PERIARTERITIS NODOSA—A CLINICAL AND PATHOLOGICAL REVIEW OF THE DISEASE

WITH A REPORT OF TWO CASES *

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INTRODUCTION

A number of diseases which are to-day not uncommon and which are recognized clinically without much difficulty were at one time quite rare, owing largely to the fact that so little was known about them that they either escaped notice or were incorrectly diagnosed. It is quite possible that the rather rare but exceedingly interesting affection known as periarteritis nodosa is a case in point. Most of the cases have been observed in Germany, where the disease was first recognized and where the clinicians and pathologists have come to be familiar with it, whereas in this country, where the disease has attracted very little attention, only three cases have been reported up to the present time.¹

Within the past year at the Presbyterian Hospital, we have had the exceptional opportunity of seeing two cases. Including these, the total number of reported cases now numbers but thirty-eight. Most of the reports have concerned themselves largely with the pathologic histology of the disease and, except for some minor differences of opinion, this aspect of the affection has been well covered. We are still quite in the dark as to the cause, however, and many of the histories are too brief to aid greatly in arriving at a correct idea of the symptom-complex. Indeed, many observers are inclined to the belief that, barring the presence of the subcutaneous nodules, which are present in only a small minority of the cases, there is no set of symptoms on which a diagnosis can be made. One cannot escape the conviction, however, that an increasing familiarity with the disease may lead to some means of diagnosis whereby more cases may be recognized and that the chance for study during life thus afforded may clear up the present obscure etiology. It, therefore, seems most desirable that all cases of periarteritis nodosa be reported as completely as possible. And, in view of the extreme rarity of the disease in this country, the present seems an opportune time for a complete review of the known facts concerning it.

* Submitted for publication, June 1, 1914.

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1. The two cases here given were very briefly reported at the New York Pathological Society during the past year.

REPORT OF TWO CASES

For permission to use the clinical records of these two cases I am greatly indebted to Drs. Janeway, Bovaird and Lambert on whose services in the hospital they occurred.

CASE 1.—Man, aged 26, mechanic, ill about seven weeks, was admitted to the hospital, Dec. 7, 1912. The family history was unimportant.

Past History.—The patient had typhoid at the age of 4. Two years ago he had an attack of grip. Venereal disease is denied. He does not use tobacco; takes an occasional glass of beer.

Present History.—For the past two years patient has had asthma. At first the attacks came about once a month, lately as often as two or three in a week. About three weeks before admission he noticed intense itching about the right ankle and in eight or ten hours an oval, node-like swelling the size of an egg appeared. The overlying skin was tense, shiny and covered with bright red macules measuring about 4 mm. in diameter. The swelling gradually lessened and the macules underwent the color graduations of a contusion. In two or three days the swelling and eruption had entirely disappeared. Pain and tenderness were severe at the height of the swelling, disappearing with its subsidence. The night after the swelling appeared he had a severe asthmatic attack lasting all night. Expectoration was quite profuse and contained clotted blood. Since then he has had a purpuric eruption appearing on different parts of the body roughly every other night with asthmatic attacks on the alternate nights. All parts of his body have been affected except the face. For the past two weeks, accompanying the rash, he has had severe abdominal cramps lasting for ten or twelve hours and ceasing after vomiting. Vomitus consisted of a thin green liquid with a few blood-clots. At times, with the appearance of the eruption he would have pains in various joints and these would be swollen, slightly red, tender and very painful on any motion. Bowels moved once or twice a day and were normal as far as he knows. Appetite is good; no loss of weight; no fever or night-sweats. For the past two weeks patient has been up ten or twelve times at nights to urinate.

Physical Examination.—Pale and sallow. Superficial lymph-nodes slightly enlarged. Eyes normal. Gums firm. No throat lesions. Lungs: Moderate relative dullness at right apex posteriorly; feeble inspiratory murmur with prolonged expiration and high-pitched piping râles over all. Heart: Apex in fifth space, 10.5 cm. to left of mid line; sounds normal, no murmurs. Arteries small, soft and just palpable. Blood-pressure 145-105. Abdomen rather full and tympanitic; liver not felt; edge of spleen just felt at costal margin on deep inspiration; no masses or rigidity. Both legs show numerous small hemorrhagic areas in various stages of involution. These areas vary in size from petechiae to irregular confluent areas about 1 cm. in length. The larger ones are grouped about the ankles and are deep wine color. The lesions are somewhat raised, firm and dry with a tendency to scaling. On the left thigh, just above the knee, there is a large, somewhat elevated, firm area the size of the last joint of the thumb. It is pale green, somewhat tender and apparently in the course of the internal saphenous vein but not connected with it. On the right thigh there is an elongated, raised area measuring 3 by 1 cm. It is reddish brown with dark red spots in the center, is very slightly tender and for its whole length lies over a superficial vein. About the knees there are a few pale green discolorations. Over the lower end of the right tibia there is an irregular depressed ulcer. It is dry and the floor is made up of a deep red blood-clot. Below the left patella there is some thickening in the region of the bursa, with slight pain on flexion of the leg. The most probable diagnosis seemed to be Schönlein's "purpura rheumatica."

Course.—The temperature on admission was 100.4 F., gradually falling to normal on the fifth day. It remained normal for three days and then rose

gradually to 101.8. In a few days it was again normal and then subnormal for five days. There was another short rise to 100.4, followed by another normal period and a terminal rise to 102. The pulse varied between 85 and 130 and was generally more rapid than one would expect for the temperature. When the temperature was subnormal, the pulse was between 80 and 110.

Urine.—Eight examinations. The specific gravity varied between 1.010 and 1.018. There was always a trace of albumin present and on five occasions it was estimated at from 0.15 to 0.22 per cent. No sugar was found. There were always hyaline and granular casts present and at times epithelial and waxy casts as well; also a moderate number of leukocytes and a few to many red blood-cells.

The blood-counts showed the following result:

Date	R. B. C. No.	Hb. Pct.	W. B. C. No.	Polys. Pct.	Lymphos. Pct.	L. Monos. Pct.	Eosin. Pct.
December 9		75	17,200	50	14	2	34
December 10	3,500,000	65	20,200	51	11	0	38
December 12		..		32	12	5	51
December 31	3,384,000	42	20,900	58	17	2	23

December 9: Sputum shows many red blood-cells and ciliated epithelial cells but no Charcot-Leyden crystals, Laennec's pearls or Curschmann's spirals.

December 12: Eye-grounds negative.

December 14: Wassermann reaction (Noguchi modification) negative.

December 17: Since yesterday afternoon patient has complained of constant, sharp abdominal pain without any other change in the physical signs. No vomiting. Stools normal. No tubercle bacilli found in the sputum.

December 18: Phthalein test: Color appeared in twelve minutes. Amount at the end of two hours too small to estimate. Sputum bloody. Coughs less. Feels better. Abdominal pain has disappeared. Lips and nails quite cyanotic. No tubercle bacilli in sputum.

December 20: Slight pain in the shoulders and neck this morning. Has a considerable amount of yellowish-green sputum with considerable fresh blood. The lungs show nothing more than the signs of asthma and bronchitis. No pain in the chest. Considerable relief from epinephrin.

December 29: White, rather glistening lines are seen along the vessels of the left retina as they come through the disk.

December 31: Gastric contents: Total acidity, 38. Free hydrochloric acid, 6. No lactic acid. Moderate reaction for blood. No ova or parasites in the stool. A second phthalein test showed the color in seventeen minutes, but the amount at the end of two hours was again too small to estimate.

January 1: The veins and glands in both inguinal regions are very sore and tender. In the left femoral region there is a small, red, tender area.

January 2: There is more redness and swelling in the left femoral region. On the back of the left leg there is a slightly swollen, reddened area measuring about 4 by 6 cm. The right hypochondrium is distinctly tender and resistant.

January 5: There is a pericardial friction-rub present this morning and a pleural friction-rub at the left base. Lumbar puncture: Twenty c.c. of clear fluid obtained. Cultures sterile. Urea, 0.323 per cent. Sodium chlorid, 0.812.

January 6: Died to-day after increasing stupor for two days. Gradual failure of pulse and respiration before death. During the last sixty hours voided only 1,000 c.c. of urine. The blood-culture taken in two-broth flasks, January 3, remained sterile. Blood-pressure varied between 135 and 165. The urine quantity varied between 690 and 1,920 c.c. On thirteen days it was below 1,000 c.c.

Post-Mortem Examination.—The diagnosis of periarteritis nodosa was not suspected at the time of the necropsy. When the microscopic sections were examined several days later and the characteristic lesion found in the kidney, the organs from the patient were again carefully examined; but the only sug-

gestion of arterial lesions was found in the heart, where there were one or two pin-head-sized whitish nodules on one of the small coronary branches. No nodules were found in any of the other organs. Unfortunately, none of the subcutaneous tissue in the regions of the eruption and swellings was examined.

The essential points in the necropsy were the following:

The body is strikingly pale and considerably emaciated. There are ecchymoses about the right knee and about both elbow-joints. The peritoneal cavity contains a small amount of cloudy yellow fluid, and the intestines show a scattered fibrinopurulent exudate. The lungs are adherent to the chest-wall and to the outer surface of the pericardium by fresh fibrinous adhesions.

Lungs: Both are edematous and show scattered areas of bronchopneumonia. The bronchi are intensely congested and contain mucopurulent material. The vessels appear normal.

Bronchial Lymph-Nodes: Moderately enlarged, deeply pigmented and firm.

Heart: The pericardium contains about 50 c.c. of cloudy yellow fluid; there are several fresh fibrinous adhesions stretching between the two surfaces and the surfaces are covered with a shaggy, fibrinopurulent exudate and show scattered petechial hemorrhages. The heart is not enlarged. There is a small, firm, irregular nodule at the base of one of the pulmonic cusps and the mitral cusps show small, irregularly nodular, reddish vegetations, the largest about the size of a small pea. The other valves and the heart chambers show no change. In general the heart-muscle is homogeneous and dull reddish-brown, but there are scattered areas of a more dirty yellow color. The main portions of the coronary arteries show no sclerosis. The aorta is smooth and elastic throughout its course.

Spleen: Measures 12 by 7 by 3 cm. There is perisplenitis. Otherwise the organ appears normal.

Liver: Measures 29 by 19 by 6 cm. There is a small area of superficial atrophy in the right lobe. On section, the liver shows no abnormal change.

Gall-Bladder: Normal. Ducts patent.

