PERIARTERITIS NODOSA AND ALLIED CONDITIONS

By

ALEXANDER LYALL,

M.B., Ch.B., F.R.F.P.S.G., F.R.C.S.Ed.,

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Glasgow University.

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

C O N T E N T S.

PERIARTERITIS NODOSA AND ALLIED CONDITIONS.

Periarteritis nodosa was first described as a distinct disease and given its present name by Kussmaul and Maier[1] in 1866. The condition, although unrecognised as a specific affection, was present in medical literature before this time and one of the earliest accounts may be found in a paper by Rokitansky[2] in 1852 entitled "The Formation of Aneurisms of the Arteries in General, Except the Aorta and Most of Its Important Primary Branches, with the Further Exception of the Cerebral Arteries." He gives a very good gross description of the disease. Eppinger[3], thirty five years later, re-studied Rokitansky's case and described the typical microscopic appearances of the condition in the mesentery, bringing it into the group of periarteritis nodosa.

Kussmaul and Maier described the disease as "a hitherto undescribed disease of the arteries which is accompanied by Bright's disease and a rapidly progressive general paralysis of the muscles."

Meyer[4] in 1878 described the following triad of symptoms as characteristic: (a) chlorotic marasmus, (b) polymyositis and polyneuritis, (c) gastro-intestinal.

The earliest complete monograph on the disease in English was that by Carnegie Dickson[5] in 1908. He it was

who first recognised the important distinction between true periarteritis nodosa and a somewhat similar arterial condition which was of syphilitic origin. He divided the recorded cases into two groups: (1) True periarteritis, because, as the name suggests, it affects mainly the outermost layer of the vessel wall, the media and intima being secondarily involved. Most of these cases were of syphilitic origin and should not be included in the specific disease entity we are studying. (2) The other group was marked by its widespread distribution, the destruction of the muscular coat of the vessel at one part, the formation of multiple nodules on the walls of the medium sized and smaller arteries, and certain secondary effects such as aneurism formation or thrombosis. For this condition, which was truly a very rare disease, he suggested the name "Polyarteritis nodosa acuta" and suggested that the old name of "Periarteritis nodosa" should be applied to the first group which had a syphilitic origin.

Although this differentiation of the two conditions has proved very valuable, and has served to limit still further the number of authentic cases of this rare arterial disease, the original name suggested by Kussmaul and Maier has become too firmly rooted in medical nomenclature; and we thus feel that it should be retained to avoid added confusion; and that the somewhat similar condition due to the treponema pallidum should be called syphilitic arteritis.

Brinkmann[6] in 1922 and Christeller[7] in 1926 emphasized nephritis as a cardinal symptom of the disease. Other excellent monographs are those of Lamb[8] in 1914, Klotz[9], Spiro[10], Ophüls[11], and Arkin[12] in 1930. Arkin has given us a very valuable pathological account of the lesions and has added five new cases.

Up to the present about 150 cases of periarteritis nodosa have been reported, most of them being in European, especially German, clinics. In Britain and America the disease appears to be very rare, and at the Los Angeles County Hospital in a series of 10,000 post mortems during 1918 to 1930 only one showed the classical features of periarteritis nodosa.[13] Schroetter[14] regretfully admitted that he had never found one case of the disease although he had looked carefully for it in Vienna and elsewhere. Our own experience suggests however that the disease is not so rare as this, and would be more frequently found if looked for. It is probably frequently undiagnosed, or mis-diagnosed, unless a very careful histological investigation be carried out in certain obscure cases which are usually classified under one of the countless commoner medical or surgical conditions which the condition may mimic so closely. Klotz[9] and Spiro[10] suggest also that although the fully developed lesion is admittedly rare, rudimentary lesions may be much more frequent than is imagined.

It is interesting to note the present position of the condition in the world of pathology by examining the description

of the lesion in certain of the better known textbooks. The fullest description is probably that given in Sir Robert Muir's textbook[15], "The essential feature is a focal periarteritis with involvement of the media and a tendency to the production of aneurisms. The condition is on the whole commonest in adult life, and is more frequent in males than in females. The disease runs a relatively rapid course and death is usually produced by haemorrhage. The lesions are especially common on the visceral arteries, e.g. coronary arteries of the heart, renal, splenic, mesenteric, hepatic, etc., and are indicated by the presence of nodules or patches of thickening along the course of the blood vessels. Aneurisms at various stages of formation may be present and comparatively numerous. On microscopical examination it is found that in the affected parts there is a subacute inflammatory lesion with extensive infiltration of leucocytes in the adventitia, and that, along with this, there soon occurs a necrotic change in the adjacent media. The necrosis rapidly spreads inwards, so that the whole thickness of the wall is involved, A certain degree of compensatory thickening may be found in the intima, but this rarely reaches a marked degree. There soon follows a stretching of the degenerated and necrotic tissue, and an aneurism soon forms. With regard to the etiology, nothing definite can be said. It appears certain that the affection is not of syphilitic nature, and no characteristic organisms have been found in the lesion. The picture however is that

of some unknown infective agent spreading along the perivascular lymphatics and producing the changes described in the adventitia and media....."

Boyd[16] in "The Pathology of Internal Diseases" writes thus: "This rare and mysterious disease has been better named polyarteritis nodosa by Carnegie Dickson, for it usually affects a number of vessels, and the inflammation is not confined to the adventitia. It is the medium sized arteries of the muscular type which are attacked, those of the elastic type escaping completely. In this respect the disease presents a marked contrast to syphilis and rheumatic fever. The principal arteries to be affected are those of the gastro-intestinal tract (mesenteric and coeliac axis), the kidney and the heart, but the vessels of the brain, the lungs and the limbs, may more rarely be involved. Occasionally there are nodules in the skin, and when one of these is excised a correct diagnosis may be made from the lesions of the vessels. The lesions take the form of small nodules scattered along the course of the vessels. There may be dozens or even hundreds of them, arranged like peas in a pot. These nodules represent either inflammatory foci or actual aneurisms. The adventitia and the media are infiltrated with polymorphonuclear leucocytes; and there is extensive necrosis of the middle coat as the result of which multiple aneurisms are formed. The inflammation extends to the intima with rupture of the internal elastic lamina, destruction of the endothelium and thrombosis. If recovery occurs,

the acute lesions are replaced by scarring of the wall and the thrombus becomes organised. Owing to the vascular occlusion, infarct-like lesions are produced in the organs supplied by the affected vessels. The cause of the disease is unknown. Syphilis has frequently been suggested, but appears to be out of the question. A streptococcus has been found in a number of cases." I feel that it is well to give a very full quotation from these two textbooks as they give a very good idea of the modern conception of the pathology of the disease. Textbooks of surgical pathology do not even mention the condition. This appears to me to be a great pity, for the disease very frequently resembles an acute or subacute surgical process; and unless familiar with it, the surgeon may be greatly mystified at operation by the very unexpected appearances found.

There is great difficulty in diagnosing the condition clinically unless one constantly has it in mind. This difficulty is readily explained by the variety of signs and symptoms which may be present in different cases of the disease. As Manges and Baehr[17] remark, "the rare diseases have, as a rule, a clean cut, clinical picture which enables one to recognise them readily. Periarteritis nodosa, however, is most bizarre in its manifestations, and the fact that the disease at its onset or during its course in not a few instances resembles that of an acute surgical abdominal condition, makes it of interest to both internists and surgeons."

We have been fortunate in studying six cases of the disease and have also found typical lesions in certain other affections which have helped us in our search for the etiology of this rather curious and little known disease.

Report of First Case.

Clinical Study.

R.H., aged 16 years, apprentice engineer, was admitted to the medical wards complaining of swelling of his face and general weakness. A little more than a week before, the patient had felt fevered and had sweated profusely. A few days before admission he had noticed that his face was swollen.

On admission the patient was found to be a well-nourished male subject. Oedema of the face and lumbo-sacral region was present. The urine contained albumen (12 parts of Esbach) and some epithelial and blood casts. The heart sounds were normal and the blood pressure was 136/80. The day after admission the patient complained of severe abdominal pain which appeared to be of colicky nature. He became restless and drowsy. A lumbar puncture was performed and the cerebrospinal fluid reported to be under normal pressure and to show no turbidity. The patient sank into coma and died on the day after admission. The clinical picture during the short time the patient was in the wards suggested an acute nephritis.

Pathological Study.

A post-mortem examination was performed on the day after death. The body appeared extremely pale and some oedema was evident in the soft tissues of the face. A large quantity of amber fluid was present in both pleural cavities and a lesser quantity in the pericardium. No abnormality of the serous linings was noted. The heart showed some hypertrophy and weighed 310 gm. The myocardium was paler than normal. The valves showed no evidence of disease. Some nodular thickening of the terminal branches of the coronary arteries was noted. The aorta showed fairly diffuse fatty degenerative change. Upon dissecting amongst the loose cellular tissue around the aorta, many minute white nodular thickenings, on an average of pinhead size, were found associated with the small vessels in this tissue.

A large quantity of amber fluid was found in the abdominal cavity. The whole gastro-intestinal tract showed oedema of moderate degree. On the anterior and posterior surfaces of the stomach were seen minute white nodules, many of them just visible to the naked eye, and irregularly distributed on the smaller arteries. By the aid of a lens many of these were seen to lie at the points of branching of the vessels. No nodules were apparent on the large or small bowel. No ulceration of the gastro-intestinal tract was present. The pancreas appeared normal. The liver weighed 1,174 gm. and had a reddish-purple colour. Here and there, under the capsule, were tiny white nodules similar to those of the stomach. They did not project and had no hyperaemic margin. A few similar nodules were seen in the interior of the organ. No abnormality was found in the gall-bladder or bile ducts. The spleen weighed 70 gm. and showed prominent Malpighian bodies. Each kidney weighed 180 gm. and appeared somewhat enlarged and swollen. The capsules stripped readily, leaving a smooth surface. On section the parenchyma was more turgid than normal. The cortex appeared congested, having a pinkish colour. The peculiar feature was the presence of many small tubercle-like nodules scattered throughout the cortex, these being slightly larger than those of the stomach and liver, and being distinctly seen by the naked eye. At places they were somewhat elongated or spindle shaped, running at right angles to the surface (fig. 1). The bladder and ureters were normal. The suprarenals showed post-mortem autolysis. No abnormality, apart from slight oedema, was found in the meninges or brain.

Histological examination of the heart, kidneys, stomach, spleen and para-aortic tissues was carried out. The sections were stained by hemalum and eosin, Weigert's elastic tissue stain, Gram's staining method for organisms, and Levaditi's method for spirochaetes.
Serial sections were cut of the lesions in the stomach, kidney and para-aortic tissue so that the whole pathological process might be followed out from the beginning to the end (figs. 2-9). Starting in the normal vessel, the first change observed was a slight increase of leucocytes in the adventitia and outside the vessel. These cells were mainly of the polymorphonuclear leucocyte class (fig. 2). This periarterial infiltration gradually increased and polymorphs were soon observed inside the vessel, some of them lying inside the lumen and others being in the subintimal region, the condition being an early acute endarteritis (fig. 3). The media now commenced to show some separation of the muscle fibres or oedema and polymorphonuclear cells appeared between them (fig. 4). Closely following this, the muscle coat became swollen and homogeneous, at first only one side, but later in its whole circumference. These necrotic areas stained a homogeneous pink and no remains of

nuclei were apparent (figs. 5 and 6). As the process was followed still further along, a gradual reversal of the changes was found to take place, the necrosis of the media gave way to an oedema of the muscle fibres, and this faded into intact media, the vessels still showing a leucocytic response in the intima and adventitia, and finally only in the adventitia and around the vessel (figs. 7, 8 and 9). It was noted in our serial section that the lumen of the vessel was widest at the point of necrosis, being much more so than at its afferent and efferent parts. It was also noted that the muscle fibres were fractured at points in the circumference just above and below the area of necrosis of the media and polymorphs were seen at these areas going from the exterior to the interior of the vessel (figs. 4, 7 and 8). A section through a nodule in the para-aortic fibrous stroma at the point of necrosis showed the very marked polymorphonuclear leucocytic response which could take place where the vessel was situated in loose tissue (fig.10). Longitudinal sections of the affected vessels gave the same results, the media being necrotic at one point and fading into intact muscular tissue in either direction. The cellular infiltration was most marked at the site of necrosis, and was obviously the cause of the white nodule so typical of the condition. The infiltration faded off in either direction, and tailed off on the outer aspect of the vessel (fig. 11).
The necrotic process in the above sets of serial sections involved the smallest arteries and surrounded the whole circumference of the vessel. Serial sections were also made of the medium sized arteries where the lesion appeared to lie at one side of the vessel only. If only one or two of these sections were examined, the appearances suggested that the process was involving only one part of the vessel wall (fig. 13). When the whole series was examined however (figs. 12-16) a very interesting picture was got. In every such case the process was found to be associated with the origin of a branch from the parent trunk, the necrotic process being situated at this point and fading off along the course of the branch (fig. 16). This infiltration extended for a short distance along the parent vessel where it was found in both the adventitia and the intima, causing a degree of acute endarteritis in the parent trunk (fig. 12). As the serial sections are followed, there is noted first of all a leucocytic collection in the intima of the larger, apparently affected vessel (fig. 12). The media is next found to be necrotic and the histology at once suggests that the necrotic process has affected only one side of the artery (fig. 13). At this stage a very abundant leucocytic collection is found both within and without the necrotic media. The vessel wall also bulges slightly and we know from our subsequent sections that this is because a branch is arising here. In certain of the older descriptions of the disease this appearance was described as being that of early aneurism forma-

tion[5]. The next section still shows necrotic media, but it is now becoming obvious that this is no mere bulging of the vessel wall (fig. 14); and the subsequent ones (figs. 15 and 16) show the process fading off along a branch of the vessel. This appearance was very noticeable and was present in all the blocks in which the necrotic process was associated with the larger arteries.

