numerous hemorrhagic areas. These hemorrhages formed nodular masses at times 1.5 centimeters in diameter. Similar areas of interstitial hemorrhages were observed in the fatty tissues at the tail where the pancreas was in contact with the spleen. No direct communication could be made out between the areas of hemorrhage and the arteries in the tissue. Some of the small arteries had nodules. The splenic artery was followed throughout its length and showed no evidence of thrombosis. At its distal extremity, however, just before it entered the spleen its inner walls were quite corrugated, though intimal hyperplasia could not be made out. The vessel was slightly tortuous and its inner surface somewhat pouched. The splenic vein was normal in appearance.

Spleen: Weight 235 grams; measured 13.5 x 8.5 x 3.5 centimeters. The surface of the spleen on its inner aspect was covered by loose recent blood clot and the omentum and tail of the pancreas were adherent to the hilus. The organ was large and soft with no evidence of a notch on its surface. The capsule showed a few fine tags of fibrous adhesions, but it was not thickened. On section the cut-surface was soft, red, and almost diffluent. The trabeculæ and the follicles were not well seen. The pulp could be easily scraped away with the finger. There was no hemorrhage into the tissues.

Left kidney: Weight 275 grams; measured 14 x 6 x 5 centimeters. The kidney was enlarged and rather soft. The capsule of the kidney was thin and somewhat difficult to peel from the cortex. The surface of the cortex was smooth and of a pale yellowish-red color, showing numerous fine hemorrhages studded over the surface. On section through the kidney, thickening and swelling of the cortex was observed. The cortical tissue was grayish yellow in color. Its markings were not very distinct and it was well studied by tiny red points of hemorrhage. The renal artery and its branches showed no change. A great deal of peripelvic fat was present. The pelvis and ureter had pale, healthy linings and appeared normal. The right kidney weighed 200 grams; measured 13.5 x 7 x 5 centimeters. The kidney was similar to its fellow on the left side. The arteries were without change.

Adrenals: The adrenals were small and covered by a thick layer of fat in which there was a great deal of hemorrhage. The cortex was yellow and well marked, while the medulla was small and somewhat softened.

Bladder: The bladder was of normal size. The lining of the bladder was smooth and pale. The blood vessels appeared normal. The prostate was not enlarged. The cut-surface had a white and fibrous appearance.

MICROSCOPICAL.

Brain: Section of the brain and meninges showing nothing of note. Sections of the Gasserian ganglion showed a normal structure.

Lung: The lung showed some congestion of its alveolar walls and the presence of a small amount of granular débris in the alveoli. There was no evidence of inflammation and the blood vessels were without change.

Heart: The heart muscle was somewhat loose and the intervening stroma fairly cellular. The musculature showed a considerable amount of fragmentation, but its staining qualities were good. Scattered through the interstitial tissue were occasional small foci of cellular infiltration associated with the small coronary radicals. The infiltration was perivascular and usually quite localized. The larger coronary branches were in no way involved and there was no evidence of true periarteritis nodosa. The cellular aggregations consisted mainly of lymphocytes and resembled mild reactions to infection. In other areas there were small patches of fibrosis in the myocardium. These islands of connective tissue replaced small areas of heart muscle and indicated an old healed inflammatory focus.

Omentum: Sections of the omentum showed the presence of much hemorrhage in the fatty tissues. The main amount of this hemorrhage showed no evidence of inflammatory infiltration. Occasionally, however, small foci of leucocytes and lymphocytes were found in the fatty tissues. The injured blood vessels from which the hemorrhage had arisen were not demonstrated.

Liver: Everywhere the liver showed more or less fibrosis. This fibrosis was present in bands which commonly encircled one or more lobules. These bands were at times quite heavy, but in the majority of instances they were only of fair extent. The fibrosis followed the portal sheathes and did not invade the individual lobules. The liver columns lying close to the bands of fibrous tissue were well preserved and did not appear to be injured by its presence. A few lymphocytes were scattered through this fibrous tissue. Some of the liver cells contained a brown pigment. At times the lobules showed a poor arrangement of the liver columns, appearing somewhat jumbled. Scattered at various intervals the blood vessels in the portal sheathes showed an unusual distortion. Varieties of degeneration and inflammation could be observed similar to that described in the pancreas. The vessels which were particularly involved were the hepatic arteries. These arteries, both large and small, showed periarterial inflammation with hyaline degeneration of the media and aneurysmal dilatation. Laminated thrombi undergoing hyaline degeneration frequently occupied the dilated vessels. Some of the affected arteries were so disorganized that no remains of their walls could be found. Both muscle and elastic fibers suffered severely in the degenerative process so that little remained of their original substance. However, all gradations of this process could be seen in different arteries. In those situations where an artery was severely involved it was found that other vessels, including the veins, also suffered when they were in close proximity within the same portal sheath. Evidences of repair were seen in the granulation tissue surrounding the artery as well as in the organization of the central clot. The main reactions were always of the nature of an acute or sub-acute inflammation in the periarterial tissues, accompanied by a diffuse hyaline degeneration of the media. The inflammatory products did not always enter the medial tissues, but often remained confined to the outer tissues. Likewise, the inflammatory reaction of the intima was variable, sometimes being evidenced in a proliferative response, at other times showing a loosening of its structure accompanied by a cellular infiltration. Where the intima was damaged, and in part desquamated, a thrombus was prone to form. This thrombus, often from the beginning, had a very hyaline character. In viewing the damage upon the various coats of the arterial wall it is not surprising to find extensive pouching of the vessel. In places where the artery had given way, and hemorrhage had occurred into the liver tissue, it was difficult to orient the individual tissues amidst the disorganization. In no place was there evidence of a primary inflammatory process of the liver tissue itself. In each instance it appeared that the arterial affection was quite individual from the functional or structural character of the liver.

Main hepatic artery: The arterial wall itself showed no evidence of

degeneration or acute inflammation. The intimal layer of the artery was somewhat thickened. In the loose tissue surrounding this vessel were seen a number of small arteries which were involved in a mild inflammatory reaction consisting of lymphocytes and plasma cells. In none of these vessels was degeneration of the media observed.