Kidneys: Left measures 12 by 7 by 3.5 cm. The capsule strips easily, exposing a smooth yellowish-pink surface with a rather diffuse mottling of yellow. On section the cortex does not average more than 5 mm. in thickness and is slightly less than this in some places. The striations are indistinct and quite distorted. The glomeruli are quite distinct as colorless dots. The pelvis and ureter are normal.

Right: Measures 11.5 by 6 by 3.5 cm. and is quite similar in all respects to the left.

Adrenals and esophagus appear normal.

Stomach: Contains a little brownish fluid and a moderate amount of mucus. There is considerable injection of the mucous membrane and a few small petechial hemorrhages.

Pancreas and Ducts: Normal.

Mesenteric Lymph-Nodes: These are enlarged, many to bean-size. Several of them are broken down and ooze creamy-yellow pus on section.

Intestines: Show nothing more than a few areas of congestion in the lower part of the ileum.

Bladder and Prostate: Normal.

Brain and Spinal Cord: Permission could not be obtained for their examination.

Microscopic Examination.—Lungs: Many sections from various parts of the lungs were examined. These show a thickened pleura, extensive pulmonary edema with congestion of the alveolar walls and swelling of the alveolar epithelium and scattered areas of hemorrhagic bronchopneumonia. There is some increase of connective tissue about the bronchi together with numerous mononuclear wandering cells and eosinophils. Scattered here and there in the alveoli are small clumps of Gram-positive cocci. The large vessels appear quite

normal and in most of the sections even the smaller arteries show no change; but one does find a few small arteries both about the bronchi and in the lung-tissue proper which are not normal. The changes consist in an adventitial and periarterial infiltration with mononuclear wandering cells and eosinophils, polymorphonuclear leukocytes being almost entirely absent. The changes are generally unilateral or at least more marked on one side, and the media and intima are normal. An occasional small artery is seen, however, whose lumen is almost entirely occluded. These changes apparently represent an early stage of the lesion seen in the arteries in other organs.

Fig. 1.—Case 1. Section of a small coronary branch just beneath the epicardium showing very pronounced periarterial infiltration with a small area of beginning necrosis on one side. The media, while still intact, takes the eosin stain rather strongly. *I*, intima; *E*, internal elastica; *M*, media; *A*, adventitia; *X*, periarterial infiltration; *Y*, area of beginning necrosis.

Bronchial Lymph-Node: In the capsule, two small arteries are found showing early changes similar to those seen in the lung. The arteries in the gland itself show no change. There is considerable pigmentation and hyperplasia.

Vegetation of Mitral Valve: Consists of a very vascular and quite cellular mass of connective tissue richly invaded by mononuclear wandering cells. On the surface is an irregular thrombus mass containing clumps of bacteria. These appear to be cocci. Smears from these vegetations show a few pairs of cocci surrounded by a small space and also some rather fat Gram-positive bacilli.

Heart: The pericardium shows an acute inflammatory exudate. There is cloudy swelling of the muscle-fibers and patchy interstitial myocarditis about the vessels. A section of one of the papillary muscles shows a most extensive fibrosis with large areas of granulation tissue and wandering-cell infiltration. Most of the vessels show no change. Some of the small arteries, while showing no changes in their coats, have a little surrounding cellular infiltration, the cells being generally mononuclear wandering cells and eosinophils. One section, taken through one of the tiny macroscopic nodules, shows the periarterial character of the lesion very well (Figure 1). It affects a small artery just beneath the pericardium. The lumen is narrowed, being encroached on by the moderately proliferated intima, and contains red blood-cells, among which are some fibroblasts extending in from the intima. The intima is thicker on one side, its texture quite loose and its cells irregular in size and shape. Some of

Fig. 2.—Case 1. Section of a small artery in the muscular coat of the stomach. Represents a very early lesion. The intima and media are normal. The elastic lamellae are not changed. The adventitia is loose in texture and is densely infiltrated with eosinophils.

them are quite definitely fibroblasts; others look like distorted endothelial cells. The internal elastica is well preserved except at one point, where it is wanting opposite a small necrotic area in the media. The media appears granular and the nuclei indistinct but it shows no cellular infiltration. There is no characteristic hyaline ring, but the media gives one the impression of approaching toward such a condition as seen in other vessels. The fibers appear more granular and take the eosin stain more intensely. The adventitia is much thickened and merges imperceptibly into the tremendous periarterial cellular infiltration and granulation tissue. The cells are wandering cells, fibroblasts and a most striking number of eosinophils. Many of them are plasma-cells. While polymorphonuclear leukocytes are scarce, one does find some. All of these cells infiltrate the surrounding fat for a considerable distance. At one side there is a small area of necrosis.

Spleen: Eosinophils are rather strikingly numerous and seem especially attracted to the vessels. The small arteries are somewhat thickened but none of them shows any characteristic change.

Liver: Shows cloudy swelling and one small area of superficial atrophy. Some of the portal spaces show a little increase of connective tissue with a few wandering cells. There are no distinct arterial changes.

Pancreas: Shows no change except for a little wandering-cell infiltration about one or two of the small arteries. Mixed with these cells are a few eosinophils.

Fig. 3.—Case 1. Section of artery in kidney. The intima, *I*, is much thickened and is surrounded for two-thirds of the circumference by the internal elastic lamella which does not show in drawing. Just external to this is the hyaline ring, *H*, which fuses with the area of necrosis at *Y*. Adventitia, *A*, apparently extends outside the area of necrosis. *E*, internal elastica as shown in other sections stained with elastic-tissue stain. It is wanting opposite the area of necrosis.

Mesenteric Glands: Many small arteries are seen both within the gland and in the surrounding tissue which show early changes.

Stomach: The various coats of the organ appear normal. In one section, in the muscular coat, there is a cross-section of a small artery (Figure 2) which is of interest as it possibly shows a very early lesion. The intima and media appear normal and the elastic lamellae are unchanged. The adventitia is loose

in texture and cannot be differentiated from the adjacent tissue. It is densely infiltrated with eosinophils and a few cells with large, oval, vesicular nuclei. No further change is made out in tracing the vessel through serial sections. While one cannot be certain that this represents a very early change, the eosinophils which are found so abundantly in the lesions elsewhere seem to point to this conclusion. Another section shows a typical lesion of a small artery in

Fig. 4.—Case 1. Section of artery in adrenal. The intima, *I*, is thickened. The internal elastica, *E*, is intact except in the region of necrosis, *Y*, where it has disappeared. The hyaline ring, *H*, in which one can still make out the cells of the media lies just external to the elastica and fuses with the area of necrosis at *Y*. Adventitia, *A*, merges imperceptibly with the periarterial infiltration.

the submucosa. An elastic-tissue stain shows the internal elastica ending abruptly after encircling about one-half the circumference while the external elastica is completely gone. Another vessel shows similar changes but with an added complete thrombosis.

Intestines: There is an acute inflammatory peritoneal exudate, intense congestion of the vessels and some hemorrhages in the mucosa. A number of the small arteries show typical early changes and two are completely thrombosed.

Kidneys: These show the most striking changes of any of the organs, and it was here that the lesion was first noticed. In this place (Figure 3) the lumen of the artery is small and the intima very much thickened, being composed of a loose connective tissue, rich in fibroblasts and containing a few eosinophils and nuclear fragments. Surrounding the intima for about two-thirds of the circumference, the internal elastica is intact but swollen in places. Just outside of it and limited by it, is the characteristic, intensely eosin-stained, hyaline ring in which one can still make out the cells of the media. It gives the impression of being a more advanced stage of the appearance seen in the section of a coronary artery. At one side, the elastica has disappeared, the hyaline ring melts into an area of necrosis and the cellular infiltration of the adventitia breaks through into the intima. The adventitia is composed of young connective tissue with some wandering-cell infiltration and at this point seems to extend outside the area of necrosis which is mainly in the media. While this is the most advanced lesion seen in any of the many kidney-sections, many of the small arteries show similar if less marked changes. There is an exquisite acute, subacute and chronic glomerulonephritis, the glomeruli showing all stages of adherence to the capsules with epithelial crescents and hyaline thrombi. There is an extensive diffuse increase of connective tissue throughout and a striking wandering-cell infiltration with many eosinophils in the interstitial tissue. The vessels are all congested and many of the tubules contain blood. Some of the tubules are practically obliterated while some are dilated and cyst-like.

Adrenals: The arteries of the capsule show the lesion beautifully, the hyaline ring being especially well marked (Figure 4). As in the kidney, this ring is situated just outside the internal elastica which is preserved for about two-thirds of the circumference and then melts into an area of intensely eosin-stained necrosis in the media. The intima is loose in texture and rather loculated. The cells are large and contain oval, vesicular nuclei. There is an intense periarterial exudate and granulation tissue with many eosinophils. The gland itself shows no change.

Bacteriologic Findings at Necropsy.—Heart-blood: Two broth-flasks show colon bacilli and Gram-positive cocci in chains. The latter were overgrown by the former and were not isolated.

Peritoneal Exudate: Smears show pus-cells and many chain cocci. No other bacteria. Cultures give a pure growth of streptococci.

Pericardial Fluid: Smears show unformed detritus, rarely a pus-cell. No bacteria found. Cultures in broth and ascitic glucose-agar are sterile.

Mesenteric Lymph-Node: Smears show cocci in chains and many pus-cells. Cultures not taken. Unfortunately the cultural characteristics of the streptococcus isolated from this case were not worked out so that it is impossible to compare it with the organism obtained in the second case.

Careful examination of many sections stained for bacteria by various methods failed to show any in the vascular lesions in spite of the fact that the necropsy cultures showed a bacteremia. No spirochetes could be found in sections stained by the Levaditi method.

CASE 2.—Girl, aged 10, ill five weeks, was admitted to the hospital Jan. 18, 1914. The family history was negative.

Past History.—Five years ago patient had a slight attack of pain in the epigastrium somewhat similar to the present attack but less severe. It lasted only one day. Had measles as a baby and diphtheria five years ago.

Present History.—Nine days before admission patient was taken suddenly ill in the night with severe pain in the epigastrium. Felt better the next day and was up and about for two days, when the pain came on again and she vomited twice. The pain was sharp and well localized to a small area high up in the midline. Since that time she has been in bed and has had the pain intermittently but always in the same place; has felt feverish, had a headache and has vomited several times. Her throat was sore but has been better for the last few days. She says that she had blood in her sputum at times. No pain is felt on micturition and no blood appears in the urine.

Physical Examination.—Patient well developed and large for her age. Appears acutely ill. No eruption present.

Pharynx: Reddened and shows a considerable thin mucoid, blood-tinged exudate. The left tonsil is enlarged, the right slightly so.