Sections of the liver showed the typical necrotic arterial lesion involving the branches of the hepatic artery in a great many of the portal tracts, the portal vein and bile duct being unaffected. The lesions had the same appearances as those already described, although the leucocytic response was less marked.

Sections of the kidney showed the arterial process to be very abundant here, much more so than in the liver or any other organ, more than half of the medium sized and smaller arteries being involved in each section examined. The process was followed out by serial sections and found to have the same pathology as the other sets, an acute peri- and endarteritis (fig. 17) being followed by actual necrosis of the media and then reverting back to the original condition of leucocytic infiltration with intact media. Necrosis of a small artery at its point of origin from the parent trunk was again found, and in one case two tiny vessels arising from a medium sized artery both showed necrosis with cellular infiltration (fig. 18). In no cases was a glomerular arteriole involved in the process, but in spite of this, a large number of the glomeruli showed the appearances of a late acute nephritis, with proliferation of the endothelial cells of the tufts, infiltration by polymorphonuclear cells, crescent formation and capsulitis (figs. 19, 20 and 21). The interstitial tissue of the kidney was overrun by leucocytes, most of them being polymorphs, with a good proportion of mononuclears however. The cells of the tubules showed cloudy swelling and desquamation at places. In some tubules large foamy cells containing granular material or blood pigment were found. By the Sudan III staining method, fat was found in the cells of the convoluted tubules.

Weigert's elastic tissue staining method showed complete disruption of the internal and external elastic laminae at the point of necrotic media, while above and below this the laminae were broken at one part of the circumference only.

Sections of the nodules in the stomach wall gave the same histological picture of the acute stage of the condition as has been already described. No ulceration of the mucosa was present but at parts it appeared more congested than normal.

Sections from the liver and kidney were stained by Gram's method for organisms and by Levaditi's method for spirochaetes. The results were negative.

Cultures were taken from the nodules of the kidney on to ordinary broth agar, glycerin agar and blood agar. No organisms were grown.

Interesting features about this case are:

(1) It shows the early acute phase of the disease with necrosis of the media and leucocytic infiltration.

(2) The disease affects the kidneys most markedly, and clinically the case resembled an acute nephritis. The lesions were also found however in various other sites when looked for. This suggests that it is really a more universal affection in the body than is usually stated.

(3) The glomeruli showed the typical appearances of acute nephritis.

(4) Serial sections showed the evolution of the process and suggested that it was essentially one of the smaller vessels and that, when the larger ones were involved, the process was eccentric and really related to the beginning of a branch.

Report of Second Case.

Clinical Study.

M. - D., aged 16 years, laundry maid, was admitted to the wards complaining of swelling of the ankles and breathlessness of two weeks' duration. The patient stated that she had been troubled with breathlessness on exertion for many years. Two weeks before admission her left ankle became swollen and slightly tender and was diagnosed as a probable tuberculous arthritis. A week later however the opposite ankle and foot became swollen and she was sent into hospital. Six weeks before admission the patient had suffered from a quinsy. She had not formerly been subject to sore throats or growing pains and had never had rheumatic fever.

On admission the patient was found to be a rather obese subject and to become breathless upon slight exertion. Oedema of both legs was present, extending up the back of the trunk to the infrascapular region. The pulse rate was 120 per minute and the blood pressure 150/120. The heart was enlarged. While in hospital the urinary output was constantly below normal, being on an average about 21 oz. daily. Blood, albumen, and epithelial and blood casts were constantly present. The blood urea upon admission was 62 mgm.per cent. and the non protein nitrogen 70 mgm. The Wassermann reaction was negative. During the five weeks the patient was in hospital her temperature was almost constantly elevated, varying from 100°F. to 103°F. (fig. 22). An obscure septic focus was suspected and at one period when she developed some pain in the right renal region for a few days, perinephric abscess was diagnosed. At another time, subphrenic abscess was suspected. The Widal reaction was negative for bacillus typhosus, paratyphosus and abortus. The patient's condition gradually deteriorated, myocardial weakness became apparent and death took place five weeks after admission to hospital.

Pathological Study.

A post-mortem examination was carried out fifteen hours after death. The body was that of a rather small but obese subject. The skin was pale and there was much diffuse subcutaneous oedema present. On opening the thoracic cavity 800 c.c. of pale amber fluid were found in the right side and 450 c.c. in the left. The heart weighed 360 gm. The left ventricle showed well-marked concentric hypertrophy with some dilatation. The right side was normal. On the mitral valve was an incomplete row of minute verrucose vegetations. There was no evidence of old disease of the valves. The aortic cusps each showed a few minute verrucose vegetations. The myocardium

was rather pale in colour but showed no other abnormality. The coronary arteries appeared normal. The right lung weighed 480 gm. and the left 600 gm. Both organs showed some general oedema with an early hypostatic pneumonia.
The peritoneal cavity contained 1 litre of clear fluid.
The stomach and small intestine were normal. The colon showed some generalised oedema of the mucosa. The liver looked somewhat enlarged, weighing 18-20 gm. and was rather paler than normal. Yellowish areas with a reddish mottling between were seen. In the left lobe especially were a number of slightly sunken reddish foci, associated here and there with an old cicatrisation. The gall-bladder was slightly contracted, with a thickened wall, suggesting old cholecystitis. It contained thick bile, but no calculi. The spleen weighed 180 gm., being slightly enlarged and firm in consistence. The pancreas was normal. Each kidney weighed 180 gm. and had a swollen tumid consistence. The capsule stripped quite readily, leaving a fairly smooth, dark red and pale mottled surface. This mottling was of rather fine type, the red areas being confluent and some slightly depressed below the surface. On section the kidney substance had a swollen pale appearance. In the cortex dark red sectors alternated with paler ones, the appearances being those of irregular closure of interlobular arteries giving rise to subacute infarction (figs. 23 and 24). The bladder and pelvic organs were normal. The head was not examined.
Pieces of aortic valve, liver, kidneys and heart were preserved for further examination. The sections were stained by haemalum and eosin, Gram's stain for organisms and Weigert's elastic tissue stain.

The arterial lesions were studied in the kidney and liver. Three types of lesion were seen: (a) acute, (b) subacute, (c) acute on subacute. These lesions affected the smaller arteries mainly.

(a) The acute lesions in most cases were typically those of the disease, there being necrosis of the media with leucocytic infiltration around (fig. 25). In certain cases, especially in the hepatic arteries, the necrosis was found not to be confined strictly to the media, but to spread as irregular strands into the tissue around (fig. 26). Necrosis of many of the vessels was unassociated with the very marked leucocytic reaction so prominent in the first case, there being simply some increase of mononuclear cells in the vicinity (fig. 27). In some of the smallest arteries a whorled appearance was seen around a necrotic process due to proliferating fibroblasts (fig. 28). The process was well marked in the interlobular vessels of the kidney (figs. 29 and 30). In one case necrosis of a glomerular arteriole was noted (fig. 31).

(b) Subacute lesion. This was seen occasionally. Fibroblasts had commenced to lay down their fibrils both outside and inside the vessel. In such cases the intima was separated from the media and internal elastic lamina and collagen fibrils were being laid down in the subintimal space (fig. 32). In other cases the lumen of the vessel was completely filled by young fibrous tissue which contained many fibroblasts and had a reticular appearance. Sometimes two or more small channels containing blood corpuscles were seen in the centre, suggesting recanalisation. Commencing periarterial fibrosis was also present in these cases (figs. 33 and 34).

(c) Acute on subacute lesion. In these cases the acute lesion appeared to have reasserted itself in vessels which had been damaged by an older similar lesion. Endarteritis by young very cellular fibrous tissue was seen, and in the centre of this a new area of necrosis was visible. The important feature about this was that the necrosis was situated immediately around the lumen, involving the newly formed fibrous stroma and not the media, which had been damaged by the old attack of the disease and was now situated at some distance from the lumen (figs. 35 and 36).

In many of the medium sized or larger vessels, an endarteritis obliterans of one side of the vessel was found. Serial sections showed that in most cases this patch of endarteritis was associated with a branch leaving the parent trunk; and this branch showed the typical appearances of old healed periarteritis nodosa with fibrosis of the media and endarteritis obliterans, which in many cases almost completely obliterated the lumen. It was the over-flowing of this endarteritis into the parent vessel which explained the picture of subintimal fibrous proliferation at one side of the circumference.

Sections of the liver showed the presence of some chronic venous congestion with fatty degeneration of the cells around the central veins of the lobules. The liver sinusoids contained an increased number of polymorphonuclear leucocytes. Some increase of fibrous stroma was seen in the portal tracts. Here and there the typical appearances of periarteritis nodosa were present, and in each case the hepatic artery appeared to be the structure involved, the portal vein and bile duct being untouched. Immediately around the necrotic lesion some increase of polymorphs and mononuclears was found but this was not a very marked feature. Concentric fibrous thickening was present around some of the lesions. Acute endarteritis was found in many of the diseased vessels and in a few thrombosis had actually occurred. The smaller vessels of the hepatic artery were those involved and the larger ones appeared normal. Associated with certain of the affected vessels were areas of liver showing

dilated sinusoids and atrophy of liver cells, the appearances being those of subacute infarction.

Sections of myocardium showed the presence of the acute lesion in some of the smaller arteries. The condition was not very prominent however. There was a good leucocytic response around the necrotic process. Sections of the aortic cusps showed that the vegetations were of the rheumatic type, being composed of fused blood platelets. The valve tissue beneath the thrombus showed many newly formed capillaries growing into and vascularising the thrombus. Scattered leucocytes were present in the thrombus and a good many of these were observed in the region of new capillary vessel formation.

Sections of the kidney were examined by haemalum and eosin and also by a modified Gallego method of staining (phosphotungstic acid, orange G and aniline blue). By this method fibrous tissue fibrils showed up exceptionally well. Areas of slight atrophy were found to alternate with hypertrophic ones, corresponding to the dark red and paler areas on the surface of the organ. These appearances were very distinctive by the modified Gallego method (fig. 37). An increase of fibrous tissue was present in the atrophic areas, separating the tubules, and in this stroma many dilated vessels were seen at places (fig. 38). The tubules were smaller than normal and lined by a more flattened type of epithelium. In the hypertrophic patches the tubules were dilated and lined by normal cubical epithelium, with little fibrous stroma separating them (fig. 39). The appearances of the glomeruli were very typical. In the atrophic areas they were small and collapsed, the capillaries of the tuft being hardly seen as such, and there being present a large increase of fibrils (figs. 40-46). In the hypertrophic areas the glomeruli were large, full-blown and lobulated. The capillaries composing the tuft were very prominent as clear rounded spaces separated from each other by little fibrous stroma (figs.47-53). The glomeruli also showed evidence of acute nephritis, there being an increase of endothelial cells with polymorphonuclears, and in some cases a capsulitis with an increase of mononuclears and fibroblasts around the glomerular capsule. In some glomeruli the endothelium was swollen and syncytial like (figs. 54 and 55), and adhesion of the tuft to Bowman's capsule was also seen (fig. 56). The appearances in the arteries of the kidney were those of acute, subacute and acute on subacute necrotising arteritis as has already been described. By Gram's staining methods, fibrinous threads were found in the necrotic areas but no organisms could be demonstrated. By Weigert's elastic tissue method, the old lesions showed solution of continuity of the internal and external elastic laminae at at least one point in the circumference. In the acute lesions the laminae were fragmented into small particles.