Gall-bladder: A number of sections were made from the gall-bladder and its thickened arteries. The gall-bladder wall showed some edema and infiltration of lymphocytes and plasma cells. Otherwise, the gall-bladder showed little change. The vascular structures, however, formed separate foci around which distinct reactions had occurred. These reactions, with their peripheral inflammatory infiltration and hyaline medial degeneration, were identical with the arteries of the pancreas and liver. There is no necessity for describing these separately. In some of the loose tissue about the gall-bladder the development of new granulation tissue about these arteries was accompanied by a marked infiltration by eosinophiles. Fibroblasts and new capillaries were everywhere abundant. A greater number of small arteries appeared to be involved than was noted in the liver or pancreas.

Pancreas: All gradations from a healthy pancreatic tissue to severe destruction could be observed in a series of sections. Sections obtained from the distal portion of the pancreas showed relatively little change and only occasional vessels were found to be involved in a periarteritis. When, however, sections were obtained from the neighborhood of the head of the pancreas all manner of destruction of tissue was encountered. Wide ranges of complete necrosis devoid of any inflammatory reaction were not infrequent. These necrotic reactions were also associated with blood vessels in which there was interference to the circulation. The arteries within the pancreas showed the most remarkable lesions. In some the adventitia was attacked in a mild inflammatory reaction showing mainly lymphocytes as the cells of infiltration. These lymphocytes were loosely scattered in the surrounding interstitial tissues and did not appear in any way localized to particular tissues or areas. In the earliest vascular changes the inflammatory response preceded the evidence of degeneration in the media. Subsequently, however, a bland hyaline degeneration occupied the entire medial ring wherein the muscle cells appeared to melt down and disappear, save for the homogeneous remnant encircling the lumen. The intima in the early reactions was in no way involved. It was only after marked lesions were found in the adventitia or had advanced into the media that a loosening like a bleb or edema occurred in the intima. This intimal reaction was often accompanied by the infiltration of a few cells. When arterial degenerations had advanced to a degree that the normal elements of the media had been destroyed, a dilatation was prone to occur along the course of the vessel. The extent of the dilatation varied, depending upon the amount

of support in the surrounding structures. Frequently the vessel wall bounding these aneurysmal sacs was entirely lost or at least could not be recognized. The muscle tissue, as we have indicated before, fused into an inert hyaline mass, while the elastic fibers of both the inner and outer coats were completely destroyed and could no longer be demonstrated. At times it was remarkable how an otherwise healthy arterial wall merged abruptly into an aneurysmal sac and was lost in a confused necrotic tissue. This line of demarcation was quite narrow, had a bluish tinge, and was outlined by a zone of leucocytes. On one side of this cellular zone the muscle cells of the media were easily defined, while on the opposite side nothing of them could be recognized. The dilated portion of the artery was filled with a laminated clot, the central portion of which was occupied by a great number of leucocytes. The peripheral portion of the clot was closely adherent to the surrounding tissue, and it was impossible to distinguish the line of demarcation between the hyaline media and the hyaline change of the fibrin clot. The tissues lying at some distance from the involved arteries showed an infiltration by lymphocytes and plasma cells alone. Similar reactions were studied in many vessels of all sizes in the head of the pancreas. The largest of the vessels having thick muscular walls appeared to be involved with as equal frequency as the small ones. Nevertheless, the splenic artery itself along the upper border of the pancreas was not attacked. While this acute reaction with widespread destruction of the arterial wall could be studied in its various stages of advance, it was also interesting to find that many evidences of a reparatory process were also at hand. Arteries were repeatedly found in which repair was present in each of the arterial coats. Of the three coats the intima showed the most active response. Granulation tissue with remnants of lymphocytic infiltration was the common finding in the adventitia. The degenerated media with its irregular bulgings was partly absorbed and replaced by fibrous tissue from the outermost layer. On the other hand, the activity of tissue growth in the intima was most remarkable. A loose fibrous tissue, having the qualities of a granulation tissue with its new-formed capillaries, tended to fill up the lumen of the artery. This organization of the thrombosed vessel was accomplished by proliferation from the adventitia through the media at the time when the intense inflammatory reaction had subsided. Evidences of repair were not alone seen within the arterial wall, but much was also observed in the tissues of the pancreas itself. A granulation tissue was found to occupy areas of pancreas which had previously been involved in acute inflammation and nutritional disturbance. The remarkable feature which struck one in reviewing the pancreatic lesions was the intense destructive character observed in the acute stages wherein the involved tissues were rapidly melted down, as compared with the activity of repair by granulation tissue as soon as the

destructive agents had disappeared. At times this very feature of intense destruction reminded one of the acute necrosis with its sharp line of demarcation, as it is seen in noma.

Spleen: The tissues of the spleen appeared very loose. The Malpighian bodies were small and the pulp substance congested. There were no localized areas of inflammation within the spleen tissue. The arteries were not involved in any unusual process. Through the pulp there was a fair amount of yellow pigment which had been phagocyted by large endothelial cells. In another section a single artery was found within the spleen, which showed some cellular infiltration in its periphery. This infiltration consisted mainly of lymphocytes and plasma cells with a few leucocytes. There was no definite degeneration of the media.

Kidney: The tubules in the cortex showed a considerable amount of change consisting mainly of a granular degeneration and widening of their lumina. Many of these tubules contained a granular débris and the lining cells appeared eroded. At irregular intervals in the cortex there was an increase in the connective tissue. The fibrosis surrounded both tubules and glomeruli and occasionally formed small patches directly beneath the capsule. The glomeruli were large and quite cellular. Occasionally small groups of lymphocytes and leucocytes were found in the glomerular tufts; in other places the glomeruli were adherent to their capsules. Here and there a cellular infiltration was found to surround the capsules in dense collections. These infiltrations often occupied areas of old fibrosis. The arteries showed no evidence of recent attack, but many of them showed thickening of their walls, mainly seen in the presence of a chronic endarteritis. It is evident that the kidney lesion was of two kinds, the one was of old standing with fibrosis; the recent reaction was seen in the granular tubular degeneration and the cellular infiltration which occupied the glomerular tufts and the interstitial tissue.