Tongue: Dry and heavily coated.

Lymph-Nodes: The anterior cervical and axillary are palpable.

Heart: Is not enlarged, sounds regular and of good force. No murmurs. Pulses equal and regular. Low tension. Walls not palpable.

Lungs: Clear except for a few transient râles at the left base.

Liver and Spleen: Not palpable.

Extremities: Reflexes normal. No edema.

Abdomen: There is general abdominal fulness and resistance which seems involuntary. No true rigidity. There is tenderness over the whole lower abdomen, more marked on the right side. No dulness in the flanks. No masses. The temperature on admission was 102.6 F. and the blood-count showed 33,100 leukocytes with 93 per cent. of polymorphonuclear leukocytes. A diagnosis of appendicitis was made and she was operated on shortly after entering the hospital. The appendix and peritoneal cavity were found to be normal. The abdomen was explored but no cause found for the symptoms.

January 20: Blood-culture, two broth-flasks sterile.

January 21: There is tenderness and evidence of fluid in both knee-joints and tenderness in both hip-joints. Heart normal.

January 22: There is tenderness in the left shoulder-joint. Temperature between 102 and 103. Wassermann reaction, three plus.

January 23: Shoulder still painful. Signs in the knees have cleared up. Heart normal. Chill.

January 27: Right knee shows a small amount of fluid. Slight amount of edema in the region of the Achilles tendon of both legs. The abdomen is distended in its upper half but not tender. No dulness in the flanks. Spleen not palpable. Heart and lungs normal. There is a little edema of the dependent part of the back.

January 28: Throat culture shows a predominant streptococcus. Patient seen by Dr. Janeway, who believes that she is suffering either from sepsis following a streptococcus sore throat and has a toxic nephritis or that she has nephritis following an unrecognized scarlet fever. Transferred to the medical service. During her stay on the surgical side the urine showed a specific gravity of between 1.012 and 1.028. Albumin, from a very faint trace to a trace. A few to many hyaline and granular casts. No red blood-cells. A blood-count taken January 19 showed 26,200 leukocytes with 92 per cent. of polymorphonuclears, and one taken January 28 showed practically the same. The temperature varied between 101 and 103.6 for a week. It was then lower reaching normal January 27 and on the following two days was between 99 and 100.4. The pulse corresponded with the temperature, varying between 74 and 128. The surgical diagnosis was acute tonsillitis, acute nephritis and acute toxic arthritis. She was apathetic at times, quite thirsty and vomited repeatedly.

On admission to the medical ward her physical examination was unchanged. There was tenderness over the whole abdomen, most marked in the midline

above the umbilicus. Very slight edema of the back. The right wrist was somewhat stiff and painful on motion. The right shoulder was somewhat painful.

January 29: White blood-cells, 17,000; polymorphonuclears, 95 per cent.; lymphocytes 5 per cent.

February 1: Liver felt 2 inches below the costal margin. White blood-cells, 52,000; polymorphonuclears, 95 per cent.; lymphocytes, 4 per cent.; large mononuclears, 1 per cent.

February 2: Blood-culture, two broth-flasks sterile. Patient is quite drowsy. There is a mottled erythema over the upper part of her forearms.

February 3: White blood-corpuscles, 66,000; polymorphonuclears, 95 per cent.; lymphocytes, 5 per cent. There is a systolic murmur at the apex. The eruption has disappeared. General condition improved. The right wrist is swollen and painful on motion.

February 5: White blood-corpuscles, 39,800; polymorphonuclears, 90 per cent.; lymphocytes, 9 per cent.; large mononuclears, 1 per cent. Wassermann reaction negative. Blood-culture, two ascitic glucose-agar plates, sterile.

February 6: Metacarpophalangeal joints of both hands swollen and tender. Right wrist better. There is a dusky mottling of the face, whole trunk and extremities, especially over the back and shoulders. It is in the nature of a diffuse erythema.

February 7: Vomitus, 175 c.c. of thick yellow fluid. Total acidity 24, no free hydrochloric acid. Faint reaction for lactic acid. Blood-count: White blood-corpuscles, 40,400; polymorphonuclears, 73 per cent.; lymphocytes, 27 per cent.

February 10: Temperature is lower and joints have cleared up. For the past three days has suffered from paroxysms of abdominal pain and complains of pain on the slightest pressure. There is no rigidity. Rectal examination negative.

February 11: White blood-corpuscles, 26,600; polymorphonuclears, 88 per cent.; lymphocytes, 12 per cent. Vomitus, 155 c.c. of a dark brownish fluid. Faint reaction for blood. Total acidity 8, free hydrochloric acid 4. No lactic acid. Stool: Yellow, fluid; contains small flecks of mucus; moderate reaction for blood; urobilin, moderate. Microscopic examination: Mucus, red cells, pus-cells and epithelial cells. No ova or parasites.

February 14: Patient died. For the preceding week was very apathetic and disliked to be moved or examined. Lay on her side with legs drawn up. At times severe abdominal pains were present which generally required morphin for relief. The pain seemed to be more in the region of the umbilicus. There was tenderness or hyperesthesia over the whole abdomen, but no resistance or rigidity. No signs of fluid. Vomited two or three times a day, generally after taking food. On the day of death, suddenly awoke early in the afternoon, cried out on account of severe abdominal pain, attempted to throw off the bedclothes, became very cyanotic and had a very rapid, almost imperceptible pulse. Relieved by morphin and went to sleep. About three hours later she cried out again, gave a few gasping respirations and died.

Her temperature varied between 99 and 103.2, during the last week between 99 and 101.5. Pulse corresponded, in rate, ranging between 74 and 120. Blood-pressure, from 104 to 60. Urine: Twelve examinations showed the specific gravity quite constant between 1.012 and 1.018, with from a trace to a very faint trace of albumin, generally a very faint trace. Most of the examinations showed hyaline and granular casts. The amount of urine varied between 150 and 1,600 c.c., being 1,000 c.c. or over on only three occasions.

Post-Mortem Examination.—Two and one-half hours post mortem. The body is that of a strikingly pale, moderately wasted young girl. There is a little puffiness of the eyelids and slight edema of the ankles. No subcutaneous nodules found. The abdomen is moderately distended. None of the joints

appears swollen. The abdomen contains about 300 c.c. of clear amber fluid. The peritoneal surfaces are smooth and glistening except for a few small shreds of fibrin over the intestinal coils. The appendix is missing, the omentum being adherent to the stump. No nodules seen on any of the vessels. On opening the thorax, the lungs are found partially collapsed and retracted, exposing a large precordial surface. There is about 100 c.c. of clear fluid in each pleural cavity and the same amount in the pericardial sac. The diagnosis was immediately apparent on exposing the heart, the coronary branches showing numerous characteristic nodules (Fig. 5). The heart weighs 320 gm.

Fig. 5.—Case 2. Heart showing thickly set nodules on coronary branches with overlying petechial hemorrhages.

Right Coronary: At the origin of the infundibular branch there is a globular swelling measuring 6 mm. in diameter, filled with a grayish-red adherent thrombus. Near the termination of this branch there is a small yellowish-white nodule of about 2 mm. in diameter. The transverse branch is almost occluded by connective tissue but shows no nodules. The marginal branch shows a small aneurysmal dilatation, partially filled with thrombus just after it leaves the main artery. In the rest of its course and in its branches are numerous, often closely set, oval and globular, firm swellings, the largest measuring about 3 mm. in diameter. On section, these appear as partially occluded vessels with a very thick whitish periphery. The descending branch shows no external change.

Left Coronary: The main stem is free. The first portion of the descending branch is quite tortuous and contains a thrombus. A little further on there is a bluish-red aneurysm measuring 1 by 0.5 cm. and showing a few petechial spots over it. It is filled with a thrombus. Near the apex there are a few firm nodular swellings. The transverse branch shows similar nodules and in the branches

Fig. 6.—Case 2. External view of kidney showing numerous dark raised areas due to hemorrhagic infarcts separated by sunken grayish tissue. The main renal artery and branches show no nodules.

which it gives off over the anterior and posterior surfaces of the ventricles there are numerous firm nodules, the largest measuring 2 or 3 mm. in diameter. Over these, discrete and conglomerate petechial hemorrhages are numerous. A section through any portion of the heart-wall shows the arteries very much

thickened, the lumen generally completely occluded or represented by a minute reddish dot and the adjacent muscle showing irregular yellowish opaque areas. The veins are not changed. The valves and the various chambers of the heart are all quite normal. The aorta and large branches show no change.

Lungs: Except for a moderate collapse, the lungs appear quite normal and one cannot make out any changes in the vessels or bronchi.

Fig. 7.—Case 2. Same kidney as Fig. 6, seen on section. Shows the infarcts distinctly. The numerous little nodules along the small arteries can also be made out.

Liver: Weighs 1,400 gm. The surface is smooth and brownish yellow with irregular areas of congestion. On section, the tissue about the portal vessels appears a little increased in amount and the vessels a little thickened. No definite nodules seen.

Gall-Bladder: Contains viscid greenish bile. The mucosa appears normal and the ducts are patent.

Spleen: Weighs 160 gm. The capsule is tense but smooth and the organ is quite firm. The cut surface remains quite flat and the pulp is firm. The color is purplish red and the malpighian corpuscles are unusually numerous and larger than normal. One obtains the impression that the small central arteries are slightly thickened.

Pancreas: Is large and of normal consistency. On section, it shows nothing abnormal. No macroscopic lesions of the arteries can be seen.

Stomach: Appears quite normal. No lesion of any of the vessels.

The esophagus, trachea, larynx, thyroid and parathyroids appear normal.

Kidneys: Are quite alike (Figs. 6 and 7). The left weighs 160 gm. and the right 150 gm. The fatty capsule is moderately thick but strips easily. The true capsule is easily removed without tearing the renal surface which has a most remarkable appearance. It is coarsely irregular and in color, a mottled red and opaque yellowish gray with a sprinkling of small yellowish points. The raised portions are a deep red with small gray dots. They are abundant, in the aggregate representing fully one-half of the surface, are quite irregular in outline, several often running together to form map-like patterns and they are separated by slightly sunken, dull, opaque, yellowish-gray tissue containing flecks of yellow. The same appearance is seen on section. The cortex averages from 6 to 8 mm. in thickness. The vessels of the pyramids are much congested. The cortex and tissue between the pyramids has a rather rough, furred appearance and one can make out numerous, small, hard pearly gray nodules along the course of the vessels. These resemble miliary tubercles. There are many, larger and smaller, deep red and more grayish-red, necrotic-looking, roughly wedge-shaped areas extending from the surface deeply into the cortex and in places into the medulla. These correspond with the raised areas on the surfaces. They are separated by slightly sunken, yellowish-gray opaque tissue in which are tiny nodules and flecks of yellow. The main renal arteries and their larger branches show no change. An attempt was made to inject the kidney but no gelatin could be forced through the vessels. The kidneys were almost exactly like the colored illustration in Dickson's article.