The interesting features in this case were:

(1) The presence of both healing and acute lesions.

(2) Where the acute lesion is superimposed on a vessel showing an older lesion with consequent endarteritis obliterans of fairly recent origin, i.e. still composed of fibroblasts and young fibrous tissue, the tissue immediately around the lumen is necrosed and not the media.

(3) The appearances of early subacute infarction with alternating areas of collapse and hypertrophy of glomeruli and tubules are interesting.

(4) The condition clinically resembled an acute nephritis.

(5) The patient appeared to have been suffering from hypertrophy of the heart and hypertension for some time before the onset of the disease of periarteritis nodosa.

Report of Third Case.

Clinical Study.

E.B., aged 39 years, electrician, was admitted to the surgical wards complaining of very marked upper abdominal pain which had come on three days before and become gradually more severe. Marked epigastric tenderness and rigidity were present and an acute abdominal emergency was suspected. Dyspnoea and cyanosis were prominent features so that the patient was too ill for surgical intervention.

On admission the temperature was 97°F., the pulse 120 per minute, and respiration 26 per minute. The leucocyte count was 19,000 per c.mm. of blood, the increase being mainly on the part of the polymorphonuclears. The day following admission the cardiac dulness was enlarged to the left and friction was heard, so that a pericarditis was suspected. The urinary output on admission was scanty but became normal two days later. A heavy cloud of albumen was present on boiling, but no other abnormality found, so that the albuminuria was thought to be of the febrile type. No improvement took place in the patient's condition after admission. The abdominal pain became less and disappeared after a few days, but was replaced by extreme dyspnoea and cyanosis. He finally sank into coma and died five days after admission. An ophthalmoscopic examination of the eye on the day following admission showed no abnormality of the fundi. A few hours before death the white cell count was 39,000 per c.mm. of blood. There was nothing important in the social or past history of the patient except that he smoked rather excessively, his average being about 40 cigarettes daily.

Pathological Study.

A post-mortem examination was carried out ten hours after death. The body was that of a rather sparsely built man. Cyanosis of the face was marked. On opening the thoracic cavity about a pint of blood-stained fluid was found in each pleural sac. The pericardial sac contained several ounces of semi-purulent fluid and this was associated with an acute fibrinous pericarditis. The heart showed moderate hypertrophy, weighing 250 gm., and dilatation of the right ventricle was present, associated with marked hypertrophy of the left one. The myocardium was soft in consistence and showed cloudy swelling. Ante-mortem thrombus was found in the right auricular appendage. The aortic cusps showed slight thickening from primary sclerosis. The other valves were normal. The aorta and coronary vessels appeared healthy. In the basal regions of both lungs a few small recent infarctions were seen. Evidence of chronic bronchitis

was present and the organs also showed emphysema and basal oedema.
On opening the abdomen the peritoneal cavity was found to be normal. The liver was enlarged and showed partial congestion and fatty changes. The gall-bladder was normal. The spleen was normal in size but was firm and on section showed evidence of chronic venous congestion. The stomach and intestines showed nothing of note.
Both kidneys were slightly larger than normal. The capsules stripped readily but were slightly adherent at places. The surface of the organ showed a very characteristic gross scarring, the appearances almost suggesting the name of geographical kidney (fig. 57). Dull red sulci separated irregular pale areas which varied in size from islets measuring ·5 cm. across to irregularly shaped anastomosing masses of pale hyperplastic tissue. The sulci were shallow and much broader than in the usual arteriosclerotic kidney. On section the cortical markings appeared quite prominent and the glomerular dots were seen at places. Dull red sectors, again varying widely in size, were seen on section and corresponded to the sulci on the surface. In such areas the cortical markings were completely obscured. These sectors faded off irregularly near the pelvis. The renal artery was more prominent than normal and on the cut surface of the organ some prominent arteriosclerotic-like channels were noted (fig. 58).
The head was not examined.

Sections of the kidney were examined by haemalum and eosin, Weigert's elastic tissue method and Gram's method for organisms.
The most marked feature in the kidney sections was the presence of periarteritis nodosa in the vessels, the medium sized and smaller arteries showing a healed stage, while many of the arterioles showed the acute lesion. The old lesion was seen in many of the interlobar vessels near the pelvis of the organ. In many cases there was no lumen left at all (fig. 59). In other cases it was represented by a narrow slit only. The media was noted in these cases to be broken in at least one part of the circumference, and through this gap the fibrous tissue of the thickened intima was seen to communicate with that outside the vessel. In other cases the media had completely disappeared, the vessel being simply a fibrous whorl. Sections of other vessels showed simply a marked endarteritis obliterans; but when serial sections were cut these showed damage to the media at a point further on. Sections stained by Weigert's elastic tissue method showed destruction of the internal elastic lamina at sites corresponding to the damaged media. It was noted however that this lamina appeared slightly more resistant than the media so that the destruction was usually less than that of the muscular coat. The external elastic lamina was similarly affected. Many

of the larger arteries showed intimal thickening of eccentric type. In most cases this was found to be associated with the vessel wall at a point where it gave off a branch, the subintimal fibrous fissue overflowing into the parent vessel (figs. 60 and 61). The acute lesion was found in the smallest arteries and the arterioles. Many of the arterioles showed necrosis of their walls, which stained a homogeneous pink colour with the eosin (fig. 62). A few polymorphs and mononuclears were found around the necrotic vessel but this was not nearly so marked a feature as was ordinarily got where the larger vessels were affected by the process. In many cases the reaction appeared to be more of a fibroblastic one, although even this was not very marked. The appearance of the necrosis starting at the point where the arteriole left its parent trunk was again prominent (figs. 63 and 64), and necrosis of a glomerular arteriole arising from one of the arteriae recti was a common finding. An occasional small area of necrosis of a glomerular tuft was seen.

The kidney substance itself showed atrophic areas alternating with hypertrophic ones. The atrophic areas showed an increase of fibrous stroma between the tubules and in many areas this tissue showed large numbers of vascular channels (fig. 65). The tubules in such areas were small and shrunken, and the epithelial lining was of flattened type. The glomeruli were collapsed so that there appeared to be an increased number of nuclei; few showed marked fibrosis (figs. 66 and 67). In the hypertrophic areas the tubules were dilated and lined by normal epithelium, lying close together with little fibrous stroma between. The glomeruli were large and lobulated (figs. 68 and 69). Groups of lymphocytes were commonly found in the shrunken capsules of the organ. In some of the dilated tubules large granular phagocytes containing changed blood pigment were found (fig. 70). A quite prominent feature of the sections was the presence of small rounded or oval, deeply basophilic areas scattered throughout the kidney tissue, being found between the tubules, where they were apparently related to the walls of small blood vessels, and also in the glomeruli. In the latter situation the evolution of these was worked out. It appeared to start off as an enlargement of the nucleus of an endothelial cell which became elongated or horse-shoe shaped and stained a darker blue than the normal nucleus (figs. 71 and 72). Some of these appeared to burst through their lining membrane and developed an irregular and granular appearance (fig. 73). In its final stage of development this body was a rounded or oval mass, the contents of which were homogeneous or granular looking and which gave the staining appearances of calcified material.

Some of the glomeruli showed the changes of acute nephritis with increase of endothelial cells, enlargement of the tufts, some of which pouted into the beginning of the ~~collecting~~ tubule (fig.74), and a syncytial arrangement of the endothelium. Patchy necrosis of the glomerular tuft was seen (fig. 75) and occasionally this was accompanied by necrosis of the afferent arteriole (fig.76).

The interesting features about this case are:

(1) The presence of both chronic or healed lesions and acute ones. Unlike the last case no acute lesions are superimposed on the more chronic ones and this may be explained by the much denser and fibrous character of the healed lesions in the present case. The acute lesion was shown in much smaller arteries and arterioles than it is usually found.

(2) The leucocytic infiltration does not appear to be so marked when the smallest vessels are involved by the disease and this might be explained by the absence of perivascular lymphatics in these.

(3) The naked-eye appearances of the kidney are very characteristic and are those of healed periarteritis nodosa.

Report of Fourth Case.

Clinical Study.

Mrs. H.M., aged 44 years, housewife, was admitted to the medical wards complaining of weakness of her hands and feet. Her illness had started about five weeks before with a so-called influenzal chill accompanying which she had a sore throat, cough, fever and sweating. The illness appeared to be getting better after about a week when she suddenly developed a prickling sensation in her right leg. Within a few days her left leg was also affected, and soon after that both arms were similarly involved. During her whole illness the patient suffered from intense thirst and sweating. There was no urinary disturbance.

Examination on admission showed the patient to be a rather obese female. She lay comfortably on her back with no dyspnoea or cyanosis. The limbs showed a fine tremor. The power of grasping was poor in both hands, but no atrophy of muscle was apparent. The sense of touch was decreased in the left hand. Some loss of power was present in the legs, and decreased sensation was found in both feet. The knee and ankle jerks, biceps, triceps, and supinator reflexes were all absent. The plantar reflex was normal. The abdominal reflexes were absent. While in hospital the paresis appeared to become stationary for a time but again commenced to get worse in spite of massage and physical therapy. While under treatment she developed pain in the right hand and the metacarpal-phalangeal joint of the index was found to be tender, swollen, and slight reddened. This condition was diagnosed as rheumatism and responded to acetyl salicylic acid.

The temperature while in hospital was of a remitting type, varying from 99°F. to 101°F. (see chart between figs. 76 and 77). The condition was first diagnosed as a peripheral neuritis of unknown origin, and various causes for it were looked for without success. Lead poisoning was excluded. The Wassermann reaction was negative. The blood showed a marked secondary anaemia, the red blood count being 2,920,000 per c.mm., and the white cells being 15,200 per c.mm. The increase of white cells was mainly on the part of the polymorphs. The haemoglobin content was 50 per cent. and the colour index 0.86 per cent. The blood urea was 55 mgm. per cent. The urine showed a haze of albumen throughout the illness, and accompanying it a small amount of blood and a few casts of the blood and epithelial types were also present. The blood pressure taken soon after admission was 115/80. In her past history the patient stated that she had had rheumatoid arthritis for many years, but this had not crippled her very much. She had been subject to frequent sore throats for some time. Her condition slowly deteriorated, and a few days before death, which took place four months after the beginning of her illness, she developed the signs of bronchial pneumonia.

Pathological Study.

A post mortem was performed fifteen hours after death. The body was that of a well-nourished woman. There was marked subcutaneous oedema of both legs. Each pleural cavity contained five ounces of clear fluid. The heart was soft and flabby and acute dilatation of both ventricles was present. The myocardium showed marked fatty degeneration. The valves were normal. The lungs showed a bronchial pneumonia which was most marked at their bases. The peritoneal cavity contained a quantity of clear fluid. The liver showed slight enlargement, and there was evidence of chronic venous congestion. The gall-bladder appeared normal. The spleen was enlarged, and the pulp soft and pale red from septic change. The kidneys, stomach and intestines showed no naked-eye abnormality.

The brain showed a very peculiar appearance. Scattered over the surface of both cerebral hemispheres were multiple small softenings giving the organ a moth-eaten appearance. Each softening measured a few millimetres or so in size. A few small softenings were also found in the interior above the region of the basal nuclei. The spinal cord showed no abnormality. The main nerves of the limbs appeared normal to the naked eye.