Adrenal: The cortex of the adrenal appeared rather loose, and the parenchymal cells were poorly staining, and appeared much vacuolated and granular. There was no cellular infiltration within the adrenal substance. On the other hand, the loose tissue surrounding the adrenal was extensively infiltrated with recent blood, the result of a retroperitoneal hemorrhage. Damaged blood vessels could not be found in the nearby tissues.

Subcutaneous tissue: Sections of the subcutaneous tissue showed a very interesting series of reactions. In places, hemorrhage, necrosis, acute inflammation, or granulation tissue were found. These different reactions appeared to be phases of a common injury induced in the tissues. The most marked reaction occurred just above the muscle layer where acute inflammation with a necrosis involved the fatty structures. At times the amount of necrosis appeared out of proportion to the amount of inflammation, suggesting that the necrosis was one of lack of

nutrition. The inflammatory reaction, though accompanied by a considerable number of leucocytes, was not of the purulent variety in that the exudate consisted in so large a measure of lymphocytes, plasma cells, and a great number of endothelial cells. These endothelial cells were often multinucleate, and lay within the pockets of the fat cells. The largest area of necrosis showed a considerable hemorrhage around it, and was probably the result of a vascular lesion in which the structure of the involved artery had been entirely disintegrated. Between the muscular trabeculæ a number of small arteries with infiltration in their outer coats were observed.

Levaditi stain: Specimens of pancreas and liver were stained for spirochetes by the Levaditi method, but none were demonstrated.

Bacteriology: Cultures from a subcutaneous nodule showed Staphylococcus pyogenes aureus and a diphtheroid bacillus. Cultures of heart's blood showed Streptococcus anginosus and Streptococcus salivarius. Cultures of bile showed Staphylococcus pyogenes aureus and Streptococcus anginosus. Cultures from sub-capsular lymph channels of liver showed Staphylococcus pyogenes aureus and Streptococcus anginosus.

Anatomical diagnosis: Periarteritis nodosa with hemoperitoneum; periarteritis of hepatic, cystic, pancreatic, mesenteric arteries and arteries of subcutaneous tissue; aneurysmal dilatations and thrombosis of involved vessels; necrosis of liver, pancreas, skin, and small intestine; chronic sclerotic, aortic, and mitral endocarditia; acute splenitis with enlargement; cirrhosis of liver (syphilis).

Notanda: The immediate cause of death was from hemorrhage into the peritoneum arising in the vessels of the gastro-colic omentum and pancreas. The arterial lesions were typical and easily recognized in the gross. The local distribution of the lesions along the course of the branches of the celiac axis and the superior mesenteric arteries was of interest

A brief summary of our two cases will bring out the important features more clearly. The first case was a woman of thirty-three years, whose past clinical history gives nothing of importance bearing upon her final illness. Syphilis was not considered as a possible factor, so that unfortunately a Wassermann was not done. Her final illness was of four weeks' duration, beginning with a severe cold following exposure to inclement weather. Muscle and joint pains were prominent, and subsequently these were followed by severe, cramp-like pains in the abdomen. She ran a

continuous temperature over 100° F. There was some leucocytosis and albuminuria and slight icterus. Death occurred suddenly in collapse. The autopsy revealed the typical lesions of periarteritis nodosa with aneurysms and thromboses distributed along the hepatic and cystic arteries. Rupture of one of these hepatic arteries led to extensive hemorrhage about the liver and into the peritoneum. There were no other serious acute lesions nor were there any infectious deposits about the heart.

The second case occurred in a man of fifty-three who previously had suffered considerable illness. He had had acute rheumatic fever. His present illness began after an exposure to rain and cold, from which he was slow in recovering. During his illness he developed tonsilitis, which in a few days was followed by the appearance of bluish nodules in the skin. Dyspnea and cyanosis were evident throughout his illness, apparently associated with an old cardiac lesion. His Wassermann reaction was positive. He had quite a marked anemia, with some leucocytosis. From the time of the onset of his tonsilitis, he ran a continuous though irregular temperature over 100° F. During life one of the skin nodules was removed, but a diagnosis of the arterial lesion could not be made owing to the rather extensive disintegration and hemorrhage which occupied the area excised. Cultures from these nodules were negative, as were also the blood cultures. Clinical manifestations of an intra-abdominal condition were not apparent. The patient died rather unexpectedly, although, during the last week of his illness, he was becoming progressively weaker. His total illness extended over a period of about three months. In this connection, however, it must be remembered that the patient sought the hospital because of cardiac decompensation associated with old heart lesions. On the other hand, the nodules in the skin, and probably also the occurrence of the nodular affection of the internal arteries; developed late in the progress of his disease and while he was in the hospital. It is evident that the patient was primarily suffering from a cardiac lesion of not uncommon type, and that the acute

periarteritis was an associated complication superadded to his other illness. The appearance of the skin nodules took place after an acute recurrent tonsilitis and twenty-four days before his death. The onset of these nodules occurred under the eye of the clinician and the progress of these lesions, as well as the manifestations of the attack upon the internal arteries, was followed during his stay in the ward. At autopsy the involvement of a considerable number of vessels belonging to localized tissues was studied. The distribution was along the ramifications of the celiac axis and mesenteric arteries, as well as the arteries of the skin.

In both of our cases the arterial attack was associated with an acute illness beginning with a cold and tonsilitis and accompanied by a certain degree of muscle and joint soreness. The Wassermann reaction was positive in one, while in the other case syphilis was clinically ruled out.

Previous reports. — As we have indicated above, observations upon periarteritis nodosa have been made upon forty cases. To this number we have added two of our own. It is unnecessary to comment upon the individual findings of previous authors in that many of the reports in the literature contain excellent discussions of them. We particularly refer to the study by Lamb, who gives an excellent review of the thirty-eight cases reported up to the writing of his paper (1914). From this group of thirty-eight cases we have removed two, Case II. of Kussmaul and Maier and the unconfirmed case of Benedict studied in life. With the addition of Lamb's two cases and the subsequent report by Guldner, as well as a case reported by Babes and Mironescu, we have a total of forty. The clinical findings have been well summarized in the report of Lamb, and the difficulty of making a clinical diagnosis during life is indicated in the mistaken conclusions arrived at prior to autopsy. In reviewing the clinical manifestations of the individual cases one is struck by the frequency of common symptoms occurring in all, and at first sight one would be led to believe that there was a certain symptom complex whereby a diagnosis could be established.