Adrenals: These are of normal size. On section there are several small vessels which seem thickened and show thrombi.

Uterus: Undeveloped. The tubes, vagina and ovaries all appear normal.

Intestines: Duodenum normal. In the ileum, there are two small, widely separated areas which show a little hemorrhage of the crests of the rugae. In the cecum, there is a small cavity at the appendix stump filled with reddish, grumous material. Otherwise the intestines show no change and the vessels are quite normal in appearance.

Omentum and mesentery are normal.

Mesenteric lymph-nodes: Moderately enlarged and show some thickened vessels with thrombi but no definite nodules.

Arteries: The celiac axis and its branches show no change. In fact, none of the larger arteries shows anything abnormal. The veins are quite normal. The blood in all the vessels is quite fluid. Permission could not be obtained to examine the nervous system, joints or extremities.

Microscopic Examination.—Heart: In one section, taken at a distance from the region of the nodules, the muscle appears fairly normal. The striations are distinct and the vessels quite normal but congested. Around one small vessel there is a little infiltration with wandering cells penetrating between the muscle fibers. Among these cells there are a few eosinophils. In another section there are several irregular areas of fibroblasts replacing the muscle-fibers. A section through the largest aneurysmal nodule shows a fair sized, dilated vessel completely filled with an adherent thrombus which shows an invasion of fibroblasts from the vessel-wall. The wall is much changed. Only in one small area is the internal elastica present and here it is in direct relation with the thrombus. Immediately external to it there is a ring of intensely eosin-stained material in

which nuclei are still seen. In places, the media appears rarefied and shows spaces, in other regions the vessel-wall is composed of fibrous granulation tissue. The adjacent heart-muscle shows granular degeneration and irregular fibrous-tissue replacement. Near the aneurysm there is a smaller vessel seen in cross-section. One can make out a delicate endothelial lining, external to which there is a very loose tissue, internal elastica, homogeneous hyaline ring and a marked adventitial infiltration with mononuclear wandering cells and fibroblasts, among them an occasional eosinophil. The adjacent heart-muscle is granular and degenerated and shows considerable fibrous tissue. Another vessel is seen in which the infiltration is largely perivascular. A final heart-section shows a large artery filled with thrombus showing beginning organization about the periphery. The heart-muscle is cloudy and shows scattered wandering cells and considerable fibrous tissue. In the artery, the elastica is quite gone. The homogeneous hyaline ring is quite distinct close to the intima and at one point it splits into two layers enclosing a granulation tissue containing beautiful fibroblasts and hemorrhage. The perivascular tissue is very cellular, showing fibroblasts, wandering cells and many eosinophils. A longitudinal section of a small vessel shows the coats normal but a considerable similar cellular exudate in the perivascular tissue. Eosinophils are numerous. A cross-section of another vessel shows the lumen filled with beautiful granulation tissue and in another there is canalization of the thrombus.

Aorta: Appears normal. Several small branches at the side of the aorta show characteristic changes of a rather late type.

Lungs: The lung-tissue shows slight collapse with some thickening of the alveolar walls. Sections taken near the surface show no vascular lesion either in the pulmonary or bronchial arteries. Sections from the hilum show very pretty lesions of the bronchial arteries but none of the pulmonics. There is a small lymph-gland present in which eosinophils are very numerous.

Bronchial Glands: The follicles are moderately well shown. The sinuses are dilated and contain relatively few cells. One or two small arteries are seen which show the changes seen elsewhere, eosinophils being quite numerous. Some of the follicles show hyaline degeneration.

Spleen: This is much congested, the blood-spaces showing up very clearly. In some of the malpighian corpuscles there is hyaline degeneration of the central cells. In one section, there is an irregular area of infarction. Eosinophils are quite numerous throughout. Several of the small arteries show characteristic changes. In some, the lesion appears as an adventitial cellular infiltration, with a rather marked invasion of the media with wandering cells and fibroblasts, the muscle being almost entirely replaced. In one or two of the small arteries of the malpighian corpuscles there is a fringe of cells just outside the adventitia, most of which are eosinophils.

Liver: The cells show cloudy swelling and in many places vacuoles. In most of the portal spaces there is an infiltration of wandering cells and eosinophils, often quite definitely about the arteries. In a few of the arteries the lesion is quite definite. Another section so taken as to give a longitudinal view of the vessels and bile-ducts gives a very good picture of the lesion and shows considerable surrounding fibrosis.

Pancreas: The lesions here are exquisite. In general, the parenchymal cells and islands are normal, but there is a moderate increase in the fibrous tissue between the lobules. In one region, there is a definite area of necrosis, apparently an infarct, the supplying arteries being severely changed. The striking thing in the section is the lesion of the vessels. Almost every artery shows most extensive changes and there is a very marked perivascular wandering-cell infiltration with fibrosis. One of the prettiest lesions in the whole case is seen in a longitudinal section of a small artery (Fig. 8). At one end the artery is perfectly normal. It then shows a wider and more irregular lumen with a moderately thickened intima in which are various-sized irregular nuclei, an internal elastica which is more or less preserved until one reaches the region

of most extensive change where it gradually fades out, a homogeneous hyaline band on either side of the vessel which is in places internal to the elastica, in other places external and for some distance divided by it. External to this one cannot differentiate between media and adventitia. One comes on a loose mass of various-sized wandering cells and eosinophils with a few fibroblasts and outside of these a young connective tissue with numerous eosinophils. In serial sections, the lesion can be traced into normal artery once more.

Esophagus: The lesion is seen in one or two of the small arteries of the serosa.

Stomach: Normal. One small artery is seen in the muscularis with a little cellular infiltration about it.

Colon: A longitudinal section of a small vessel shows it normal but on either side of its wall the branches show extensive changes.

Ileum: Normal.

Cecum: One vessel shows the lesion. External to the cecum there is an area of granulation tissue the borders of which are necrotic. This represents the softened area at the base of the appendix described in the gross. Appendix is normal.

Mesenteric Lymph-Nodes: Appear much the same as the bronchial.

Lymph-Node at Gall-Bladder: Shows various areas of hyaline degeneration but no vascular lesions.

Thyroid: Normal. Vessels unaffected.

Fig. 8.—Case 2. Longitudinal section of artery in pancreas. The rather abrupt beginning of the lesion is well seen at the left. The intima, *I*, is thickened and is indistinguishable from the hyaline ring, *H*. The internal elastica, *E*, thus apparently divides this hyaline ring. The media is represented by the hyaline ring and the adventitia, *A*, merges with the periarterial infiltration. In other sections the lesion can be traced to the right into normal artery again.

Kidneys: Sections show very numerous fresh hemorrhagic and older infarcts. A large portion of the cortex is thus affected and the infarcted areas often run down to and into the medulla. The small amount of intervening renal tissue is fairly normal except for the vascular changes which are very extensive, almost every small artery being affected. There is considerable perivascular infiltration. One fairly large artery shows an extensive thickening of the intima, the internal elastica remaining intact. The thickening consists of a bluish-pink material rich in spindle-shaped fibroblasts, many of the cells having peculiar little spaces about them. The media is composed of a similar tissue while the adventitia is more fibrous. The other vascular lesions are merely repetitions of the changes seen elsewhere.

Adrenals: Several of the small arteries about the organ show characteristic lesions. There are several infarcted areas in the cortex.

Fallopian Tube: One vessel found which shows typical changes.

Ovary: Normal.

Psoas Muscle: One small artery is seen which shows a beginning infiltration about the adventitia. The muscle-fibers are normal.

Pectoral Muscle: Very distinct changes are seen about many of the small arteries, the muscle-fibers remaining unaffected.

Uterus and Bladder: Normal.

Bacteriologic Findings at Necropsy.—Heart-Blood: Cultures were taken in various mediums, two ascitic glucose-agar shake-cultures, three ascitic glucose-agar slants and one neutral broth. These all remained perfectly sterile. At the end of three weeks they were examined, although there had been no sign of any growth. At present, three months after the necropsy, no growth has appeared.

Peritoneum: Cultures showed a *Staphylococcus aureus*.

Pericardial Fluid: One tube remained sterile, the other showed a colon bacillus. The most promising field for obtaining successful cultural results seemed to lie in the examination of the cardiac nodules and consequently most of the attention was directed to them. In the first place numerous smears were made from these nodules. These were stained by various methods but gave entirely negative results. The largest aneurysmal nodule was excised and washed in three changes of sterile salt solution. It was then divided into two portions, using Rosenow's sterile method. One portion was ground up in sterile salt solution. Of this, one guinea-pig received 0.5 c.c. intraperitoneally, one received 1 c.c. intraperitoneally and two rabbits received 0.5 and 1 c.c. respectively, intravenously. All of these animals remained perfectly well. They were finally killed, May, 1, two and one-half months after inoculation. None of them showed any lesions and the microscopic sections of the various organs failed to reveal any changes.

The second portion of the nodule was again divided and after flaming the pieces were planted at the bottom of two ascitic glucose-agar tubes. The rest of the bacteriologic work on the case was done by Dr. Coulter, and I am indebted to him for the following facts: After eighteen hours, both of the tubes were clouded. Direct examination and subcultures showed *Bacillus subtilis*. The nodules were at once removed, held within a flame until there was free spattering of fat and the entire surface was shriveled and discolored and then were replanted in ascitic glucose agar. The nodules sank to the bottom of the tube before the medium hardened. The ascitic fluid used in these cultures had been repeatedly tested for sterility. One tube has remained perfectly sterile. One tube showed no growth for two weeks.

On the sixteenth day there were two separate areas of clouding at the bottom of the tube, between the nodule and the glass. Each area was somewhat fan-shaped with the wide portion of the fan directed away from the nodule. Three days later there was very slight if any increase in the areas of clouding. A long sterile pipet was introduced to the bottom of the tube encountering considerable resistance owing to the firmness of the medium. At the very bottom, however, about the nodule, there were found several tenths of a cubic centimeter of slightly turbid fluid. About 0.1 c.c. of this fluid was inoculated into each of three ascitic glucose-agar cultures, one being a surface slant, the other two deep cultures similar to the one from which the fluid was withdrawn. Smears of this fluid showed rather large Gram-positive cocci, mostly in chains of from four to ten, but occasionally arranged as diplococci or tetrads. About the latter there was an indistinct capsule. On the following day the subcultures showed the following:

Surface cultures: Profuse growth, for the most part confluent with very numerous, uniformly distributed, more opaque areas. Growth emulsifies easily. It is not very viscid but strings out slightly when touched with the loop. The medium is not precipitated but the growth has extended between the medium and the glass. The medium was freshly slanted before inoculation so that it was quite moist.