Pieces of brain, spinal cord, the left musculo-spiral nerve, the right median and musculo-cutaneous nerves, the right great sciatic and the left common perineal nerves were preserved for histological examination. The brain was stained by haemalum and eosin, and the nerves by haemalum and eosin and by Marchi's method for degenerative changes. Sections of the brain showed the softened areas to be small in size. Most of the brain substance had disappeared in the central part, leaving only a network in which many compound granular corpuscles were present. The periphery of the softenings had an irregular appearance. The smaller arteries and arterioles in the softened areas showed varying degrees of closure of their lumina. This varied from simple thickening of the vessel wall to complete closure by endarteritis. The earliest degree of change was a simple thickening of the vessel wall which developed a very hyaline appearance. The process was often more marked at one side of the vessel, giving the lumen an irregular shape (fig. 77). In other cases, there was a more definite endarteritis obliterans present, and the subintimal fibrous reticulum, which also had a rather hyaline consistence, was seen to communicate frequently with the tissue of the original vessel wall by a breach in the original intima (fig. 78). Although these vessels were too tiny to have obvious muscle in their walls, the evidence of old damage was still often well marked and appeared to have been of the nature of rupture of the intimal lining at one point and the overflowing from here of fibrous stroma into the lumen, setting up an endarteritis which was most marked at the site of old

damage (fig. 79). Frequently the lumen of the arteriole was completely closed by the endarteritis (fig. 80), and such vessels commonly lay unsupported in the centres of the minute cerebral softening. At places the endarteritis had a very whorled cellular appearance, and the original wall of the vessel was not distinguished at all. When serial sections of these were cut, it was found that an acute necrotic process was present at one part (fig. 81), and that this gave way further down to the very concentric endarteritis (fig. 82); still further down, this gave way to an ordinary endarteritis in which the original coat of the vessel was beginning to become apparent (fig. 83).

The appearances typical of periarteritis nodosa were seen in the vessels of the subarachnoid space from which the arterioles already described in the softened areas emerged. Various degrees and stages of the process were seen. In some of the smallest arteries and arterioles complete necrosis of the vessel wall was in evidence with a marked leucocytic reaction around, most of the cells being of the mononuclear class with a few polymorphs. The vessel wall near the process showed endarteritis (fig. 85) and sometimes a marked periarteritis (fig. 86); the cellular fibrous stroma extended for a distance outwards in an irregular manner so that the definite rounded outline of the vessel was lost. Aneurism formation and thrombosis were frequently observed in these vessels (figs. 87-89). In some cases red blood corpuscles had gone through the necrotic walls without actual rupture and were seen in the subarachnoid space. In other medium sized vessels the healed process was seen (fig. 90), and when the section passed through the site of the old damage to the vessel wall, the breach in continuity of the media and internal elastic lamina was seen, and at this point the fibrous tissue appeared to grow into the lumen and become continuous with that composing the endarteritis obliterans (figs. 91-92). Endarteritis was prominent in the vessel wall above and below this process (fig. 93).

In certain cases giant cell formation was evident in the granulation tissue of the endarteritis (figs. 94-95). These cells were quite unlike those of tubercle or syphilis and resembled rather those of the Aschoff nodes or of lymphadenoma (figs. 96-98). Some lymphocytic infiltration was present in the subarachnoid space immediately around the affected artery. One arteriole was seen in the brain substance with necrosis at one side of its wall (fig. 99). No leucocytic reaction was present around it.

The nerves dissected out were stained by haemalum and eosin and by Marchi's methods. By the latter method, degeneration of the nerve fibres was shown. The vascular supply of the nerves was studied in sections stained by haemalum and eosin. Most of

the arteries seen were abnormal. The lesions on the whole were of the healed type. In some cases the sections showed only intimal and periarterial fibrous thickening (figs. 100-103). Serial sections of these showed however that the typical damage to the media was present at some neighbouring point of the vessel wall (figs. 104-105). Attached to some of the nerves dissected out were small pieces of muscle and fat and in certain of these the typical lesions of periarteritis nodosa at the healing stage were seen (fig. 106). An interesting feature found in the nerve sections was the absence of involvement of the veins of the nerve which lay in close proximity to the arteries, showing the predilection of the disease for the arterial system, and that it does not spread even to the adjacent veins as it so typically does in Buerger's disease (figs. 100 and 105). No trace of the disease was found in the sections of the spinal cord examined.

Noteworthy features:

(1) This is one of the few genuine cases of periarteritis nodosa affecting the cerebral and meningeal vessels.

(2) Degenerative changes were found in the peripheral nerves and this was associated with narrowing of the vascular channels of the nerves by healing periarteritis nodosa.

(3) Both healing and acute lesions were present in the same case.

(4) Sections of muscle and fat attached to the nerves showed the lesions and suggested that the disease was much more widespread than the post-mortem findings indicated.

Report of Fifth Case.

Clinical Study.

B.C., aged 45 years, steelworker, was admitted to the medical ward complaining of loss of power of both hands. Two months before admission the patient had been generally unfit and had developed urticaria on his back, legs and arms. Ten days later he developed intense headache, which was associated with some stiffness of the neck. Marked fever and sweating were also present. Severe pains, followed by a feeling of numbness, came on in his legs about this time. Typhoid fever was suspected by his doctor, who sent him to a fever hospital. He remained there for a month, and during that time had irregular pyrexia, sweating, and obscure pains and aches. The Widal and Wassermann reactions were negative. The cerebrospinal fluid was normal. After a month the patient improved, his temperature became more regular and normal, and he was discharged from the fever hospital. The numbness of his limbs then started to get much worse and within a week he had completely lost the power of his left arm and right hand. He then commenced to lose the power of his legs and became unable to walk. There was little or no pain in the limbs at this time.

When admitted to the wards he was found to have lost the power of walking. Decreased sensibility was present in the lower third of both legs and arms. The pulse was soft and regular and the cardiac signs poor. Two weeks after admission paralysis of the diaphragm was found to be present and a tendency to cyanosis appeared. The heart sounds became very poor, râles appeared in the chest, and death took place a little more than three weeks after admission. The white cell count on the day after admission was 8,800.

Pathological Study.

A post mortem was performed five hours after death. The body was that of a well-nourished male who looked somewhat younger than his years. There was a bedsore over the sacrum. The heart weighed 450 gm. and showed hypertrophy and dilatation of both sides, this being more marked in the left ventricle. The valves appeared normal. The myocardium showed areas of chronic infarction with haemorrhages and small patches of necrosis. The coronary arteries appeared normal to the naked eye. Preformed thrombus was present in the right auricular appendage. Each pleural cavity contained about 60 c.c. of amber coloured fluid. In the lower third of the middle lobe of the right lung was a haemorrhagic infarction and an embolus was found in the vessel supplying this lobe. Some areas of the organ were reddish brown and oedematous, especially in the upper lobe, while the greater part was very pale and well aerated.

There was a haemorrhagic infarction at the inner part of the lower lobe.

The stomach was normal. The vessels on the surface of the small intestine running from the mesenteric border outwards on the external surface of the bowel showed areas of thickening and of aneurismal dilatation, the latter being about 2 or 3 mm. in size. This appearance was found along the whole small bowel. In the ileum were some small superficial ulcers measuring on an average 2 mm. in diameter, and these were found to be related to certain of the abnormal vessels in the bowel. Many of the aneurisms were dark in colour and contained clotted blood. The liver was enlarged and weighed 2,200 gm. The surface was plum coloured and a few well-defined sunken areas were present, one of which was definitely related to a chronic infarction. Section of the organ showed "nutmeg" appearances with areas of hyperplasia. There were seen particularly (a) small white cords which were very fibrotic and most of which had a tiny lumen in the centre; being obviously partly occluded vessels: (b) aneurisms varying in size up to that of a pea and containing clotted blood: (c) areas of yellow infarction and other dark brown areas which were obviously partial infarcts: and (d) bile-stained areas in the portal tracts the appearances of which suggested aneurisms of the bile ducts (figs. 107-108). The gall-bladder appeared normal. The spleen was enlarged, and three small pale infarcts, each 4 mm. in size, were present on the convex surface. The pulp was dark red.

Each kidney appeared slightly larger than normal and weighed 160 gm. The capsule stripped readily. The surface was very irregular due to a pattern of dark red sunken areas which irregularly covered the whole surface (fig. 109). These were sharply defined but irregular in outline and joined in places. They varied from 2 mm. to 1 cm. in breadth at different parts. They were clearly of the nature of chronic infarcts. The intervening kidney tissue projecting between these areas was fairly normal. A few small yellow infarcts occurred within certain of the red areas. On section red wedges corresponding to the surface depressions extended radially through the cortex to the boundary zone. A few small aneurisms, 4 to 8 mm. in size, were seen on section near the apices of infarcted wedges (fig. 110).

The main vessels of the arms and legs showed no naked-eye abnormality. The larger nerves also showed no obvious abnormality. The brain appeared normal. About the middle of the thoracic region of the spinal cord was an area of softening.

Sections of various organs and tissues were preserved and stained by haemalum and eosin, Weigert's elastic tissue stain, Gram's stain for organisms, and Levaditi's stain.

Sections of liver were stained by haemalum and eosin, by Weigert and by the modified Gallego staining method. There was a marked increase of fibrous stroma in the portal tracts and this extended outwards into the liver tissue at places almost surrounding the lobules to give the appearance of multilobular cirrhosis. Degenerating liver cells were seen at the periphery of the lobules and proliferating bile ducts in the adjacent fibrous stroma of the portal tracts. The liver tissue at most places gave the appearances of subacute infarction, the cells being separated by dilated sinusoids and forming multinucleated masses at places (fig. 111). Small areas of complete necrosis of liver tissue were seen. Various degrees of vascular destruction were evident in the portal tracts. All the lesions were of some standing and no acute necrotising ones were found. In the least affected tracts the hepatic artery was the only structure affected, showing marked thickening of its wall due to a fibrous peri- and endarteritis (fig. 112). In other cases the hepatic artery and portal vein appeared to be both involved in the process, there being marked fibrous thickening around their lumina and only a few broken fragments of elastic tissue being got by Weigert's stain. In such cases the bile duct frequently showed some desquamation of its epithelium and increase of fibrous tissue around, but no actual involvement in the disease (fig. 113). In such cases the Gallego staining method showed the marked condensation of fibrous tissue around the affected vessels (fig. 114). The wall of the portal vein and sometimes of both the portal vein and hepatic artery was frequently defective at one point and in many cases the blood appeared to have been filtering from one to the other (fig. 115); and in cases where one was thrombosed, phagocytes carrying golden brown blood pigment were seen passing from one to the other through the breach. In other cases the lumina of the vessels were completely gone, their outlines being sometimes shown by condensed fibrous stroma (fig. 116), at others by a few young arterial channels of recent formation (fig. 117). When serial sections were cut of the hepatic artery it was found that the appearances of complete or almost complete closure of the vessel appeared to alternate with areas of aneurismal dilatation. In these aneurisms the blood was clotted and from the periphery fibroblasts were seen growing into the clot, which was becoming organised. Interesting appearances were got in the case of the bile duct. In some cases they were normal where the hepatic and portal systems were both affected. In others they were dilated into aneurisms with thick fibrous walls. In other cases the epithelial lining was destroyed and bile had soaked into the surrounding loose fibrous stroma which was condensed at some distance out (figs.118-119). Some of the portal tracts showed simply hyaline fibrous whorls which represented fibrosed hepatic arteries.

Sections of kidney were examined by haemalum and eosin, Weigert's elastic tissue stain, Gram's stain, and Gallego's stain. The medium sized and smaller arteries showed the healed lesions of periarteritis nodosa. The typical feature was the destruction of the muscular coat to a varying degree along with the internal and external elastic laminae, the remains of which at times became mixed up at the site of muscle destruction and absorption so that they appeared to form one irregular shredded mass (fig. 120). Marked endarteritis obliterans was also present and the fibrous tissue composing this was dense and well formed (fig. 121). The lumen of the vessel was frequently very minute and eccentric (figs. 122-123). The arterioles were not affected. The red sulci seen naked eye were found to have the histology of ischaemic atrophy (fig. 124), and by the fibrous tissue stain an increase of fibrous stroma was found in the glomeruli and between the tubules (fig. 125). The paler projecting masses showed some enlargement and lobulation of the glomeruli, and dilated tubules which lay quite close to each other with little stroma between. These appearances rather resembled those of Case 2 except that they were rather more advanced so that sclerosis of the glomeruli in the atrophic areas was much more in evidence so that large numbers were simply fibrous whorls. No evidence of the changes of acute nephritis were found in the glomeruli. Here and there in the atrophied areas small collections of lymphocytes were apparent, but aside from this few leucocytes were present in the sections. The fibrosis of the diseased arteries remained confined to them and did not appear to spread outwards into the renal tissue in the neighbourhood. As in cases already described, the arterial process here was again frequently found involving a branch arising from a larger vessel (fig. 126).