The majority of cases occur in males before middle life, who, through a preceding illness, have developed a predisposition for an acute infection not uncommonly beginning with tonsilitis, sore throat, and rheumatoid pains with a final localization of an inflammation upon a distinct group of peripheral arteries. When it is remembered, however, that the entire group of rheumatoid affections are so indefinite in their manifestations, and that the particular tissues and organs suffering the most intense involvement are extremely various, it will be appreciated that in this particular group of lesions the intensity of the symptoms is not constant. Furthermore, if we remember that the localization of this infective process around the arteries is not confined to one vessel or even to one group of vessels, the clinical picture presented in the different cases is quite different. In our own cases we had the opportunity of realizing this fact, particularly when our second case developed the nodular lesions about the arteries six days after we had performed the autopsy upon the first. Even with this evidence in hand we failed to recognize the true character of the disease. On the other hand, the autopsy findings are characteristic and unmistakable.

Syphilis. — From the earliest description of periarteritis nodosa syphilis has been repeatedly discussed as a possible or even probable cause of the lesion. In a number of cases syphilis was found present in other organs, but even in its absence certain authors have compared the character of the inflammatory and the destructive process with syphilitic arteritis. Support was given to the claim of an etiology of syphilis by Kussmaul and Maier, Chvostek and Weichselbaum, Graf, Schmorl and Verse, while its importance as a causative factor is either questioned or wholly denied by the remaining observers. The whole problem of the importance of syphilis in these lesions must be viewed from two angles. Firstly, it is true that in a certain number of cases syphilis was demonstrated in organic lesions by histological examination as well as by the Wassermann reaction (Lamb Case II. and our Case II.). On the other hand, and what is still more

important, there have been a series of cases in which evidence of syphilis has been entirely lacking both clinically and pathologically, and a Wassermann reaction was definitely negative (Lamb Case I., Lewis, Jonas, Veszpremi). This evidence of the absence of syphilis cannot be lightly overlooked, and although it may be claimed that the Wassermann reaction during the acute stages of syphilis is not dependable, yet the lack of any other confirmatory evidence of its presence in these cases is strong argument against the luetic nature of the arterial disease. On the other hand, we are not convinced that, in those seven cases in which syphilis was demonstrated, this disease did not have a predisposing bearing upon the subsequent bacterial invasion of another kind. It is common knowledge that syphilis induces systemic conditions whereby subsequent secondary infections of serious nature may be more readily acquired. We may, however, safely say that the infection of syphilis is not the direct cause of these arterial lesions, but may be only an influence in bringing about subsequent bacteriemias and localized tissue infections. This is furthermore borne out in the absence of true luetic tissue reactions in the involved arteries and in the uniformly negative results reported of tissues stained by the Levaditi method for spirochetes (Beitzke, Verse, Schmidt, Lamb, and both of our cases).

Comparison is made by not a few authors between the similarity of the syphilitic process in arteries and the histological lesions of periarteritis nodosa. This similarity is particularly seen in the manner of attack upon the arterial wall, beginning as an inflammatory process in the adventitia and advancing inwards to the media or even the intima. This inflammatory process is in the main a non-suppurative one, although in the very acute conditions polynuclear leucocytes are not infrequent. Furthermore, there is associated with this inflammation a process of degeneration affecting the media.

While resemblance may be found with syphilitic arteritis the comparison should not be carried too far. It is rather the disposition of the inflammatory exudate than the character

of the cells contained within it, which has given rise to some confusion. It is, however, recognized that syphilis is not the only infection attacking the arterial wall from its outer coats, and that processes of degeneration even resembling the peculiar melting down of tissues may occur in other diseases. We have repeatedly demonstrated the presence of a non-suppurative lesion in the adventitia and media of arteries, particularly the aorta, during systemic infections by the pneumococcus, B. typhosus, and Streptococcus viridans. The presence of these infections leads to a localized inflammatory reaction around the vasa vasorum and apparently occupying the periarterial lymphatic spaces. In the aortic wall the lesions may be followed into the media wherever adequate lymphatics are found about the vasa. It is interesting that under these conditions the area occupied by the non-suppurative inflammation causes a destruction of the surrounding essential elements of the artery. Under ordinary conditions these infiltrations are not extensive, but are sufficiently significant to indicate the course along which bacteria migrate and stimulate tissue reaction. The character of the reaction, being non-suppurative, bears at first glance some resemblance to an early syphilitic process. Our findings have been confirmed by Andrewes, who was able to recover the microörganisms from these foci.

Thus, although various types of bacterial lesions in the arterial wall show a superficial resemblance to those of syphilis, confirmatory evidence must be at hand that treponema pallidum was the exciting cause before arriving at a definite conclusion. This, as we have stated before, is entirely lacking in the study of periarteritis nodosa.

Gross pathology. — It is not our intention to reiterate much of the descriptions which have been so well made by previous authors, save to bring out those points which lead us to believe that the lesion is one induced by sub-acute infection having a peculiar localization dependent upon certain anatomical characters of the arteries. At first sight one is struck by the peculiar feature that periarteritis nodosa

occurs in association with the smaller vessels. This is true only in as far as we recognize periarteritis nodosa as a distinct disease. We would, however, point out that the distribution of the infection is wider than the lesions which attract our eye by gross and often by microscopical means. The arteries most commonly involved, and to which our attention is attracted, are the branches of the celiac axis, the superior mesenteric, the renal, and the coronary arteries of the heart. The distribution upon other arteries, of the skin, lung, brain, epididymis, and adrenal, has been observed in some of the cases. It is interesting that, although the majority of cases have shown lesions which were readily recognized by the naked eye, there have been at least five in which the disease was not discovered until microscopic sections had been made. These were more or less accidental findings of relatively early stages of the arterial process in which the patient had died from causes not directly referable to the vascular involvement. Whether these human cases come under observation with evidence of the early periarterial infiltration or in the later stages when the arterial damage has led to aneurysmal dilatation and thrombosis, is dependent entirely upon the simultaneous involvement and functional incapacity of vital organs. Excluding the cases in which advanced changes have been wrought upon the arteries with death from rupture and hemorrhage, or from necrosis following thrombosis of visceral arteries, death is usually the outcome of severe heart or kidney disease or the peculiar chronic intermittent bacteriemia leading to the so-called "anemic marasmus."