Deep Cultures: Uniformly clouded throughout. No gas bubbles or cracks in the medium. Smears showed organism identical with those in the original culture. Smears from the surface growth showed the cocci smaller, somewhat

flattened and generally arranged as diplococci, chain formation being very slight. Plates were made from all of the cultures. In all there was but one type of colony in twenty-four hours. This was large, 1.5 by 2.5 mm. in diameter, moist, surface convex and glistening, outline smooth and regular, color uniformly grayish, consistency only slightly viscid.

Growth in peptone broth shows a uniform clouding with very slight sedimentation in six hours. In twenty-four hours there is marked sedimentation, but the fluid remains uniformly cloudy. Smears show chains of ten or more cocci with a distinct capsule. The organism is not bile-soluble and shows the following fermentation reactions: Dextrose +, dextrin +, saccharose +, lactose +, galactose +, inulin —, raffinose —, mannite —, salicin +, litmus milk +, acid, coagulated but not dissolved.

Animal inoculations were made from the second generation of deep cultures. An emulsion was made up to the strength of 500,000,000 to the cubic centimeter and of this a guinea-pig received 0.75 c.c. intraperitoneally, a rabbit 1.5 c.c. intravenously and a monkey 1.5 c.c. intravenously. None of these animals showed any reaction. They continued perfectly well and were killed two months later. They showed no gross or microscopic lesions. Another rabbit was given 5 c.c. of an emulsion containing 1,000,000,000 to the cubic centimeter. Death resulted in eighteen hours. The organism was recovered at the necropsy. There were no gross or microscopic lesions of the vessels, especially no signs of inflammation about the vessels or in the perivascular lymphatics.

Pieces of tissue were preserved in alcohol, formaldehyd and Zenker's fluid and sections were stained by various bacterial stains. A careful search was made of many sections for bacteria, without results. In some of the sections, especially those of the pancreas, there were some small bodies resembling cocci, but they could not be differentiated from the numerous particles of chromatin present. A set of sections was also stained by the Levaditi method but with entirely negative results.

The foregoing results have been reported in detail because they represent the most extensive bacteriologic investigations yet made on the disease. The examinations can be considered quite negative with the possible exception of the streptococcus isolated from the cardiac nodule. The occurrence of a *Staphylococcus aureus* in the peritoneal fluid seems to be merely a coincidence. Had it any real relation to the disease, it seems inconceivable that it should not have been obtained from the other cultures both during life and at the necropsy. As the cardiac nodule showed a contamination at the start it is, of course, quite possible that the streptococcus was one likewise. Against this is the fact that the nodule was very thoroughly seared and that the growth did not appear until a considerable period of time had elapsed. Even if this organism did come from the nodule it may have been there merely as an accidental secondary infection. As the occurrence of a streptococcus has been the only moderately constant finding in necropsy cultures of other cases it has seemed important to me to include the cultural characteristics of the one found in this case for the purpose of comparison in case any similar organism is isolated in the future.

The animal inoculations have proved nothing except that the disease was not transmitted to them either by the direct inoculation of material from the nodules or by the streptococcus isolated. It is quite possible

that the disease cannot be transmitted to these animals. It would have been interesting to have inoculated stags with material from the nodules, but unfortunately this was not possible.

CASES REPORTED UP TO THE PRESENT TIME

The following is a list of cases of periarteritis nodosa reported up to the present time:

- Rokitansky, 1852. Studied microscopically by Eppinger thirty-five years later.
- Kussmaul and Maier, 1866.
- Zimmerman, 1874.
- Chvostek and Weichselbaum, 1877.
- P. Meyer, 1878.
- Eppinger, 1887. Kundrat's case and microscopic description of Rokitansky's.
- Fletcher, 1892. Necropsy by von Kahliden.
- von Kahliden, 1894.
- Graf, 1896.
- Rosenblath, 1897.
- Freund, 1899.
- Krzyszkowski, 1899.
- P. Müller, 1899. Two cases.
- Schmorl, 1903.
- Ferrari, 1903.
- Veszprémi and Jancsó, 1903.
- Schreiber, 1904.
- Mönckeberg, 1905.
- Versé, 1905.
- Benedict, 1907.
- Oberndorfer, 1907.
- Bomhard, 1908. Same case as that reported by Oberndorfer.
- Benda, 1908. Two cases.
- Dickson, 1908.
- J. E. Schmidt, 1908.
- Longcope, 1908.
- Hart, 1908.
- Künne, 1909. Same case as that reported by Hart.
- Datnowski, 1909.
- Beitzke, 1910. Same case as that reported by Datnowski.
- Moriani, 1910.
- Cooke, 1911.
- Veszprémi, 1912. Two cases.
- Lewis, 1912.
- Jonas, 1912.
- Beattie and Douglas, 1912-13.

REVIEW OF REPORTED CASES

So far as it is possible to decide, the preceding thirty-eight cases are true cases of periarteritis nodosa. Up to the present time it has been impossible to be sure of the diagnosis without a microscopic examination of the lesion. Consequently, a case such as that reported by Sabin cannot be included in this series, although it may well have been an instance of the affection. In order to make the record complete, several of these questionable cases are given at the end of this article. These have either been reported as periarteritis nodosa or have been considered such by some authors.

The following review is based on a study of the preceding thirty-eight cases. It is at once apparent on reading over the reported cases

that many are lacking in important details. The more detailed report of additional cases will be necessary to bring the clinical picture to completeness. There is sufficient material, however, to bring out many facts of interest and to give a clinical picture which will at least aid in the recognition of future cases.

Historical.—In 1852, Rokitsansky, in a paper entitled “The Formation of Aneurysms of the Arteries in General, Except the Aorta, and Most of Its Important Primary Branches, with the Further Exception of the Cerebral Arteries,”² gave the first complete gross description of the disease. Thirty-five years later, Eppinger studied and described the histologic changes in the arteries of the mesentery in this case. To Kussmaul and Maier, however, must go the credit for the first complete gross and microscopic description of *periarteritis nodosa* and its recognition as a distinct disease. They reported a case in 1866 as “A hitherto undescribed peculiar disease of the arteries which is accompanied by Bright’s disease and a rapidly progressive general paralysis of the muscles,”³ and proposed the name by which the disease has since been known.

There is some ground for believing that the disease was grossly recognized as early as 1755 by Michaelis and Matani, and in 1810 Pelletan reported very briefly a case in which he counted sixty-three small aneurysms on the various arteries. These reports are too brief, however, to admit of any conclusions as to the true nature of the process. From the time of Kussmaul and Maier’s publication to 1899, but eight additional cases were reported, or an average of about one case in four years. Then, as the disease became better known, the number of cases showed a considerable increase, twenty-eight being reported in the following sixteen years. Five of the cases are from the United States and two from Great Britain, nearly all of the rest being from Germany.

Name of the Disease.—As one might expect, several names have been proposed to supplant Kussmaul and Maier’s “*periarteritis nodosa*.” Thus we have “multiple aneurysmen” of Meyer, “*das congenitale aneurysma*” of Eppinger, “*arteritis nodosa proliferans*” of Fletcher, “*polyarteritis acuta nodosa*” of Ferrari, “*meso-periarteritis*” of Hart and “*panarteritis*,” “*arteritis nodosa*” or “*polyarteritis nodosa*” of Beitzke, according to the view of the author as to the nature of the process. While it is possible that some of these names are a little more

2. Aneurysmenbildung sämtlicher Arterien mit Ausnahme der Aorta, und der meisten ansehnlichen primitiven Aeste derselben, ferner mit Ausnahme der Gehirnarterien.

3. Eine bisher nicht beschriebene eigenthümliche Arterienerkrankung die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht.

accurate than the one originally used, the disease has come to be known under the title "periarteritis nodosa" and it seems better to continue this name, at least until the etiology of the disease has been established, rather than to introduce confusion by using one or other of the various substitute titles proposed.

Etiology.—The fact that the etiology of periarteritis nodosa is still quite unknown lends added fascination to the study of the disease and emphasizes the desirability of recognition of cases during life in order that complete bacteriologic studies may be carried out. The history of the etiologic views falls into three main groups.

Syphilitic: Influenced by Virchow's opinion, Kussmaul and Maier were inclined to the view that the disease was a syphilitic affection of the arteries. Chvostek and Weichselbaum, Graf, Schmorl and especially Versé have been the chief exponents of this view, while Müller and Benedict have found it impossible to rule out. Many pages have been written upholding and combating syphilis as the causative factor. It would lead too far afield to go into all the arguments. Suffice it to say that the great majority of observers are opposed to the idea even when they limit themselves to purely histologic studies; the Wassermann reaction has been negative in the few cases in which it has been applied; no one has been able to find spirochetes in the lesions; a syphilitic history fails in most of the cases; in only a very few have any other syphilitic lesions been found at necropsy, and a similar, if not identical, disease occurs in stags as pointed out by Lüpke.

Mechanical: While no one seriously considers this view at the present time it is interesting historically. Meyer, in 1878, believed that the disease was due to high blood-pressure rupturing the media, which was either imperfectly formed or later injured by some toxic substance such as alcohol. Nine years later, Eppinger upheld the view of a congenital debility of the internal elastica with rupture. A variation of the mechanical theory is encountered in Ferrari's idea that the lesion is produced by the central or local action of a toxic substance, such as alcohol, causing a paralysis of the smooth muscle-fibers. All of the facts are against these various ideas and it is scarcely worth while to discuss them.

Infectious or Toxic: All observers, with the exception of those above mentioned, believe that periarteritis nodosa is the result of an acute infection, the arterial lesion being caused by bacteria or their toxins. The nature of the infecting agent is still unknown. Cultural investigations during life have been few and yet it is rather striking that in the four cases in which blood-cultures have been taken the results have been quite negative. In Datnowski's case these were repeated three times and the same was true in our second case, the last

blood taken being plated in ascitic glucose-agar. While in no way conclusive, these results would seem to point against any one of the commoner organisms as the causal factor. Anaerobic cultures have not been taken. In our second case, ascitic glucose-agar shake-cultures were made from the heart's blood post mortem, but also with negative results.