Sections of the heart showed the healed lesions of periarteritis nodosa with marked intimal proliferation causing excessive closure of the vessels (fig. 127). These lesions were got in the medium sized and smaller branches of the coronary arteries. The larger ones were not involved. Associated with the diseased vessels areas of ischaemic atrophy of the myocardium were found (fig. 128).

Sections of the bowel showed the presence of old healed lesions. These were of two types: (a) At places aneurisms containing clotted blood and with fairly thick fibrous walls were seen. Fibroblasts were growing into the organising blood clot from the periphery. (b) Very marked endarteritis of vessels was noted and in some of these almost complete or complete closure was present (fig. 129). In most of these no remains of muscle tissue was observed, the vessels being merely represented by a fibrous whorl. Some of these lay near the ulcers noted on naked-eye inspection.

Sections of lung showed a very interesting feature. Many of the bronchial arterial branches gave evidence of periarteritis nodosa of old standing with varying degrees of endarteritis obliterans. The pulmonary arteries did not show the lesion, however, and in sections a diseased bronchial artery was frequently found lying alongside a normal pulmonary artery (fig. 130). The lung tissue itself showed no abnormality.

Sections of skeletal muscle gave the appearances of the healed disease, the smaller arteries being those affected. Some of these vessels showed destruction of internal and external elastic laminae and muscle coat with marked endarteritis obliterans (fig. 131). Others showed marked endarteritis alone (fig. 132). In still others two lumina of small size were apparent in the centre of the fibrous intimal proliferation (fig. 133). The muscle itself showed proliferation of interstitial fibrous tissue with disappearance of the muscle fibres; and at these areas large multinucleated masses of muscle were frequently seen (fig. 134).

The peripheral nerves were sectioned. Degeneration of the fibres was got by the Marchi method. Many sections were examined for arterial lesions. These were found in a few sections but at such areas were quite prominent. The lesions were much more acute than in the other organs, showing leucocytic infiltration, mainly of the mononuclear type, and, at places, actual thrombosis had occurred (fig. 135).

Even the vessels of the tongue showed the healed lesion (figs. 136-137).

No organisms were found in any of the organs by Gram's staining method.

Noteworthy features of this case are:

(1) The presence of both acute and chronic lesions, the acute ones being found in the vessels supplying the nerves.

(2) The universal character of the disease in the body so that the vessels of the tongue even were affected.

(3) The absence of involvement of the pulmonary arterial circulation in spite of the fact that the bronchial artery arising from the systemic circulation was involved.

Report of Case 6.

This case was one which we found on going over the Museum specimens of the Glasgow Royal Infirmary. It is obviously one of periarteritis nodosa with multiple aneurism formation which was unrecognised at the time, and as far as we can find has not previously been reported.

Clinical Study.

Mrs McL., aged 49 years, housewife, was admitted to the medical wards complaining of severe pain in the legs, back and shoulders. Four weeks before admission the patient had an attack of influenza accompanied by marked anorexia and pain in the limbs. She improved generally but the pains became very much more severe up till her admission to hospital.

Ten days after admission the patient developed severe abdominal pain accompanied by sickness and vomiting. Examination disclosed the presence of a mass the size of a small football to the right of the middle line. This mass was solid to the touch and gurgling was elicited on handling it. A strangulation of the bowel was diagnosed and operation performed under general anaesthesia. A large blood tumour was found in the lower part of the mesentery and lying behind the lower half of the ascending colon. The cyst was opened and partially clotted blood evacuated. It was found necessary to resect the lower part of the ileum and part of the ascending colon and caecum. For six days after operation the patient made an uneventful recovery, but on the seventh day she developed severe abdominal pain and marked collapse so that death took place within a few hours.

Pathological Study.

A post mortem was performed fourteen hours after death. The cadaver was that of a fairly well-nourished middle-aged woman. The heart showed marked hypertrophy of the left ventricle and slight hypertrophy of the right. No valve lesions were present. The lungs showed some emphysema and hypostatic congestion. The abdomen contained a moderate amount of slightly altered blood. The caecum and a piece of the ascending colon had been removed and an anastomosis effected between the ileum and colon. There was a considerable amount of intraperitoneal haemorrhage present, chiefly on the right side and extending down the psoas sheath as far as the inguinal ligament. A considerable quantity of blood was present behind the right kidney and this had broken through into the abdominal cavity at one point. Swellings which felt like enlarged mesenteric glands were found in the mesentery. Section showed these to be aneurisms which were clotted at the periphery but contained fluid blood in their centres (figs. 138-139). Similar swellings were seen on the lesser curvature of the stomach near the

cardiac orifice. On the surface of the liver were a number of cicatricial depressions rather suggesting a syphilitic cirrhosis but on cutting into these there were found pale areas with intense congestion around like infarctions. Related to two such areas, one on the right lobe and one on the Spigelian lobe, were thrombosed aneurisms each the size of a hazel nut (fig. 140). The spleen was slightly enlarged but showed no other abnormality. The kidneys were pale and granular with some irregularity of the cortex, resembling small white kidneys although they were not much smaller than normal. About the middle of the upper half of the pancreas was found an aneurism the size of a hazel nut and containing partly clotted blood. The stomach and intestine were normal apart from a small dark vascular area on the surface of the jejunum about three feet down.

Sections were examined from several of the red masses in the liver. Most showed laminated thrombus enclosed in a fibrous capsule. In one the arterial wall was present on one side in a practically intact condition. From the histological description the condition was obviously one of periarteritis nodosa with multiple aneurism formation.

Interesting features about this case are:

(1) The case resembled an acute abdominal surgical condition for which operation was deemed necessary.

(2) This was a gastro-intestinal type of the disease with multiple aneurisms on the branches of the visceral arteries.

Important features noted in our series of cases are:

(1) Age and sex incidence. All our patients were comparatively young and the average was 35 years. The sex incidence was equal.

(2) Acute lesions may be got along with the healed lesions. These may be found together in different organs, in the same organ or even in the same part of an artery.

(3) The media of the artery is the structure usually affected and the damage to it is a very characteristic feature of the healed stage of the disease. The disease may however also affect arterioles with no obvious muscle coat, and also arteries showing early endarteritis obliterans. In such cases the innermost part of the vessel appears to be that affected.

(4) The process is typically found at the point where the vessel arises from its parent trunk and the necrosis is seen spreading from the point of origin in an outward direction along it.

(5) It appears very likely that the disease is much more universal in the body than has been formerly thought. We have found it in all manner of out of the way places such as the para-aortic fibrous tissue and in the tongue. This is also suggested by the reports of certain other workers. In a case reported by Barnard and Burbury (20), the fingers and toes were gangrenous due to the involvement of the peripheral arteries by the disease (fig. 141).

(6) There is a microscopical form of the condition in which the damage is not sufficient to cause the marked leucocytic infiltration which gives the nodular appearance naked eye or sufficiently virulent to cause aneurismal dilatation or thrombosis. This is the type which may very easily be missed if careful histological examination is not pursued.

PATHOLOGY OF PERIARTERITIS NODOSA.

As the disease is essentially one of arteries it will be well to consider the various stages and complications of the disease in the arteries and leave the pathology of the disease in individual organs to be discussed along with the clinical features.

(1) Necrotic Stage. The earliest stage of the process is a sudden acute necrosis of part of the vessel wall, this being usually the media, associated with fragmentation of the internal and external elastic laminae. We have shown from our studies however that the media is not invariably the structure involved; for in certain of our cases where the acute process had reappeared in a vessel showing healing of an older periarteritic lesion the central fibrous tissue forming the subacute endarteritis was the tissue involved in the necrotic process. It would appear that this can only happen where the fibrous stroma of the endarteritis is still loose and recently formed. Where the old lesion is of longer standing and the fibrous proliferation hyaline and dense, no necrosis takes place, as was shown by one of our cases. The vessels usually affected by the process are the smaller arteries, but also to a lesser degree the medium sized arteries and arterioles. A noteworthy feature in one of our cases was the very marked involvement of the arterioles and, in this case, the medium sized and many of the smaller arteries showed thick fibrous

unyielding walls due to an older attack of the process, the appearances thus suggesting that the condition prefers the smaller arteries but falls back on the arterioles when the former are not available. The whole circumference of the vessel is usually affected at one part of its length, the muscle having a homogeneous necrotic appearance with disappearance of the nuclei. The adjacent muscle fibres show some separation by oedema above and below the necrotic lesion. A notable feature is the presence of the lesion very commonly at the beginning of a small vessel, the necrotic process being most marked at the point where it leaves the parent trunk and fading off along its course.

Clinically at this stage there is probably some rise of temperature; but the lesions are microscopic, the blood flow along the affected vessels is not interfered with, and there are probably no other symptoms.

(2) Reactive Stage. At this stage, which follows close on the last, there is an emigration of leucocytes to the affected area and these cells arrange themselves around the necrotic vessel wall. They are most abundant at the site of the necrosis, where they form the white tubercle-like nodule seen naked eye, and fade off in a spindle-shaped manner on either side of this, a section of the vessel near the periphery of the process showing simply a slight increase of cells in the adventitia.
The leucocytes find their way through the necrotic media to the

intima and may separate the intimal endothelium from the wall, forming an acute endarteritis (fig. 3). Towards the periphery of the area of actual necrosis the leucocytes are seen between the oedematous muscle fibres. Gram's stain for organisms shows the presence of fibrin threads in the necrotic media. Elastic tissue stains show fragmentation of the elastic laminae, especially the internal one. The leucocytic reaction consists mainly of polymorphonuclear leucocytes, but at the later stage these are replaced largely by mononuclears, lymphocytes and plasma cells.

It should be noted that this stage does not always follow the last one, and this appears to be specially so where the condition affects either the arterioles or vessels which are already the site of marked fibrosis from older disease. In both these cases the leucocytic response is usually scanty, and the probable reason for this is that in the former case there are no perivascular lymphatics to carry the leucocytes, and in the latter such channels have been largely obliterated by the old fibrous reaction.

Naked eye this stage is marked by the presence of white tubercle-like thickenings along the course of the smallest vessels or at the sides of the larger ones. This appearance is usually most marked in the kidney, is prominent in the liver, heart, gastro-intestinal tract, but in fact may be found anywhere and, as in our own case, even in the para-aortic connective tissue.

Clinically at this stage there are high fever, sweating, leucocytosis and frequently a secondary anaemia with an icteric hue of the skin.

(3) Stage of Complications. These complications are (a) narrowing of the vessel and (b) aneurism formation.

(a) Narrowing of the vessel - the tendency for the polymorphonuclear infiltration to extend through into the intima has already been described, and in some cases the necrotic process appears to involve the intima as well as the media, and thrombosis is the natural result. Short of actual thrombosis, very marked narrowing of the lumen of the vessel may result from the endarteritis, which at an early stage is acute, and caused by separation of the intima from the internal elastic lamina by leucocytes, but later becomes fibrous (fig. 32). The result of this vascular closure is of course necrosis of the tissue supplied, and various degrees of infarction are therefore seen naked eye in the organs containing the affected vessels.

(b) Aneurism formation - the musculo-elastic elements in the vessel wall have been destroyed and it is therefore not surprising that the lumen should frequently dilate. In this process of stretching, the intima has of course been destroyed. The blood flow is slowed due to the increased size of the channel. There is therefore a tendency for thrombosis to occur in the aneurism, and this commonly takes place when it lies supported within a solid organ; and when opened is there-

fore found associated with an area of infarction caused by the thrombosis. If it be near the surface of an organ however, rupture frequently occurs and may be the cause of the fatal termination of the disease.

Clinically at this stage the fever usually drops a little as the acute necrotic stage of the process has passed. The symptoms are due to vascular occlusion in the kidneys, heart, brain, peripheral nerves, and are therefore those of nephritis, coronary disease, cerebral softening or peripheral neuritis. Occasionally gangrene of the fingers or toes may occur. A sudden haemorrhage into the abdomen or perirenal tissues from a ruptured aneurism may give the signs and symptoms of an acute abdominal lesion or an internal haemorrhage.