Although the underlying characters of the arterial lesions are fairly constant in the different cases which have been closely analyzed, a considerable variation in the intensity of the inflammatory process and the associated degeneration has been observed. These findings indicate differences in the intensity of the bacterial attack as well as the different stages at which the observations were made. There is every reason to believe that the same infectious agent acting over similar periods of time will produce, when the tissues are

equally susceptible, fairly constant injuries to the arterial wall. Thus, when the damage has been sufficient to produce arterial weakening, dilatation results, which we are justified in comparing with the so-called mycotic aneurysms. This interpretation is borne out in the further analysis of the lesions. Eppinger has classified the manner in which acute mycoses may become localized in certain arteries or upon particular portions of the arterial wall. Some of these begin by direct extension of the infectious process from lesions upon heart valves. These begin in the intima and extend outwardly. In another group intimal lesions are likewise primary, having their origin from infected emboli locating at the bifurcation of vessels. Similarly, infections of the arterial wall arise in the outermost coats of the arteries from neighboring suppurative lesions bringing about focal destruction of tissues, with the erosion of media and eventual saccular aneurysms and rupture. Finally, a fourth type is indicated in which the distribution of the infectious agent takes place by means of the vasa vasorum from a distant focus. Under these conditions several foci may become implanted in the wall of the artery and simultaneously progress to a destructive lesion sufficient to produce multiple mycotic aneurysms. It is with this last group that our interest chiefly centers. Whereas the discussion in regard to this type of mycotic aneurysm has constantly brought to the fore the importance of the vasa vasorum in the process of distribution, it is found that these minute vascular channels play only a temporary part in the progress of the lesion. If, under certain circumstances, bacteria are brought by way of the vasa vasorum to the artery they soon make their way into the surrounding lymphatics and then continue their migration and tissue destruction from these sites. This gives rise to a true perivascular reaction about the vasa, and has a harmful influence upon the larger artery. We are not convinced that the initial infection about the vasa is always implanted by the arterial stream of the nutrient vessels. It seems more probable, and this we have been able to follow in a number of cases of pneumonia, that the infection has

from its beginning been one of the lymphatic structures and that its distribution has been of the nature of a lymphangitis. Thus, within the thorax with its rich lymphatic centers in the tissues of the mediastinum, infection radiates along the course of the lymphatic channels and involves those tissues which are in closest proximity or are most readily reached by the distribution of the lymph channels. We find that the majority of acute arterial mycoses are localized in the same situations in which the syphilitic virus is found. The common acute mycotic aneurysm of the aorta lies in the ascending limb of this vessel, and when we study these lesions in their various stages of development we find that they begin in the outer loose tissues of the adventitia and extend into the arterial wall in the vicinity of the nutrient vessels. This portion of the aorta has a rich lymph supply, and is in direct communication with the lymph nodes of the anterior mediastinum. Next in frequency mycotic aneurysms are found upon the transverse and descending arch. In the abdomen the localization of infectious processes upon the aorta is in the vicinity of the root of the celiac axis, in which position an unusual cluster of lymph nodes and channels surrounds the large vessel. Thus in the study of the distribution of mycotic aneurysms of the aorta, we must bear in mind the richness and complexity of the lymphatic bed of the part. Furthermore, it would not be amiss to include the cases of multiple mycotic aneurysms of the aorta in the consideration of periarteritis nodosa, remembering always that, because of the difference in the structure and function of this large vessel, the lesions have some features distinct unto themselves, and, therefore, present a picture not directly comparable to those of the smaller arteries.

The importance of the perivascular lymphatics is not sufficiently appreciated by most investigators when considering the mode of distribution of bacteria in and about the vascular tissues. Every one who is familiar with the pathology of inflammatory reactions in the human subject has had his attention attracted to the presence of perivascular exudate

in the periphery of the focal inflammation. It is not uncommon to observe the advance of infection and inflammation in tissues surrounding the small arteries of the mesentery of the appendix during acute inflammatory lesions of the appendix. It is probable that the thromboses so commonly occurring in the vessels of these outlying tissues have their cause in the damage induced through infections of the arterial coat arising from the perivascular involvement. The same perivascular responses are also to be observed in the Fallopian tubes, the broad ligament, the umbilical cord, and elsewhere. In this respect it is interesting to note that Cullen reports a case which might be regarded as periarteritis nodosa of the umbilical vessels. He quotes Runge as saying "that where infection of the umbilical vessels exists the disease first starts in the perivascular connective tissue. . . . Often the process extends to the adventitia and the vessel itself is involved. The inflammatory infiltration of the vessel wall causes a paresis of the muscularis or dilatation of the vessels or gives rise to a thrombus which soon breaks down." This migration of the inflammatory exudate is not a condition which per se tends to follow the artery, but which, because of the lymphatics, is the line of least resistance in this process. This is true not only of infections of the suppurative type, but also of the non-suppurative lesions. Of the latter it has always been frequently demonstrated that the infections associated with acute rheumatic fever and the various rheumatoid processes are for the most part periarterial in their distribution. The focal inflammatory deposits that are so constantly found in the myocardium in rheumatism are excellent examples illustrating the localization in the lymphatic spaces and channels of the nutrient vessels. Thus we are led to believe, and we have further demonstrated in experiment, that periarteritis nodosa differs from the common periarterial inflammations only in the peculiar manner of damage to the arterial wall. The distribution and the progress of the disease along particular branches of arteries is not unique for this lesion which has received a special name.