Another striking fact is that the examination of sections of the lesions for bacteria has almost uniformly failed to show any organisms. Graf found a few short rods in his sections, but felt that they could not be considered, as the necropsy was done many hours post mortem. Longcope found a few chain cocci in sections from the kidney, but they were not in relation to the nodules.

In only eight cases have cultures been taken at necropsy. In one instance they were accidentally destroyed, leaving the following seven observations:

Oberndorfer: *Staphylococcus aureus* cultivated from the kidney and spleen.

• Datnowski: Streptococcus cultivated from the heart's blood. There was a terminal perforative peritonitis in this case.

Veszprémi: Cultures sterile.

Jonas: Streptococcus obtained from the kidney and an influenza bacillus from the adrenal.

Beattie and Douglass: Streptococcus obtained from the renal hemorrhage.

Lamb, Observation I: Streptococcus from the heart's blood associated with a colon bacillus. Streptococcus from the peritoneal exudate. In this case there was a vegetative endocarditis and terminal peritonitis.

Lamb, Observation II: Streptococcus from the cardiac nodule. *Staphylococcus aureus* from the peritoneum and colon bacillus from the pericardial fluid.

Thus, in all but one case in which cultures have been taken, some organism has been obtained. In five of these it was some variety of streptococcus. In two out of these five there was some complicating condition and in two there was also some other organism isolated. In Longcope's case a few chain cocci were found in the kidney sections, but not in association with the nodules.

In reviewing the etiology, one finds no support for the syphilitic or mechanical theory. The course of the disease, the irregular temperature, the high leukocytosis, the complications and the nature of the lesion all point to some infection. Cultures taken during life have been uniformly negative, but have also been limited in number. The failure to demonstrate any bacteria in the lesions may indicate their early

disappearance as is supposed to be the case in rheumatic lesions. While one is not justified in excluding the occasional finding of such an organism as the *Staphylococcus aureus* or influenza bacillus in post-mortem cultures, the most striking point in the examinations so far made is the occurrence of some variety of streptococcus in five of the seven cases, or in 71 per cent. In another case they were seen in sections. It is for this reason that we have included a full description of the streptococcus isolated in our second case. Animal inoculations with this organism and with material from the nodules have been negative.

At present, one can do no more than call attention to these facts as they have occurred. The final solution rests with the future.

It is contended by some that the disease is not specific, but that it is merely an acute infectious lesion of the arteries due to any one of a number of bacteria.

Heredity.—There is no indication that it plays any part.

Sex.—Of the reported cases, twenty-eight were in males, nine in females and in one the sex is not stated. Thus it would appear that the disease is about three times more frequent in males than in females.

Age.—It is essentially a disease of adolescence and early adult life—71 per cent. of the cases occurring between the ages of 10 and 40. It is not limited to this period, however, the youngest case being in a child 2½ months old, and the oldest occurring at the age of 57. The number of cases in the second decade is slightly larger than in any other. The following table shows the number of cases in each decade:

Years	No. of Cases
1-10	1
10-20	10
20-30	8
30-40	9
40-50	5
50-60	5

Occupation.—This is most varied and it is quite impossible to discover any connection with the affection.

Past History.—In about one-third of the cases this is not given. In only four cases is there a definite history of syphilis. In a few there is a history of symptoms similar to but antedating the symptoms of onset by some months or years. In a few there is a history of some immediately preceding infection. There is thus no apparent relation to any other disease, and one gathers the impression that the previous illnesses are entirely irrelevant. It is, however, interesting to note that some cases do show similar symptoms in their past history either as isolated occurrences or in recurring attacks.

Symptoms.—Onset: In the 32 cases in which this is mentioned, we find a more or less acute invasion in 14 cases and a more gradual onset in 18. The symptoms of onset in order of frequency were as follows: Pains in the muscles or joints, 13; fever, 9; abdominal pain, generally in the epigastrium, 8; edema, 8; weakness, 5; disturbances of sensation, 4; diarrhea, sweating, purpuric eruption, sore throat, 3 each; chilliness, headache, vomiting, anorexia, constipation, cough, 2 each; and scattered symptoms of dizziness, urticaria, pain in the chest, eruptions, hemoptysis, cyanosis, dyspnea, icterus, swelling of the testis and asthma.

General: Mentioned in 32 cases. Weakness, generally progressive, 24; emaciation, 13; sweating, 7; jaundice, 6; sleeplessness, 4; chilliness, 4.

Subcutaneous Nodules: In two cases (Schmorl, Benedict) the diagnosis has been made during life by the examination of excised subcutaneous nodules. Everyone has been impressed with the importance of these nodules and it is generally agreed that they offer the only certain means of diagnosis. And yet they were present only eight times or in about 21 per cent. of the cases. In Kussmaul and Maier's case, small, firm, pea-sized nodules appeared beneath the skin of the abdomen and thorax four days before death. Freund merely states that there were subcutaneous nodules of the face, neck and arms noticed during the patient's eight days in the hospital. Müller (Case 1) found the nodules about one knee at the necropsy.

Schmorl reports very briefly the case of a woman who showed nodules in the abdomen and thigh which on excision were characteristic of the disease. They were apparently cured by antisyphilitic treatment. Mönckeberg noticed a few, small, elastic, painless nodules in the thigh on the day before death. Benedict has described the nodules in more detail. At the end of the fourth week, in his case, a fist-sized tumor appeared in the abdomen and increased somewhat in size. This was finally considered an intramuscular hematoma. At about the same time, four or five hazel-nut-sized, round, painless, easily movable nodules appeared in the skin of the thorax and several pea-sized nodules in one leg and in both forearms. A thoracic nodule showed only clotted blood. Later, eleven pea-sized, round or oval, moderately hard, freely movable, nodules were found under the chin and in the buttocks, arms and legs, three hazel-nut-sized tumors under the left breast and a goose-egg-sized nodule containing pus under the left trochanter. A second small nodule removed from the leg showed changes characteristic of the disease. In Datnowski's case there was slight periosteal thickening of the tibia, and four days before death small elevations of the abdomen appeared. It was suggested that both

these represented subcutaneous nodules, but no examination was made. In the first of the cases here reported, there was a peculiar small firm area in the course of the internal saphenous vein, a raised reddish-brown area 3 by 1 cm., in the right thigh, lying over a superficial vein and the early appearing goose-egg-sized hematoma-like swelling of the ankle. These were not in evidence at the necropsy and so, unfortunately, no examination was made.

Superficial Lymph-Nodes: These were noted as enlarged in only four cases.

Edema: The most striking fact in this connection is that in twenty-one, or 61 per cent., of the thirty-four cases in which histories are given, there was edema at some time during the course of the disease. In only two cases is it definitely stated to have been absent. In the eleven remaining cases in which the histories are more or less completely given it is not mentioned and was presumably absent. The edema was generally of the ankles, less often of the face or body.

Skin Eruptions: In seven cases there was an eruption of hemorrhagic character, petechial, purpuric or ecchymotic and at times this was associated with urticaria. In a few instances, such hemorrhagic spots were the first things noticed at the onset of the disease, at other times they appeared during the course, generally in recurring crops. In one case there was an eruption of uncertain character, considered to be that of either syphilis or scarlet fever. In another there was a desquamation of the whole body typical of scarlet fever, but without any known preceding eruption. In one of our cases there was a rather late diffuse erythema of the face and body.

Pains in the Joints: In fifteen cases, or 39 per cent., there were definite joint-pains, often quite severe, usually involving more than one joint and behaving very much like acute rheumatic fever.

Pains in the Muscles: In eighteen cases, or 47 per cent., there were pains in the muscles, generally of the extremities, usually quite severe and described as "tearing." In three cases these pains were associated with distinct muscular atrophy.

Temperature: In four cases no mention is made of the temperature. In two cases it is definitely stated to have been normal, while in the remaining thirty-two there was fever. Thus 94 per cent. of the cases have shown a definitely febrile course. In some, it is merely stated that there was slight fever, in others it is perhaps a little difficult to separate the fever of the disease from that of the complications. In reviewing the cases in which there is more detailed information, it is apparent that the temperature is generally irregular, at times reaching 104 or even 105 F., and at other times being subnormal. It is apt to be of a remittent type, the remissions being accompanied by marked sweating.

There are often periods of several days when the temperature is quite normal.

Circulatory System: Symptoms and physical signs directly referable to the heart and vessels are rather strikingly absent. Thus in our second case in which the coronary arteries were most extensively involved, there were no signs to direct one's attention to the heart until near the end. In 7 cases there was enlargement of the heart, murmurs in 7, dyspnea in 5, cyanosis in 4, precordial pain in 1 and pericarditis in 1.

Blood-Pressure: There is information on this point in only five cases. In Benedict's case it was 140, in Datnowski's 215, in Künne's 77 to 100, in the first of our cases 130 to 165, and in the second 104.

Pulse: In five cases the pulse was not mentioned, and in one it was quite slow. In the remaining thirty-two, or 97 per cent., it was increased in frequency, and in sixteen, or in one-half of the cases in which it was increased, it was more rapid than one would expect from the height of the temperature.

Blood: Anemia is a striking feature of the disease. It is stated definitely as being present in 55 per cent. of the cases and is generally described as being most conspicuous. In only five cases is there any record of a red cell-count or hemoglobin estimation. In these counts the red cells varied from 3,500,000 to 2,800,000, and the hemoglobin from 75 per cent. to 42 per cent. **Leukocytosis:** Observations have been made on the white cells in only twelve cases. Leukocytosis failed in only one case, that of Dickson, in which there was an associated tuberculosis of the lymph-glands and lungs. In two cases it is simply stated that there was a leukocytosis. In the nine cases in which the figures are given, the count varied from 9,000 to 66,000. The low count was in a case in which other, later counts were as high as 24,000. The count is generally high, between 16,000 and 30,000. In only four cases were differential counts made. Of special interest in this connection is the fact, first mentioned by Datnowski, that the eosinophils are increased. In his case they were 10 per cent. In Lewis' case they were from 22 to 30 per cent., and in our first case from 32 to 58 per cent. In all of these cases the usual causes for eosinophilia were excluded. In our second case they were not increased. It is most important to have more observations on this most interesting point, as it may furnish a most valuable means of diagnosis. It is rather significant that the cellular infiltration of the arterial lesions is generally rich in eosinophils. The polymorphonuclear leukocytes are increased in number. **Blood-Cultures:** Taken in only four cases and sterile in all. In Datnowski's case they were repeated three times. In our second case, three different cultures were taken and one of these was plated in

ascitic glucose-agar. Wassermann Reaction: Taken in only three cases and negative in two. In our second case one test was positive and one was negative. The first was taken when the temperature was high. We have become very suspicious of the accuracy of positive reactions in the presence of high fever. The second test we believe more reliable, as the temperature was low. In one case a negative reaction was obtained with cadaver blood.