(4) Healed Stage. Only the comparatively mild cases of the disease actually reach this stage as death usually occurs from the complications of the third stage. The necrotic material disappears, the leucocytes are replaced by fibrous tissue, and the final stage is thus one showing marked overgrowth of fibrous stroma (fig.131). The most characteristic histological feature of this stage is the replacement of the musculo-elastic elements of the vessel wall, completely or in part, by fibrous tissue, and by the elastic tissue stains the internal and external laminae are seen to approach each other at the fibrotic patch and at times almost to fuse. The cellular infiltration in the adventitia and outside the vessel is replaced by fibrous stroma

which later becomes dense and hyaline. The fibrous tissue of the intima proliferates in an attempt to strengthen the weakened wall and an endarteritis obliterans is thus produced. Naked-eye these affected vessels appear as white, concentrically thickened rings with often an almost microscopic lumen. Aneurisms in the internal organs are found in various stages of organisation, their walls being thick and fibrous, and fibroblasts being seen growing from the intima into the organising blood clot. The effect of this process on the internal organ will obviously be that of ischaemic atrophy, and the final pathology will be that of contracted kidneys, liver cirrhosis, chronic interstitial myocarditis, encephalo-malacia, parenchymatous nerve degeneration.

Clinically at this stage the fever is absent. The symptoms depend upon the organs particularly involved, and these symptoms are often progressive; for it should be noted that, although the acute process has subsided, healing is proceeding by fibrous tissue and the lumina of the vessels are becoming slowly narrowed so that the nephrosclerosis, interstitial myocarditis or peripheral neuritis will be of slowly progressive character, and death usually takes place from one of these at some stage of the healing process. It seems possible however that some may go on to complete healing where the primary illness has been localised to one area of the body as was suggested by an appendix case, (vide infra) or where it has been of comparatively slight severity.

Although we have described the pathological process in stages from the acute to the healing stages, we may add that it is very common to find both the healing and active phases present in the one case, in the same organ, and, as we have already mentioned, even at the same site in an artery.

GENERAL CLINICAL FEATURES.

Males appear to be affected four times oftener than females. In the period immediately preceding the onset of the illness there is frequently a history of single or recurrent attacks of tonsillitis or quinsy, and the patients frequently state that the illness actually started with a sore throat. This is well seen in the cases of Lamb[8], Klotz[9] and Manges and Baehr[17]. The age of the patients affected varies from two and a half months (Krzyszkowski[18]) to seventy eight years (Arkin[12]). Fifty per cent. of the cases however occur between the ages of twenty and forty years. The duration of the illness again varies. Fishberg's case[19] died within six days; while Arkin's[12] case died four years after his acute illness. In the latter case at post mortem the lesions of healed periarteritis nodosa were found, the patient having died of renal and myocardial insufficiency following the healing of the process. During the period between his acute attack to the time of his death he showed no evidence of acute exacerbations of the disease.

In many of the reported cases a skin eruption was present. These appeared to be of great variety and of little value in actual diagnosis. The eruption may be purpuric in type, as in Barnard and Burbury's[20] case and in one of Lamb's[8] cases which, because of its rheumatic symptoms, was actually diagnosed as Schönlein's purpura haemorrhagica. A rheumatic like purpura was also present in the cases of Zimmermann[21],

Schreiber[22], Frommel[23], and Hutinel and his co-workers[24]. In Jancsó and Veszprémi's case[25], a boy aged 14 years, there was an uritcarial rash accompanied by multiple subcutaneous haemorrhages. An urticaria was present in one of our cases. In Klotz's case[9] there was said to be a typical erythema nodosum present. In Manges and Baehr's[17] case, a diffuse maculo-papular rash was present on the hands and forearms. These very varied eruptions may usher in the disease or occur later in successive crops. Their causation is unknown, but they are thought to be of toxic or haemorrhagic origin.

Subcutaneous nodules may be found and are said to be present in twenty five per cent. of cases. They are usually very firm and feel like shot along the course of a vessel. They resemble the nodes found in acute rheumatism, but are found along the course of a vessel and not on the extensor aspects of joints particularly. In Manges and Baehr's[17] case the nodules were first felt along the course of the right brachial artery and were the size of small peas. Later, similar nodules appeared along the left brachial, third right intercostal artery, shin, and frontal region of face. Most of the nodules are due to small aneurisms, but as thrombosis occurs very early in them, pulsation is rarely got, and in those found by Manges and Baehr were only obtained in those on the face. In other cases they appear to be due to marked fibrous thickening around an affected area or vessel. In two cases in the literature, those of Schmorl[26] and Benedict[27], the correct

diagnosis of the condition before death was reached from the examination of an excised nodule. Occasionally the nodule may not show the specific features of the condition as happened in Klotz's[9] second case where the condition was not diagnosed from the excised nodule.

The blood shows a well-marked leucocytosis of the polymorphonuclear type and this is prominent even when the temperature is normal and the condition is undergoing healing. An increase of eosinophils in the blood was described by Datnowski[28], Lewis[29], and Lamb[8].

The temperature varies markedly. In most cases it is moderately high during most of the illness, but shows some remissions. In other cases, it may be normal for a few days and then rise again, as in Lamb's second case.

Joint pains are said to be present in thirty nine per cent. of cases and are frequently quite severe. More than one joint is usually involved, and an appearance resembling acute rheumatism may be presented.

The onset of periarteritis nodosa may be acute or more gradual. In its typical acute form it commences with a high temperature, marked sweating, emaciation and a slightly icteric hue, giving the so-called chlorotic marasmus appearance. Thereafter the clinical picture may be extremely varied, as was illustrated by the many suggested diagnoses in Haining and Kimball's[13] case which was variously diagnosed as coronary sclerosis, subdiaphragmatic abscess, echinococcus liver cyst,

tuberculosis, coccidioidal granuloma, pyelonephritis and Malta fever. Diagnoses which have been made in other cases are nephritis, meningitis, miliary tuberculosis, generalised peritonitis, obscure sepsis, dysentery, trichiniasis, morbus maculosus Werhlofii, encephalitis, typhoid, polymyositis, polyneuritis, dermatomyositis, cerebral haemorrhage, appendicitis, Schönlein's purpura, rheumatism.

In spite of this variety of diagnoses, most of the cases may be placed in one of four main clinical groups:-

(1) Polyneuritic or muscle-nerve type - in this group, which appears to be the largest one, shooting pains in the limbs accompanied by marked tenderness are followed by weakness, hyperaesthesia and loss of power. These cases are only too apt to be diagnosed as peripheral neuritis due to an unknown toxin or dietetic deficiency factor, and the real causative lesion be found only upon histological examination of the affected nerve.

(2) Renal group - this group is also a large one and patients belonging to it have also frequently got polyneuritic symptoms. The main signs point to kidney dysfunction, the picture being that of an acute, subacute or chronic nephritis. In such cases however there are usually odd features which make the physician hesitate in his diagnosis, features such as an inexplicable temperature, attacks of abdominal colic, or myocardial impairment of

fairly rapid onset. In one of the cases which we reported (Case 3), and which was diagnosed clinically and post mortem as a chronic nephritis, the physician had added in his notes, "There are certain features about this case which make it quite unlike any other nephritis case I have dealt with" (Dr. Cowan).

(3) Obscure sepsis group - into this category we place those cases of the disease which have a high remitting temperature with emaciation, sweating, marked prostration, leucocytosis and a secondary anaemia - really a continuation of the chlorotic marasmus which is so usual at the onset of the illness. Such patients usually have + Widals, B abortus reactions, blood cultures, faeces examinations, urinary tests carried out with negative results. The physician frequently feels that there is a collection of pus somewhere but that he cannot localise it; so that, should the patient develop transient pain in the subcostal or renal areas, he is at once suspected of harbouring a subdiaphragmatic or perinephric abscess.

(4) Acute surgical group - the patients in this group have the signs and symptoms of a surgical emergency such as acute appendicitis, peritonitis, renal calculus, perinephric abscess, subdiaphragmatic abscess, suppurating retroperitoneal glands. They are usually operated upon

under this mistaken diagnosis, and in certain cases have then been correctly diagnosed by the finding of the typical nodules of periarteritis nodosa in the abdominal cavity or elsewhere.

THE DISEASE AS IT AFFECTS SPECIAL ORGANS AND SYSTEMS.

It may now be well to study the disease as it affects some of the more important organs and tissues and discuss the pathological effects produced with the corresponding clinical picture.

According to Arkin(12), the organs commonly affected in their order of frequency are kidneys (80 per cent.), heart (70 per cent.), liver (65 per cent.), gastro-intestinal tract (50 per cent.), pancreas (35 per cent.), mesenteric artery (30 per cent.), muscle (30 per cent.), peripheral nerves (20 per cent.), central nervous system (8 per cent.). It is obvious that this can only be a very rough estimate of the true incidence of the disease in the tissues of the body as certain ones, such as muscle and nerve, are not examined as a routine in the course of post-mortem work as are the kidneys, heart, liver and gastro-intestinal tract. It is our belief that the disease is really a very widespread one in the body, although the lesions must be searched for histologically. In two of our cases where the diagnosis was made naked eye

at autopsy, the only gross lesions were those in the organs mentioned. However when sections of tissue from many other areas of the body were examined, the lesion was found to be almost universal, and found in such tissues as nerve, muscle, tongue and para-aortic cellular tissue. In a case published recently by Barnard and Burbury[20] the patient, a young girl, had multiple lesions in the peripheral vessels so that she even developed gangrene of her fingers and toes. It is therefore our belief that the disease is much more widespread than statistics indicate, and that this universal character of the lesion is not recognised because (a) the lesions in the viscera of the chest and the abdomen are usually gross and are accepted blindly by many an investigator as being the only site, so that he looks no further afield. (b) Not infrequently the condition is only recognised microscopically when it is too late to go back and examine other tissues of the body, as happened in three of our own cases.

The Kidneys in Periarteritis Nodosa.

Considering that the kidneys are involved in periarteritis nodosa in seventy four per cent. (Grüber[30]) to eighty per cent. of cases (Arkin[12]), it is not surprising that the symptoms of a kidney lesion may overshadow all others.

The pathology of the kidney in periarteritis nodosa is very well illustrated by our own series of four renal cases, although it must be understood that they are all really stages

in the one condition:- (see album between figs. 141 and 142)

(1) First stage - the organ may be slightly enlarged and more turgid than normal. The characteristic feature of this stage is the presence of multiple white tubercle-like nodules which are best seen in the cortex. They have no area of hyperaemia around them and are, of course, due to the perivascular accumulation of leucocytes. The glomeruli may appear normal, but some stand out as prominent white dots as in acute nephritis. The surface of the organ shows no abnormality apart perhaps from slight pallor.

Microscopically, the typical vascular lesions of periarteritis nodosa are seen with necrosis of the media, of the medium sized and smaller arteries, and the presence of a cuff of leucocytes which are mainly of the polymorphonuclear class. The glomeruli show all the changes of acute or subacute nephritis with endothelial proliferation, polymorphonuclear infiltration, crescent formation and capsulitis.

(2) Second stage - the kidney appears slightly smaller than normal. The surface of the organ is smooth, but the characteristic feature is the presence of a very typical, moderately fine dark and light mottling; and on section this is seen to be due to wedge-shaped pale and dark areas in the cortex, the dark areas being wedges of subacute infarction from fairly rapid closure of certain of the arcuate vessels. As a rule no abnormality can be made out in the vessels naked eye.

Microscopically it is seen that the vessels show acute and subacute lesions, endarteritis being more prominent, whereas the periarteritis is not so concentrated and localised, and the cells show many more of the mononuclear class. In the dark areas of subacute infarction there is a moderate increase of connective tissue fibrils between the tubules which are smaller than normal. The glomeruli in such areas are small and collapsed looking and by special staining methods an increase of fibrillae is recognised. In the paler areas the appearances are those of hypertrophy, the tubules being large and open with slight flattening of the epithelial lining and the glomeruli being large, full blown, and lobulated, the capillaries being rounded and opened out.

(3) Third stage - the kidney is somewhat smaller and on the surface are seen pale infarctions and commencing scars from the absorption of infarcts and ischaemic atrophy of areas of kidney tissue. Aneurisms may be seen under the capsule, but do not appear to be very prominent in this situation. Section of the organ shows the presence of aneurisms, many of which contain clotted blood and also white round fibrous nodes, many of which are seen to have a small central lumen and which are really greatly thickened arteries. These appearances are really due to two pathological processes in the vessels; firstly, there is a continuance of the endarteritis seen in the last stage so that some of the vessels may become almost completely closed and seen as white fibrous nodes; secondly, aneurisms

have formed from the weakening of the vessel wall and these appear to clot very readily, so that an infarction of the kidney substance results. At this stage the glomeruli in the areas of ischaemic atrophy are becoming fibrosed and shrivelled up and the tubules are becoming separated by fibrous tissue proliferation. Here and there in the more normal areas a damaged glomerulus is seen, as evidenced by the firm adhesion of its tuft to Bowman's capsule.