Microscopical analysis. — Here again we need not review in detail the observations by others nor enter into a lengthy description of the lesions, save in as far as they present characters differentiating them from periarteritis so commonly met with. In periarteritis nodosa the inflammatory reaction is in the main a non-suppurative one, but one which in the same individual may show foci of more intense inflammatory reaction and the presence of large numbers of leucocytes. In the later stages of the lesions these leucocytes are often eosinophiles. The presence of large numbers of the neutrophilic leucocytes is an indication of a heavier focal infection of the same microörganism, or a response following upon tissue degeneration and necrosis not unlike the leucocytic involvement of typhoidal focal necrosis of the liver. In the early stages of the periarterial attack the infection appears to lie in the tissues outside of the artery, and only at sporadic intervals does the inflammatory exudate involve the adventitia. In many positions the artery shows no further involvement and does not suffer damage to its walls proper. These areas constitute the portions intervening between nodules and aneurysmal dilatations. In the region of the nodules the inflammatory processes proceed into the arterial tissues proper, where products of degeneration are soon observed in the muscular portion of the media. Degeneration of the middle coat may proceed to great lengths without the presence of exudate, but it is not uncommon to find more or less cellular infiltration accompanying the reaction. The medial degeneration is hyaline in character and appears to result from both toxic and nutritional disturbances. That it is not alone toxic is often observed in the localized position of the degeneration, where the entire circumference of the artery is equally involved in inflammatory response. Under these conditions the nutrient vessels as well as the lymphatic drainage are seriously damaged or occluded and the tissues dependent upon their efficiency suffer complete asphyxia. We have in several instances observed the presence of hyaline medial degeneration in the arterial wall beyond the acute inflammatory response, in which it was found that the vasa

supplying wide stretches of the artery were involved. It is probable that the diffusible toxins of the infection play a part in bringing about the characteristic degeneration. Whether interference with the circulation in the vasa vasorum alone can bring about the widespread and peculiar medial degeneration is not clear, but we rather doubt it.

For the most part the presence of nodules along the course of an artery indicates aneurysms. On the other hand, however, smaller nodules may be recognized which, on histological examination, show no aneurysmal dilatation of the vessel, but a marked inflammatory infiltration with edema and granulation tissue. Aneurysms may be observed in all stages of development as well as in a variety of types. At times the dilatation is fusiform or spindle-shaped, there being a uniform distention of the arterial wall in its entire circumference. In these specimens the artery is equally involved in all its coats and on every side. Small saccular aneurysms are also encountered in which the bulging is more pronounced in one direction, owing to the more marked attack at one point than another. Again we have observed the development of a false aneurysm where the tissue of the artery has given way with rupture and the development of a blood sac in tissues outside of the artery and not bounded by its coats. A common and almost constant characteristic of these aneurysms is thrombosis, occupying not only the sac, but also much of the natural arterial lumen. This thrombosis differs considerably from that observed in the more common aneurysms. Under ordinary conditions an aneurysm develops through the dilatation of an artery in which the inner coats, though modified in their architectural arrangement, still remain intact. The thrombus which develops within such an endothelial-lined sac is laminated and undergoes change slowly, as the granulation tissue replaces it. The thrombus in periarteritis nodosa might more appropriately be spoken of as an acute thrombus, developing not only in consequence of the slowing of the blood current within the sac, but more particularly because of peculiar changes in the arterial wall with which it is in

contact. It must be remembered that the aneurysm in periarteritis nodosa is an acute one, becoming established within a few weeks. The arterial wall suffers an acute degeneration and inflammation in which its wall from adventitia to intima is involved. The endothelial lining is either destroyed or exfoliated, so that the underlying damaged structures are in direct contact with the blood stream. It is upon these tissues in a state of necrosis that the blood rapidly coagulates without showing the laminated arrangement so commonly present in thrombi of slower production. It is furthermore observed that the fibrin coagulum is firmly attached to the arterial wall and even appears to suffuse the tissues to some depth. In this position the fibrin becomes altered and assumes a bland hyaline appearance, so that it is indistinguishable from the similar degeneration of the musculature of the media. Thus in the aneurysmal sacs containing thrombus it is impossible to recognize demarcation between the original arterial wall and the hyaline clot within it. It would appear that those substances which act upon the musculature of the media and convert it to a homogeneous product of degeneration have a similar effect upon the constituents of blood clot. When thrombosis has once begun it rapidly progresses to the occlusion of the entire artery.

It is well to call attention again to the finding in microscopical studies of inflammation about arteries, that inflammatory processes with marked cellular exudate follow the course of the lymphatics in the outer arterial wall and are common to a variety of infections. The inflammatory reaction showing a non-suppurative exudate and having a predilection for the adventitia and periarterium is most commonly associated with the bacteria belonging to the Streptococcus viridans group. Systemic infections by these microörganisms regularly involve groups of arteries in one or more organs. The arteries of the heart, kidneys, meninges, muscles, and subcutaneous tissues are so frequently the points of localization of this infection that, depending upon the persistence of the attacking microörganism and the progressive damage done in local areas, our attention is

particularly attracted to one of these tissues. The bearing of these findings under conditions other than periarteritis nodosa is more clearly brought out in an analysis of the bacteriology which has been made upon some of the reported cases.

Bacteriology. — Several cultures were made from different fluids in each of our cases. In Case I. no blood culture was obtained during life, but a culture was taken from the arm vein within a few minutes after death. No growth was obtained. At autopsy a culture made from the heart's blood gave negative results, but a culture of the bile from the gall-bladder showed the presence of Streptococcus mitis and B. proteus vulgaris. In Case II. a blood culture obtained during life was negative as was also the culture of the necrotic material obtained by excision of one of the skin nodules. Another blood culture made immediately after death was negative. At autopsy a culture from a nodule over the pectoral muscles gave Staphylococcus pyogenes aureus and a diphtheroid bacillus; heart's blood gave Streptococcus anginosus and Streptococcus salivarius; bile gave Staphylococcus pyogenes aureus; nodule of liver gave Staphylococcus pyogenes aureus and Streptococcus anginosus; lymphatics of capsule of liver gave Staphylococcus pyogenes aureus and Streptococcus anginosus.