Respiratory System: The respiratory symptoms bear very little relation to the disease with the possible exception of the asthma, which is at times cardiac, and the blood in the sputum. In one of our cases asthma was a most striking feature from the outset, and in one other of the reported cases it was severe. In three cases there has been blood in the sputum. The other symptoms have been the following: cough in 8; pulmonary edema, pneumonia, pain in the chest, 2 each; pleural effusion, emphysema and hemoptysis, 1 each.

Gastro-Intestinal System: A large number of the cases show some symptoms referable to the gastro-intestinal system. In order of frequency they have been the following: Vomiting, 17; anorexia, 9; constipation, 7; diarrhea, alternating with constipation, 5; diarrhea, 4; blood in the stools, 1; *Ascaris lumbricoides*, 1. In the only 3 cases in which gastric analyses were made the free hydrochloric acid was either reduced or entirely absent.

Abdomen: The abdominal symptoms are most important. It is this aspect of the disease which is of interest to the surgeons, for at times the symptoms have been severe enough to persuade one that an acute surgical condition existed. The second case here reported is a striking illustration of this. In seventeen cases, or 50 per cent. of those in which the facts are given, there was abdominal pain. In one-half of these it was located in the epigastrium or upper part of the abdomen. In the rest it was generally diffuse over the whole abdomen. In three cases it was in the region of the kidney. In eight cases the abdominal pain was one of the marked symptoms of onset. The character of the pain is fairly constant. In most cases it comes on in recurring attacks and is severe, colicky or cramp-like. At times it is severe and constant for several days at a time. In a few cases it radiates to the back. It is generally associated with abdominal tenderness and distention. In seven cases the liver was palpable and in four cases the spleen could be felt.

Urogenital System: The lesion affects the small arteries of the kidney in nearly every case. Therefore, the symptoms referable to the kidney are most important. In ten cases no mention is made of the urine. In five cases it is definitely stated that albumin was not present. Often, however, there was only one examination of the urine and the

condition of the kidneys at necropsy suggested that, in some of the cases at least, albumin would have been found had repeated examinations been made. In twenty-three cases, or eighty-two per cent. of those in which the condition of the urine is given, albumin was present, generally in moderate amount, but varying from a faint trace to as high as 6 per cent. In the cases in which repeated examinations were made, the albumin was not always present but showed exacerbations and remissions. It was sometimes present at the onset, clearing up as the patient improved and reappearing later. In other cases it was not present until near the end. In fourteen cases, casts were present. These were generally of the hyaline and granular variety, but occasionally they were epithelial. The amount of the urine was reduced in nine cases and in a like number blood was present. In one case there was a faint trace of sugar found. In one of our cases the phenolphthalein output for two hours was too small to estimate on two occasions. The necropsy showed a very severe glomerulonephritis. In the other case the test was not done. In two cases there was infarction of the vessels of the testis.

Nervous System: The following symptoms were noted: Headache, 6; disturbances of sensation, 6; palsies, 4; convulsions, 4; visual disturbances, 3. In one case in which lumbar puncture was done the spinal fluid was sterile and in one of our cases the urea content was 0.323 per cent. In one of the cases showing visual disturbances a lesion was found in one of the retinal arteries. In the other two cases the retina was not examined post mortem.

Pathology.—The lesions of periarteritis nodosa consist in the peculiar arterial nodules and aneurysms and the changes in the various organs dependent on an insufficient or completely obliterated blood-supply. The larger arteries are not affected, the changes being limited to those of the size of the coronary and smaller. The veins and capillaries have never been found affected. The distribution of the lesions is practically that of the small and medium-sized arteries, that is, any arterial area may be involved. There are certain peculiarities, however, in that the arteries of the brain and spinal cord and the pulmonics are very rarely affected. Changes of the former have been found only four times and of the latter only twice. In some of the cases the central nervous system has not been examined. While the pulmonary arteries almost regularly escape, it is not at all uncommon to find the lesion in the bronchial arteries. The lesion has been found in practically every region of the body, including the retina, arteries to the nerves, the muscles, subcutaneous tissue, spermatic cord, diaphragm, etc. In nearly every case there are lesions in the heart, gastro-intestinal tract and kidneys. In 1905, Mönckeberg gave a table showing the site of the

lesions in all the cases published up to that time. It does not seem necessary to enlarge on this table at present, especially as in many of the cases complete examinations were not made and all of the vascular areas were not investigated. Consequently, a table gives a rather erroneous impression.

Two important facts should be borne in mind. In the first place, in no less than five cases, no changes were noted in the arteries at the necropsy and the disease was not suspected until demonstrated in the sections. It is therefore possible that some cases may be overlooked both clinically and pathologically. That this is not often the case and also that the disease is in reality quite rare is shown by the fact that in a recent review of the sections of all cases of nephritis occurring at the Presbyterian Hospital during the past six years, no case of periarteritis nodosa was found, although the disease was carefully looked for.

In the second place, in five cases, the disease was limited to a relatively small vascular area or to one organ. Some time ago this was used as an argument against such a case being truly periarteritis nodosa, but it is now well recognized that such limitation may occur.

The gross appearance varies somewhat. In most cases there are both solid nodules and aneurysms. These occur with especial frequency at the points of branching, the size of the nodules having no relation to the size of the artery. The nodules are whitish to yellowish-white, moderately firm, later quite firm, and vary in size from those just visible and resembling miliary tubercles to those the size of a pea or slightly larger. They are generally situated at one side of the artery, but at times the whole wall of the artery seems thickened. As indicated above, many of the lesions are quite invisible to the naked eye. On section, they appear homogeneous, yellowish-white, and often show an associated occlusion of the artery. The larger nodules are generally aneurysmal dilatations, are generally softer in consistency and vary from a yellowish-white to a grayish-red or dark-red. These are almost regularly filled with thrombus and may slightly exceed a hazel-nut in size. The aneurysms and nodules may occur together on the same artery and often occur in thickly set bunches or are strung along the branch, giving it a corded or nodular feel. There may be petechial hemorrhages over the lesions and hemorrhagic extravasations into the surrounding tissues. The aneurysms may rupture resulting in hematomata. Quite regularly one finds infarcted areas in some of the organs from occlusion of the arteries at the site of the lesion. The portions of the arteries in which there are no nodules show no changes. The lesion may be quite early in one region and more advanced in another.

Perforation of the intestine may occur through an ulcer caused by infarction.

Microscopic Findings.—One of the chief points of controversy has been the question as to which coat of the artery is the seat of the primary change. The majority of observers believe that the disease begins in the adventitia, a fair proportion are equally insistent that the media represents the primary change. While there have been a few exponents of a primary intimal inflammation, all recent observers are agreed that the process does not begin there. It is believed that the injurious agent probably enters by way of the vasa vasorum or possibly the perivascular lymphatics, and affects one or other of the two outer coats. The reason that there has been so much difference of opinion concerning the relative degree of involvement of the different coats is that the lesion varies considerably in various portions of the same nodule and in the early and late stages of the disease. It is only by the study of serial sections and a review of the various histologic descriptions in the different cases that one can obtain a proper idea of the whole picture. Summing up these changes, we find the picture in the various coats as follows:

Intima: Is frequently not involved. No one has found changes here without simultaneous changes in the other coats. It is on this basis especially that the intima has been ruled out as the site of primary change. As a rule, with the changes in the other coats there is some degree of involvement of the intima. At times there is simply a proliferation of the endothelial cells, at times this is sufficiently marked to cause narrowing of the lumen. The cells then often appear large and polygonal in shape with clear, spindle-shaped or irregular nuclei; the tissue appears vacuolated; there may be some edema and fibrin with an occasional polymorphonuclear leukocyte and wandering cell and some nuclear fragments. A little later fibroblasts appear and with the formation of thrombi these cells grow into and organize the thrombus mass, at times leading to complete fibrous occlusion of the vessel. The changes may affect only a portion of the circumference or the whole intima. The cellular exudate of the media and adventitia may break through the internal elastica and invade the intima. The intimal thickening may extend for some distance beyond the nodule.

Internal Elastica: Generally at the site of the lesion it is wanting. In some cases it is quite sharply broken, the ends tending to curl up; more often it fades away into the exudate of the other coats. Often one can find it quite intact on the other side of the lumen. It may show definite small breaks in continuity in this region. At times it appears distinctly swollen at the site of the nodule.

Homogeneous Hyaline Ring: This is a very characteristic peculiarity of the lesion and consists of a zone of varying width, of more or less homogeneous appearance which takes the eosin stain quite intensely. It is generally situated just external to the internal elastica which is often preserved. In some cases it has been described as lying internal to the elastica and, as mentioned in one of our cases, it may lie both external and internal to it. In the more advanced lesion the band or ring is hyaline and structureless in appearance; but it seems quite possible to trace its formation from the degenerated media. Certainly, in the early stages the inner portion of the media can be seen to be more or less degenerated, its elements fusing together and taking the eosin stain more intensely. At a little later stage one sees the hyaline ring in this location quite distinctly, but it is quite possible to make out the degenerating smooth muscle cells within it.

Media: This coat is almost regularly involved. Mönckeberg even goes so far as to say that when no changes are demonstrable they really exist and that our present means of examination are not delicate enough to make them out. The early changes consist of swelling of the muscle-cells with a loss of their nuclei. One then finds a beginning inflammatory exudate of polymorphonuclear leukocytes, wandering cells and eosinophils, increasing to an extensive similar exudate with some fibrin, edema, nuclear fragments and vacuolization with increasing degeneration of the media, the formation of the hyaline band and later the appearance of fibroblasts and the gradual replacement of the exudate by fibrous tissue. At times, as in the aneurysm formation, the media is greatly thinned. The external elastica shows changes comparable to the internal.