(4) Fourth stage - this is the final scarred stage of the disease. The organ is smaller in size and on the surface there is a gross scarring. This resembles the senile arteriosclerotic kidney, but differs from it in its regularity. It will be remembered how irregular is the scarring in the typical senile arteriosclerotic kidney, depending of course upon the irregular distribution of the causative arterial degeneration. In periarteritis nodosa, the involvement of the vessels appears to be regular and diffuse, so that the scarring has a very uniform pattern. Its gross character differentiates it from the regular but very fine granularity of the arteriolosclerotic kidney of hypertension.

Microscopically the scarred areas show various degrees of ischaemic atrophy, the interstitial fibrous tissue showing marked overgrowth so that the tubules are becoming more separated, smaller in size, and less obvious. The glomeruli show various stages from pericapsular and tuft fibrosis up to the

appearance of dense hyaline fibrous balls. The smaller arteries related to these areas show the healed stage of periarteritis nodosa. The wall shows marked fibrous thickening, both outside and inside the vessel and, very characteristically, the media is destroyed at one point so that the fibrous tissue outside and inside communicate. Fibrous tissue stains show destruction of the internal and external elastic laminae at this point, and the broken ends of these laminae may approach one another and almost join at times.

It should be noted that the acute process may reassert itself and be found in the more chronic stages accompanying the old lesion. We have shown that where this happens in a vessel scarred by the old disease, the young fibrous tissue elements immediately around the intima appear to suffer rather than the remaining media. Where the lesion in the arteries is still older, and the fibrous tissue of the endarteritis is thickened and hyaline so that it will not be readily damaged, the process affects the smallest arteries and arterioles, as was seen in the kidneys of our third case.

The naked eye appearances of these various stages may be seen from the figures in the album.

A very interesting feature about the acute kidney lesion is the glomerular involvement, the appearances being those of an acute nephritis and, in fact, if the arterial lesion were not present, this would be the proximate diagnosis. Moreover, our first case clinically resembled very closely an acute

nephritis. Other writers have noted glomerular changes and have regarded them as being due to the extension of the arterial inflammation into the glomerular capillaries.(11) We have seen this occur in nephritis acris, although even here the appearances are as if some hyperacute process had struck the whole kidney, including glomeruli, vessels, and interstitium, at once. In periarteritis nodosa, however, at least in the uncomplicated acute stage, the process affects the medium sized and smaller arteries and stops here so that no spread is seen along the glomerular arterioles. This tempts us to conjecture on the etiology of acute intracapillary glomerulitis and suggests the possibility of the tuft changes being due to some degree of narrowing of the arcuate vessels, due perhaps to prolonged spasm.

The rapidity of progress from one stage of periarteritis nodosa to the other would appear from the recorded cases to be fairly rapid so that the kidney lesion may go from the acute stage with its tubercle-like periarterial foci to the final stage of nephrosclerosis within some months and certainly under a year. Keegan's(31) case is interesting in this respect. His patient was a female aged twenty four years whose right kidney was removed because of acute surgical symptoms. The organ showed the appearances of acute periarteritis nodosa with miliary nodules and a few infarctions, but no contraction or pitting of the surface, the histology putting it into a late stage one according to our classification. Two months later the patient died, and the other kidney was studied. It was

decreased in size and was mottled with dark red and lighter areas. The cut surface showed distinct thinning of the cortex, which measured on an average 4 mm. compared with 6 mm. in the right kidney. The interlobar arteries showed little cellular infiltration, but their lumina showed very marked diminution due to enormous intimal thickening which extended occasionally into the interlobular arteries. The tubules showed marked atrophy and there was a diffuse increase of interstitial tissue. More complete fibrosis was apparent at areas throughout the kidney substance. The description places this organ into a stage between two and three. It should be noted that the pathological process appears to be more diffuse than in our cases of about this stage. This suggests that, just as we have acute diffuse or acute focal nephritis, so may we have acute diffuse or acute focal periarteritis nodosa of the kidney; and as far as the kidney is concerned, the more diffuse the process, the sooner will the patient die of kidney insufficiency; and only in the very focal type of lesion will he carry on to the final stage of nephrosclerosis.

Clinically the symptoms from renal involvement are frequently very prominent so that we actually speak of a "renal" type of the disease along with the "muscle-nerve" and other types. Apart from those cases where an acute surgical kidney lesion is suggested, the picture is that of an acute, subacute or chronic nephritis, depending upon the stage of the pathological process. Oedema may be present at any stage, but

is commoner in the later subacute or chronic ones. Albumen is present in the urine, but is usually not a prominent feature. The urine has a low specific gravity. Red blood corpuscles are usually at least intermittently present. Hyaline, granular and blood casts may be got. As the disease progresses the urinary excretion tests become less satisfactory and the blood urea rises, but usually not to much above 50 mm. per 100 c.c. of blood. The blood pressure does not appear as a rule to rise much during the progress of the illness. Nocturia and frequency not uncommonly appear, cardiac decompensation may arise and death occur from retention of fluids, late uraemic symptoms and pulmonary oedema. This clinical course is simply that of vascular nephritis of the arteriosclerotic form, which, according to Volhard and Fahr[32], includes all forms with vascular change which do not involve the glomeruli.

Kountz's[33] case differed rather markedly from this picture. The patient was a male aged sixty seven who suffered from generalised periarteritis nodosa. Upon admission his blood pressure was 115/70. The non protein nitrogen was 33 mm. Soon after admission the blood pressure rose to 160/100 and continued to rise so that three weeks after admission, at the time of death, it was 200/100 and the non protein nitrogen, 95 mgm. per 100 c.c. The surface of the kidney showed a fairly fine scarring, but at places large scars were present, extending downwards from the cortex, and at these areas the kidney tissue was destroyed so that only a few shrunken tubules

and sclerosed glomeruli were left. In the remaining kidney substance the greater number of the glomeruli were enlarged and some had plugs of fibrin in the afferent vessels. Kountz describes the changes in the afferent glomerular vessels as resembling closely those described by Fahr as the lesion of malignant hypertension. He therefore ascribes the marked terminal hypertension to the changes in the renal arteries, especially in the afferent glomerular vessels, and suggests that periarteritis nodosa may be a cause of malignant hypertension. We do not agree with this. It should be noted that his patient had suffered from nocturia for four years, for which no local cause was found at post mortem, and from dyspnoea on exertion for two years. The heart was noted to be enlarged upon admission and at post mortem weighed 473 gm. The author also mentions that the kidney, apart from the acute process, showed the changes of chronic interstitial nephritis. From his description we therefore believe that his patient was suffering from the primary granular contracted kidney or the "genuine schrumpfnière" for some time before the onset of the periarteritis nodosa. The only suggested point against this view is the sudden rise of blood pressure during his three weeks in hospital, The fact that his blood pressure on admission was only 115 mm. does not mean, however, that it was not up before this. The enlargement of the heart and his symptoms all suggest that it was, and the fall at the early acute period of his periarteritis nodosa might very well be attributed to the acute

necrotic condition of the affected arteries which would have a temporary paralytic effect on the neuromuscular mechanism of the cardiovascular system so that the blood pressure would fall and remain thus until the circulation had become attuned to the changed conditions.

Thus from our own cases, and those of others, it appears that periarteritis nodosa when it affects the kidney leads to a chronic interstitial nephritis of vascular type with albuminuria, haematuria, urea and nitrogen retention and oedema. There is no definite evidence that it leads to the hyperpiesis of malignant hypertension and as we shall later show, a great many periarteritis nodosa cases probably have hyperpiesis as a precursor to the acute necrotising arterial lesion.

The Heart in Periarteritis Nodosa.

The heart is very frequently hypertrophied, but this is due to the hypertension which appears to be so frequently a precursor of the illness, but which is attributed by a few to the renal lesion caused by the disease. The coronary arteries and their branches show the diagnostic lesions. At the earliest stage of the disease the minute nodules composed of perivascular leucocytic accumulations are seen at the sides of the coronary arteries and their larger branches and actually on the smaller branches. Later in the healing or chronic stage of the process the characteristic feature is the presence of aneurisms. These appear as white nodules, usually larger

than those of the acute stage, but also related to the vessels and, in fact, at the same sites as the original nodules. They contain clotted blood usually. Patches of thickening of the arteries are also found, and these correspond to the areas of endarteritis obliterans. These patches have not the yellow colour of atheroma, nor do they contain calcified material. The myocardium shows a pale mottling due to interstitial fibrosis and, at areas, more definite fibrous scars are seen. Fatty degeneration has been described and is probably due to fairly rapid partial closure of one of the larger coronary branches. Large infarctions are not the rule, and this is of course due to the fact that the larger branches of the coronary are not themselves actually involved in the disease.

Histologically, the appearances are those of chronic interstitial myocarditis with overgrowth of fibrous stroma, disappearance of muscle fibres, and the hypertrophy of those adjacent to the fibrosed patches. There is nothing really typical in these appearances, except perhaps the presence of more necrotic muscle fibres than are got in the usual fibrosis of myocardium; and this is due to the more acute closure of the related vessels.

Clinically there are all the signs and symptoms of coronary disease of fairly acute onset. One of the characteristic features at the commencement of the illness is the rapid pulse. It should be noted however that Lamb[8] has drawn attention to the fact that symptoms and signs referable to the heart

may be notably absent or slight, whereas gross disease of the coronaries is found at autopsy. Manges and Baehr (17) corroborate this statement from the study of their case.

The not infrequent presence of verrucose endocarditis in cases of periarteritis nodosa may be noted here. As will be shown later, it is used by some to suggest a very close association between periarteritis nodosa and the rheumatic infections.

The Liver in Periarteritis Nodosa.

In the acute phase of the disease the liver shows relatively few signs of abnormality. Close naked-eye examination usually discloses the presence of at least a few tubercle-like nodules under the capsule which have not, however, the hyperaemic border of miliary tuberculosis. Section of the organ may show similar nodules in its substance, but they are usually inconspicuous here. At a later stage, that of endarteritis and aneurism formation, the surface of the organ shows commencing irregularity due to fibroid atrophy. On section, multiple aneurisms, most of which are thrombosed, are visible, and elsewhere white fibrous nodes, which are partially obliterated hepatic arteries with much fibrous thickening around them. The liver tissue has a mottled, red and paler appearance due to the presence of irregular areas of chronic infarction. The final stage is that of hepar lobatum where the organ is small and scarred from the vascular closures.

Histologically the appearances in the vessels are those of acute, subacute and chronic periarteritis nodosa as seen in any of the organs. The marked increase of fibrous tissue in the portal tracts, amounting at places almost to a multilobular cirrhosis, is noteworthy. It extends between the lobules from the portal tracts and might appear, as has been suggested by other investigators in the case of the kidney, to be an actual extension of the inflammatory process. This is probably not so, the appearances being more likely to result from vascular closure. It should be noted that the process appears to originate in, and affect mainly, the hepatic arteries of the liver. An appearance seen in one of our cases (Case 5), and not hitherto described, as far as we are aware, was that of aneurism of the bile ducts. This was present throughout the whole organ, and certainly suggested a very acute lesion starting in the hepatic artery of the tract and spreading outwards to involve the other structures so that weakening of the wall of the bile duct took place, forming an aneurismal dilatation or else allowing the bile pigment to seep into the newly formed fibrous stroma of the tract.

Clinically symptoms and signs referable to the liver are not usually present. At the beginning of illness there is an icteric hue, but this is due to haemolysis rather than liver dysfunction, and is associated with a secondary anaemia. Even at the last stage of hepar lobatum symptoms of liver disturbance do not appear, although very probably efficiency tests, such as the laevulose tolerance one, would show some insufficiency.

Nervous System in Periarteritis Nodosa.

Arkin[12] states that the peripheral nerves are involved in twenty per cent. of cases. We consider that this is probably too low an estimate of nerve involvement, especially when we remember how frequently polyneuritic symptoms predominate. If the literature be studied, it is found that it has been the exception rather than the rule to examine the peripheral nerves histologically; and then only if the peripheral neuritis were a very predominant symptom. The lesions found may be either of the acute or chronic type, and in our cases both were found although the chronic predominated in one and the acute in another.