With these findings it is difficult at first sight to conclude which, if any, of the organisms played the important part in the inflammatory process of the arteries. The presence of the staphylococcus and the diphtheroid bacillus in the softened nodule beneath the skin is a finding which does not particularly attract our attention. The presence of these microörganisms in lesions of these tissues is a not uncommon finding. On the other hand, the presence of streptococci in different regions as well as the rather wide dissemination of the staphylococcus offer points difficult of interpretation. We are, of course, aware that microörganisms invade widely the dead body and continue to spread with the increase in time after death. It is also important to remember that an

agonal invasion not uncommonly takes place by bacteria having no direct relation to the disease present in life. In our two cases, however, such an agonal invasion was not demonstrated. On the other hand, it is a not uncommon finding to demonstrate bacteria in local foci in the absence of them in distant body fluids. It is possible that infective agents localized in and about the liver do not make their appearance as a bacteriemia, but only after death find opportunity to advance by growth into neighboring organs. Thus the heart blood may easily show the presence of infection several hours after death when bacteria have grown to it in the blood medium from a neighboring organ like the liver. It is probable, however, that the variety of organisms isolated in Case II. was not present at the onset of the arterial affection, but that some of them were true secondary invaders attacking a damaged tissue.

Relatively few of the cases of periarteritis nodosa have had a bacteriological investigation. It is interesting, however, that of seven previous reports one was negative (Veszpremi); five showed the presence of some type of streptococcus (Datnowski, Jonas, Beattie and Douglas, Lamb Cases I. and II.); two showed the presence of Staphylococcus aureus (Oberndorfer and Lamb Case II.); two showed the presence of B. coli (Lamb Cases I. and II.); one showed the presence of B. influenzæ (Jonas). Besides this we find that Longcope and Babes and Mironescu observed the presence of streptococci in sections of the arterial lesions. In taking all of the cases (nine including our own) in which cultures have been made, we find that seven gave streptococci either alone or mixed with other bacteria. In the absence of cultural differentiation it is impossible to say what types of streptococci were most commonly found. It is probable that the streptococcus isolated in Lamb's second case was a Streptococcus mitis. From our own findings we are led to believe that the infecting agent is not always the same, and that, therefore, we are in no way dealing with a disease entity. The finding in both of our cases of a streptococcus of the viridans group as well as of another type belonging to the

hemolytic streptococci suggests strongly that this variety of bacteria plays an important part in the development of the peculiar arterial lesions. As we have already pointed out, a number of these cases present a previous history which we are wont to associate with infections by this group of microorganisms; while furthermore, not a few clinical manifestations which are so commonly seen during infections by the viridans group were observed in these patients.

Respecting the importance of the syphilitic virus we are inclined to agree with Lamb and others that it plays only a secondary part. It is possible, as we have intimated above, that the systemic influence of syphilis permits a secondary invasion more ready access. It is of importance that these lesions of periarteritis nodosa which are met with in their acute process have never shown the presence of the spirochete. It is furthermore important that nodular lesions of arteries similar to those in man have been observed in deer (Lupke and Jaeger), pig (Joest), and calf (Guldner).

Animal experiments. — Although in a number of cases bacteria have been isolated from the lesions, Lamb alone has attempted to reproduce the process in animals. He inoculated a guinea-pig, a rabbit, and a monkey with the Streptococcus viridans which was obtained in his second case. These animals showed no manifestations following the injections, and when killed two months later showed neither gross nor microscopical lesions. Another rabbit inoculated with a large dose of the same microörganism died in eighteen hours without showing anything definite.

We have carried out a series of animal experiments using the three types of streptococcus which were isolated from our cases. Rabbits were used in all experiments. Five animals were inoculated with Streptococcus mitis, two with Streptococcus salivarius, and five with Streptococcus anginosus. The manner of inoculation was the same for all animals. The method of the experiment attempted to place the microörganisms into the periarterial lymphatic spaces so that the inflammatory reaction would, from the

beginning, be localized about the arteries, and would have an opportunity of progressing in these channels along the course of the artery and its branches. For this purpose two regions in particular were selected for the points of injection; the regions being selected because of the rich lymphatic supply about the neighboring arteries. One of these was in the abdomen, the other in the thorax. The abdominal inoculation was made, following a laparotomy for exposure, into the periarterial tissues of the celiac artery just after it was given off from the aorta. At times the tissues about the mesenteric artery were also infected. The inoculation was made by syringe with a fine needle. The cultures were usually concentrated by centrifugalization so that only a small bulk was necessary to be introduced. The laparotomy wound was then carefully closed, care being taken to avoid infection of the peritoneum. Only one animal developed peritonitis. The second region chosen for inoculation was the anterior mediastinum of the thorax. It was found, after several trials upon dead animals, that an inoculation could be made into the loose mediastinal tissues, rich in lymphatics, by introducing the hypodermic needle from above downwards behind the sternum. It was found not difficult to reach a position just below the aortic arch. The results of our experiments will be given only in summary, reserving the details for a later and more extensive analysis.

The Streptococcus anginosus was found to have an unusual pathogenicity for rabbits, so that the dose had to be reduced much below that given for the Streptococcus mitis and Streptococcus salivarius. Out of the five animals inoculated with Streptococcus anginosus, four died in less than twenty-four hours, the fifth was killed at the end of eleven days. The marked feature resulting from the inoculation of Streptococcus anginosus was the local necrosis of tissue surrounded by an inflammatory zone of limited extent. Even in the animals dying in less than twenty-four hours, the tissue necrosis was quite marked. The inflammatory reaction was accompanied by much edema with widening of the tissue

spaces and an infiltration by varying quantities of inflammatory cells. The migration of the inflammatory reaction could, at times, be followed for a considerable distance along the blood vessels. At times a sub-acute periarteritis appeared along the hepatic artery in the liver or along the splenic or the branches into the pancreas. Non-inflammatory necroses were found in various portions of the pancreas. Similar reactions were also observed in the mediastinum, but here it was more difficult to follow the inflammation along the individual vessels. Occasionally the reaction followed the vasa vasorum on to the aortic wall, but more definite responses were observed about the small arteries of the mediastinum.