Adventitia: An increasing number of observers have found changes in this coat without the occurrence of recognizable lesions elsewhere in the arterial wall. The earliest change consists of a small periarterial or adventitial collection of mononuclear wandering cells, polymorphonuclear leukocytes and eosinophils. I have been rather impressed with the occurrence of the eosinophils. It has been recognized for a considerable time that they are numerous in the lesions. In our sections, they seem attracted to the region of the arteries even when these show no change. The earliest lesion seen in our sections was in a small arteriole of the stomach-wall. This showed a small unilateral periarterial collection of cells almost all of which were eosinophils. With the older lesions the infiltration of cells increases until the adventitia becomes several times its normal width and merges imperceptibly with the periarterial infiltration which may extend for some distance into the surrounding tissue. The adventitia shows a beginning degeneration and then goes on to the formation of granulation tissue and finally

fibrous tissue. At times one finds the perivascular lymphatics filled with an exudate similar to that described, never, however, to the same extent as seen in such streptococcus infections as erysipelas. The lesions do not go on to suppuration, and in this respect resemble the lesions in the organs in *Streptococcus viridans* endocarditis.

The lesion bears no relation to the supra-arterial epicardial fibroid nodules described among others by Knox. On gross examination these nodules are somewhat suggestive of periarteritis nodosa, but their histologic structure is quite different.

Brief mention has been made above to the occurrence of a similar disease in stags. Lüpke first described this condition in 1906. There has been some divergence of opinion as to the exact relationship between the two conditions. The descriptions of the lesion are rather brief and as we have had no opportunity of seeing sections taken in the cases we feel in no position to judge of their similarity. The consensus of opinion seems to be that the two conditions are very similar if not identical.

Duration.—The most acute case resulted in death in ten days. One case was followed for two years and ten months and was, as far as I have been able to discover, lost sight of at the end of that time. In general, the course is relatively rapid, 71 per cent. of the cases resulting fatally inside of three months. The duration is not always accurately given and in the following table I have considered only the period of acute symptoms.

Duration	No. of Cases
Not given	3
Less than 1 month	5
1-2 months	10
2-3 months	10
3-4 months	5
6-7 months	1
7-8 months	1
8-9 months	1
Over 1 year	2

Prognosis.—This is bad. Only one case in the series did not result fatally. This patient was followed for nearly three years and was alive at the end of that time. One patient in whom the diagnosis was made during life by the examination of an excised nodule was apparently cured of the disease, but died two years later of portal thrombosis. The necropsy showed no evidence of periarteritis nodosa except some small fibroid foci in close relation to the arteries. These were considered healed nodules. Other cases have shown similar but less marked tendency to healing in some regions, but always with progression of the process elsewhere.

Diagnosis.—One need but glance at the following list of diagnoses which have been made in the foregoing cases to obtain some idea of the puzzling nature of the disease: nephritis 7, meningitis 3, general miliary tuberculosis 2, general peritonitis 2, sepsis 2, dysentery, trichiniasis, morbus maculosus Werhlofi, encephalitis, typhoid, polymyositis, polyneuritis, dermatomyositis, cerebral hemorrhage, appendicitis and Schönlein's purpura rheumatica. One thing which one notices about these diagnoses, in reading over the cases, is that they were not considered quite typical and that they did not fully explain the picture.

While some few observers are inclined to the belief that the disease is not a distinct entity, but that it is merely an unusual incident in the course of some acute infectious disease, the majority of those who have studied it clinically and pathologically have come to the conclusion that periarteritis nodosa is a disease *sui generis*. Until the etiology is cleared up this point cannot be definitely determined; but the facts seem to point to the latter point of view.

The difficulty in arriving at a symptom-complex on which a diagnosis may be made lies in the wide-spread distribution of the lesions throughout the arterial system, with the corresponding symptoms in one or more regions or organs. Add to this the tendency of the disease to spread to new vascular areas and the occurrence of numerous overshadowing complications and one can appreciate the difficulties in the way of reaching a correct diagnosis.

Is it, then, possible to construct a symptom-complex of periarteritis nodosa sufficiently definite to make a diagnosis possible? Such a diagnosis has been correctly made only twice during life and then by the excision and examination of the subcutaneous nodules. Barring the presence of these nodules, an answer to the foregoing question must be in the negative. I believe, however, that a consideration of certain symptoms and groups of symptoms should make it possible to suspect the disease and should lead to more careful examinations for subcutaneous nodules. When the disease is once suspected every possible examination should be made to aid in clearing up the etiology. Since the occurrence of the above cases in the hospital, there have been at least two cases in which periarteritis nodosa has been suspected. In both of these there was a purpuric eruption and in both some of the spots were excised for microscopic examination. Neither case turned out to be an instance of this affection.

In practically all of the cases there is fever of a more or less irregular type, rapid pulse, often disproportionately so, anemia and progressive weakness and a striking leukocytosis with a high percentage of polymorphonuclears and in some, at any rate, a distinct eosinophilia. It is most important to have this eosinophilia confirmed by future

observations, for if it be at all constant it will furnish a most valuable means of diagnosis. The above facts stand out clearly and represent a pretty definite background against which one must form the clinical picture. Of almost equal importance, even if not of quite as common occurrence, is the presence of edema and the symptoms of nephritis. While one would, of course, hesitate in making any diagnosis on these symptoms one should be equally reluctant in suspecting periarteritis nodosa without them. If one finds, in addition, some of the following less common but quite frequently present symptoms, it seems justifiable to suspect the disease: pains of tearing character in the extremities; pain and swelling of various joints; attacks of acute abdominal pain, colicky in character and generally located in the upper abdomen; vomiting; hemorrhagic eruptions; cyanosis; asthma. If subcutaneous nodules appear, the diagnosis can be easily settled by excision and histologic examination. In addition it should be remembered that the course of the disease is relatively short and that there may be distinct periods of remission of symptoms and improvement.

OTHER DOUBTFUL CASES

In addition to the list of cases considered in the preceding review, there are a few which have many points in common with periarteritis nodosa and which have been included in reviews of the disease by some authors. Some of them are possibly and even probably instances of this affection, but the failure of histologic examinations makes a decision impossible. The authors of these cases with the dates of publication are the following: Gee, 1871; Thompson, 1877; Sabin, 1901. In addition, there are the cases of Matani, Michaelis and Pelletan already referred to. The cases of Geipel and Eichorst are apparently not cases of this affection.

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The following references to the true cases of periarteritis nodosa are arranged alphabetically:

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- Beitzke: *Virchows Arch. f. path. Anat.*, 1910, cxcix, 214; *Verhandl. d. deutsch. path. Gesellsch.*, 1909, xiii, 213.
- Benda: *Berl. klin. Wchnschr.*, 1908, xlv, 353.
- Benedict: *Ztschr. f. klin. Med.*, 1907, lxiv, 405.
- Bomhard: *Virchows Arch. f. path. Anat.*, 1908, cxcii, 305.
- Chvostek and Weichselbaum: *Allg. wien. med. Ztg.*, 1877, xxviii, 257.
- Cooke: *Proc. Path. Soc., Philadelphia*, 1911, New Series, xiv, 96.
- Datnowski: *Wien. klin. Rundschau*, 1911, xxv, 469, 488, 503, 520; *Inaug. Diss., Berl.*, 1909; *Ueber Periarteritis nodosa*, E. Ebering, Berlin, 1909.
- Dickson: *Jour. Path. and Bacteriol.*, 1908, xii, 31.
- Eppinger: *Arch. f. klin. Chir.*, 1887, xxxv, Sup., p. 126.
- Ferrari: *Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's)*, 1903, xxxiv, 350.
- Fletcher: *Ibid.*, 1892, xi, 323.
- Freund: *Deutsch. Arch. f. klin. Med.*, 1899, lxii, 537.
- Graf: *Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's)*, 1896, xix, 181.

- Hart: Berl. klin. Wchnschr., 1908, xlv, 1305; Veröffentl. d. Hufeland Gesellch., Berlin, 1909, ii, Teil 7-18.
- Jonas: Munchen. med. Wchnschr., 1912, dxcii, 1685.
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- Lewis: Proc. Path. Soc., Philadelphia, 1912, New Series, xiv, 134.
- Longcope: Bull. Ayer Clin. Lab., Pennsylvania, Hosp., 1908, v, 1.
- Meyer: Virchows Arch. f. path. Anat., 1878, lxxiv, 277.
- Mönckeberg: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1905, xxxviii, 101; Verhandl. d. deutsch. path. Gesellsch., 1909, xiii, 213.
- Moriani: Inst. d'anat. Path., Siennese, 1910; abstr. Arch. d. mal. d. coeur., 1911, iv, 460.
- Müller: Festschr. z. Feier d. 50 Jahr. Bestch. d. Stadt Krankenhaus z. Dresden, 1899, p. 457.
- Oberndorfer: München. med. Wchnschr., 1907, lii, 2618; Berl. klin. Wchnschr., 1907, xlv, 1496.
- Rokitansky: Quoted by Eppinger, Denkschr. d. kaiserl. Akad. d. Wissensch., Wien, 1852, iv, 49.
- Rosenblath: Ztschr. f. klin. Med., 1897, xxxiii, 547.
- Schmidt: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1908, xliii, 455.
- Schmorl: Verhandl. d. deutsch. path. Gesellsch., 1903, 203.
- Schreiber: Inaug. Diss., Königsberg, 1904.
- Versé: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1906, xl, 409.
- Veszprémi and Jancsó: Beiträge, Ibid., 1903, xxxiv, 1.
- Veszprémi: Ibid., 1912, lii, 476.
- Von Kahlen: Ibid., 1894, xv, 581.
- Zimmermann: Arch. d. Heilk. (Wagner), 1874, xv, 167.
- The following is a list of the literature on the other cases mentioned and other articles dealing with the disease:
- Eichorst: Deutsch. Arch. f. klin. Med., 1904, lxxx, 75.
- Gee: St. Bartholomew's Hosp. Rep., 1871, vii, 147.
- Geipel: Munchen. med. Wchnschr., 1907, xx, 1057.
- Jaeger: Virchows Arch. f. path. Anat., 1909, cxcvii, 71; XIII, Verhandl. d. deutsch. path. Gesellsch., Leipsic, 1909, 209.
- Lüpke: Verhandl. d. deutsch. path. Gesellsch., Stuttgart, 1906, 149.
- Matani: De aneurysmatis praecordiorum morbis, Florenze, 1755.
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- Pelletan: Clin. Chir. on Memoires et observations de chir. clin. et sur d'autres Objects, etc., Paris, 1810, T. I.
- Pertik: Centralbl. f. allg. Path. u. path. Anat., 1908, xix, 90.
- Sabin: Bull. Johns Hopkins Hosp., 1901, xii, 195.
- Thompson: Med. Times and Gaz., 1877, 56.
- Thorel: Ergebn. d. Path. (Lubarsch and Ostertag), 1910, ii, 528.
- Knox: Supra-arterial Epicardial Fibroid Nodules, Jour. Exper. Med., 1899, iv, 245.