Somewhat better results were obtained with the use of Streptococcus mitis and Streptococcus salivarius. The animals were examined after a period of from two to eleven days following the inoculation. In no instance was a true periarteritis nodosa obtained. Nevertheless, very interesting lesions, in many respects simulating the early responses of periarteritis nodosa, were obtained. It was found that, by the method employed for infecting the arteries, it was not difficult to obtain a periarteritis of various grades of intensity. Where larger doses of bacteria were inoculated at a single point, a reaction by polymorphonuclear leucocytes was the result. With smaller doses and in regions at some distance from the point of inoculation the cellular reaction was mainly composed of lymphocytes and plasma cells with relatively few leucocytes. The majority of these reactions were truly perivascular, as are those so often found in many human infections of various tissues. These perivascular reactions lie outside of the arterial wall and occupy the lymphatic spaces which follow the course of these vessels. On the other hand, we also obtained in these experiments a type of perivascular reaction, which at different intervals along the route of the artery advanced towards the arterial wall proper, leading to an inflammatory zone in the adventitia as well as in portions of the media. In two instances arteries were observed in which a hyaline change occurred in the tissues

of the adventitia and outer portion of the media. In one other instance we obtained a complete hyaline destruction of the media without any evidence of inflammatory cells occupying the arterial wall proper. The only inflammation in this latter instance was found in the perivascular tissues. In none of the arteries had sufficient weakening of the walls occurred to permit of the characteristic dilatation and thrombosis. Although our experiments have not been successful in reproducing the lesions, we are sufficiently encouraged to continue the methods used in these experiments for the reproduction of the lesions. One of the difficulties which we have found hard to control is the proper gauging of the dose to be inoculated when the virulence of the microörganisms changes so markedly on artificial media. It is possible also that the rabbit is an unfavorable animal for carrying out these experiments, and it may be found that the reproduction of the particular injuries can be more readily accomplished in other animals.

CONCLUSIONS.

Periarteritis nodosa, a disease process of man and animals, is of rare occurrence. Records of forty human cases have been found in the literature, to which we have added two of our own.

The lesions are distributed along one or more arteries and their branches. The distribution is by way of the periarterial lymphatics.

The process is an inflammatory one, beginning in the outer portion of the artery and accompanied by a hyaline degeneration of the media. The intima is only secondarily involved, as it is disturbed by inflammatory or degenerative conditions in the outer arterial coats.

Secondary aneurysms with rupture are not uncommon. Thrombosis of the involved arteries may lead to nutritional disturbances of organs and tissues supplied by the vessels.

Syphilis, although present in a number of cases, is not the exciting factor, but may play a rôle in inducing greater susceptibility of tissues.

The most important agent which has been found as the probable cause of the lesion is the group of streptococci. It is probable that no particular member of the streptococcus group is alone responsible for the arterial lesions.

Animal experiments have shown that various types of streptococci may induce individual reactions similar to those observed in periarteritis nodosa, but up to the present no characteristic damage has been produced upon the arterial wall whereby aneurysm, thrombosis, and rupture have presented the picture seen in the human form of periarteritis nodosa.

[I am much indebted to Dr. H. H. Permar for the illustrations which accompany this paper.]

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(A full review of the literature is contained in the articles by Lamb and by Dickson.)

EXPLANATION OF PLATES I. AND II.

PLATE I., FIG. 1. — Periarteritis nodosa in wall of gall-bladder. (Case II.)

FIG. 2. — Periarteritis nodosa of hepatic arteries. (Case II.)

FIG. 3. — Acute degeneration of hepatic artery with aneurysm and thrombosis. (Case I.)

FIG. 4. — Acute periarterial inflammation with hyaline degeneration of media. (Case I.)

PLATE II., FIG. 5. — Acute non-suppurative periarteritis with advancing hyaline degeneration of the media. (Case II.)

FIG. 6. — Experimental periarteritis with secondary mesarteritis and endarteritis.

FIG. 7. — Experimental periarteritis with early hyaline degeneration of outer media.

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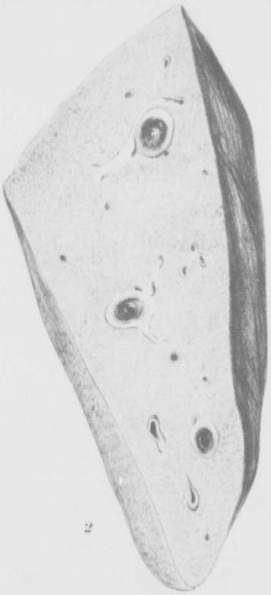

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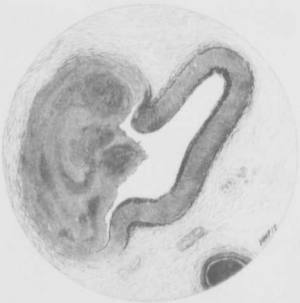

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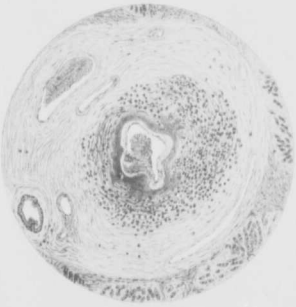

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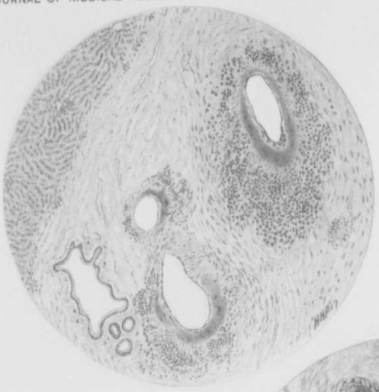
Klotz. Periarteritis nodosa.



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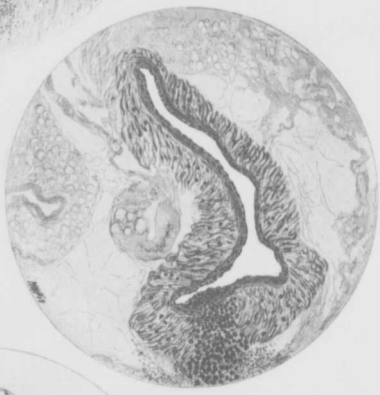

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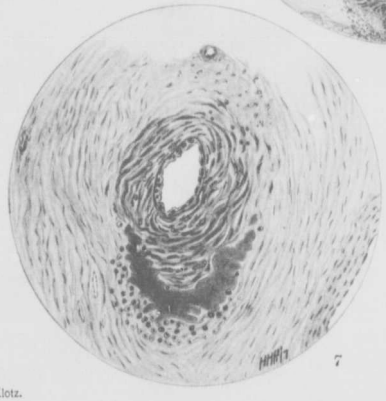

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Klotz. Periarteritis nodosa.