In certain cases which showed the polyneuritic train of symptoms clinically, the histologists have failed to find any vascular lesion in the nerves examined, although they found them elsewhere in the body. This has occasionally affected their views as to the etiology of the arterial lesion, and thus Ferrari[34] and later Carr[35] and Wohlwill[36] believed that the process was primarily one of the nerves of the body which acted secondarily on the arteries. They founded these views upon the parenchymatous degeneration of the nerves with the absence of involvement of the vessels supplying them. I can only suggest that they did not look thoroughly enough for the lesion, for in one of our cases (Case 5) many blocks had to be cut before the lesion was actually found in the vessel nourishing the nerve; and it should be noted that the vascular supply

to a nerve is frequently a solitary vessel which comes off high up, such as the comes nervi ischiadicii from the inferior gluteal artery or the comes nervi phrenici from the internal mammary, and this being so, occlusion of the supplying vessel by the diseased process, even only at one point, may produce very serious functional effects in the nerve beyond.

Clinically there are pains along the limbs and in the muscles, and so severe may these be, that poliomyelitis or trichinosis may be suspected; and indeed trinchinosis was the diagnosis which Kussmaul[1] attached to his original case of periarteritis nodosa. As the disease progresses, hyperaesthesia is followed by paraesthesia, paralysis of muscles with foot drop, wrist drop, loss of tendon reflexes, and indeed the picture becomes that of an ordinary peripheral neuritis.

The central nervous system itself appears to be but rarely involved in periarteritis nodosa, according to Arkin[12] in only eight per cent. Cerebral types of the disease have been recorded by Chvostek and Weichselbaum[37], Dickson[5], Müller[38], Longcope[39], Fletcher[40], Arkin[12], and Haining and Kimball[13]. Many of these reports are unsatisfactory however. In Haining and Kimball's case no microscopical appearances are given and, besides, everything is overshadowed by an acute purulent meningitis. In Arkin's case a large haemorrhage existed in the region of the left basal ganglia. No vascular lesions of periarteritis nodosa were seen in the brain, but the author refers to the small periarteriolar

haemorrhages as being due to a vascular abnormality. These are however commonly got in cases of cerebral apoplexy in vessels at some distance from the lesion and are due to blood cells travelling along the perivascular spaces; and in this case they were thus probably secondary to the apoplexy and not due to an arteritis. Ophüls[11], in his masterly monograph, states that only four cases of cerebral periarteritis nodosa have been reported. In two of these (those of Chvostek and Weichselbaum and of Dickson) multiple aneurisms had developed and one of these had burst, causing a subarachnoid haemorrhage. In Müller's case the disease was limited to the small vessels of the pia and multiple fine haemorrhages were present in the brain substance. In passing we should note that the typical picture of the disease was got in the retinal arteries in this case. In his last case, that of Longcope, a large area of softening was present due to thrombosis of a diseased artery. Bennet and Levine[41] have reported a case in which the genuine lesions of periarteritis nodosa were found on histological examination of the brain. In our own case, the conspicuous feature was the presence of multiple small softenings scattered over the surface of the brain, giving it a moth-eaten appearance. These were totally unlike the softenings of arteriosclerosis or those got in hypertension, which when multiple are usually found in the region of the basal nuclei. Their distribution did bear a resemblance to that of subacute tuberculous meningitis in which softening of the brain is caused by an acute endarteritis of

the pial vessels; but the meningeal exudate of this disease was lacking. The lesions of periarteritis nodosa were typically present in the pial vessels and both acute and chronic phases were seen, the softenings being due mainly to the marked endarteritis present in the affected vessels and, to a lesser degree, to thrombosis on an acute lesion.

The symptoms in such cases vary with the degree of involvement of the brain by the disease. Lamb[8] mentions headache, visual disturbance, insomnia and death in convulsions as symptoms. Others mention that there may be mental symptoms and delirium or that the mind may be clear to the end. Aphasia has been described. If it be remembered that the disease is one of the smaller arteries and arterioles of the brain, and that these are widespread throughout the meninges and the organ itself, and also that the disease may be of varying degrees of severity, it will be appreciated that no clean cut description of cerebral periarteritis nodosa can be given. Thus, in the type where aneurism formation is a prominent feature, the patient suffers only from headache until one of the distended vessels ruptures. Varying degrees of unconsciousness with blood in the cerebrospinal fluid and other signs of subarachnoid haemorrhage will then ensue. Where closure of the smaller meningeal vessels by thrombosis or endarteritis is a prominent feature, the signs will be those of tuberculous meningitis, with headache, dimmed consciousness, varying degrees of palsy and paraplegia, and finally coma and death. More rarely, where a larger vessel is

involved and thrombosis takes place, the signs and symptoms are those of apoplexy, as was seen in Longcope's[39] case. Bennet and Levine's[41] case is interesting and warrants special mention. The patient had been ill for some months with a variety of perplexing symptoms and pyrexia, for which no cause could be found. He then developed nuchal rigidity, suggestive of meningitis. Ten c.c. of slightly clouded cerebrospinal fluid were withdrawn. The cell count was found to be 176 per c.mm., and at later dates 800 and 350 per c.mm., and practically all were polymorphs. No organisms were found. It was thought that the patient had been suffering from a meningococcaemia for the preceding four months and that the condition had terminated in meningitis. He was therefore given antimeningococcal serum intraspinally and intravenously, but without effect. At post mortem, the typical lesions of periarteritis nodosa were found. The interesting feature of this case was, of course, the turbidity of the cerebrospinal fluid with a cell count consisting of polymorphs reaching 800 per c.mm. at one stage, thus making the resemblance to a meningococcal meningitis very close.

In summarising therefore, we may classify periarteritis nodosa of the brain into four main groups, depending on whether they resemble (a) subarachnoid haemorrhage, (b) apoplexy, (c) tuberculous meningitis, (d) meningococcal meningitis. It should be remembered that in these cases there are symptoms referable to other organs such as those of myocardial

insufficiency, nephritis, peripheral neuritis; and these should aid the clinician to come to a correct diagnosis.

Abdominal Symptoms in Periarteritis Nodosa.

Abdominal symptoms may occur during any part of the illness in periarteritis nodosa and may even usher in the condition. If it be remembered that the gastro-intestinal vessels are involved in fifty per cent. of cases, this is not surprising. The degree of severity of the pain and the signs accompanying it depend upon the degree of involvement of the affected arteries. Most commonly there are severe colicky attacks, usually in the upper abdomen but sometimes widespread; and these may recur over a period of several days. They are probably due to localised spasm of segments of bowel with a subminimal blood supply and remind one of the recurring anginoid syndrome not infrequently got in cases of syphilitic aortitis with narrowing of the orifice of the left coronary artery. If it be remembered that these patients have also a high temperature, are usually sweating and show a marked leucocytosis in the blood, it is not surprising that many of them are operated upon as surgical emergencies. Occasionally the pain is more localised and very severe, and in one of Lamb's[8] cases - a girl of ten years with a temperature of 102.6° and a leucocytosis of 33,000, with 93 per cent. of polymorphs - an operation was performed for acute appendicitis. The peritoneal cavity was found to be normal and nothing seen to explain her acute abdominal

symptoms. Laparotomies in such cases were also performed in those reported by Schmidt[42], Lemke[43], Ophüls[11] and Grüber[30]. In other cases ulceration of the gastro-intestinal tract is present and there may even be diarrhoea with blood in the stools. In such cases perforation of the bowel has even occurred and death taken place from peritonitis (Zimmermann[21], Lorenz[44], Verse[45], Beitzke[46] and Meyer[47]). A dysenteric-like ulceration of the bowel was got in Rokitansky's[2] case. More rarely, where involvement of the mesenteric arteries is severe, haemorrhagic necrosis of the bowel has been found. This was noted in one of our cases (Case 6).

Death may occur from an intraperitoneal haemorrhage simulating an acute abdomen. Teacher and Jack's[48] case was that of a man aged 43 years who had severe pain in the right lumbar and hypochondriac regions. At post mortem he was found to have an intraperitoneal haemorrhage due to a ruptured aneurism of a hepatic artery. Both of Klotz's[9] cases are interesting in this respect. His first patient, a woman aged 33 years, complained of intense abdominal pain. She had a slight continuous pyrexia, a trace of icterus, and a moderate polymorphonuclear leucocytosis. Her gall-bladder was palpable and tender, and an acute cholecystitis was diagnosed. Six days after the onset of her acute abdominal symptoms she died suddenly. At the autopsy periarteritis nodosa with aneurisms of the hepatic and cystic arteries was found, and one of the hepatic aneurisms had ruptured, causing an extensive intra-abdominal haemorrhage.

His second case, a male aged 53 years, showed few intra-abdominal symptoms, but post mortem there was marked involvement of the branches of the coeliac axis artery with an intraperitoneal haemorrhage.

In Manges and Baehr's[17] case, four shallow ulcers were found on the posterior aspect of the stomach near the lesser curvature.

An acute surgical condition of the kidney is not infrequently suspected. Manges and Baehr's[17] case, a man of 39 years, had severe pain in the right lumbar region radiating to the testes near the beginning of his illness. He had similar attacks later, and during one of these passed blood-stained urine. The symptoms suggested, of course, renal colic.

In Wever and Perry's[49] case, a male aged 29 years, there was a complaint of pain in the lumbar region. Palpation disclosed a rigid tender abdomen with a mass in the right loin. Such signs and symptoms with a persistent irregular fever rising to a maximum of 100.4°F., and a leucocytosis, made the diagnosis of perinephric abscess fairly certain. At operation a perirenal haematoma was found, and examination of the excised kidney showed this to have its origin in a ruptured subcapsular vessel.

Keegan's[31] case, a woman aged 24 years, showed tenderness in the right side of the abdomen, a leucocytosis of 20,000, and pyrexia. An acute surgical condition of the right kidney was diagnosed and the offending organ removed. It showed the lesions

of acute and subacute periarteritis nodosa.

In two of Hauser's[50] cases, operations were carried out because of a mistaken diagnosis of an acute surgical affection of the kidney.

Wordley's[51] case was that of a boy aged 13 who was admitted with severe pain in the right side of the abdomen and the passage of bright red blood-stained urine. The appearances suggested a renal calculus. He then began to waste markedly, and with the absence of oedema and of a high urea blood content, a renal neoplasm was suspected. At post mortem, periarteritis nodosa of the kidneys and heart was found. The photograph of the kidney is almost identical with that of ours in Case 5.

Gray[52] reported a case in which a pre-operative diagnosis of perinephric abscess was made. The patient, a female aged 29 years, had pain in her back with scalding on micturition. The pain appeared more marked on the right side of the abdomen. Albumen and casts were present in the urine. These signs, together with a remitting temperature and profuse sweating, made the diagnosis of perinephric abscess a very likely one. At operation only slight oedema of the subcutaneous tissues was said to be present, and the kidney felt normal. At the post mortem a week later, the lesions of periarteritis nodosa were found to be present.

In at least eight of the cases reported in the literature death has actually been due to renal or perirenal haemorrhages (Schmidt[42], Walter[53], Janssen[54], Mertens[55], Harris and Friedrichs[56], Löwenberg[57], Laux[58], Powell and Pritchard[59]).

DIAGNOSIS OF PERIARTERITIS NODOSA.

I have already remarked upon the difficulty in diagnosing periarteritis nodosa and pointed out that, unlike other rare diseases which usually display a clean-cut clinical picture, periarteritis nodosa presents no set clinical syndrome, and, in fact, may imitate a large variety of diseases which differ widely in both their clinical pictures and pathology. The only real way of diagnosing the condition appears to be to keep it at the back of the mind when brought into contact with a symptom complex which suggests diseases of widely differing systems. Even in such cases, moreover, the lesion in one system is frequently much more severe than in the others so that the symptoms referable to them may appear quite insignificant and be looked upon as complications of the main lesion suspected. As an example of this, the patient may have the high temperature of the typical chlorotic marasmus phase at the early stage of the illness. An obscure septic focus or typhoid may be diagnosed. He has pains in his limbs but this is looked upon as a toxic neuritis. He has albumen with some casts in the urine and this is looked upon as a febrile albuminuria. His heart shows some weakness and the pulse appears excessively rapid; this is put down as a toxic myocarditis. Thus the obvious diagnosis of a pathological process affecting many different systems may early be missed.

If the disease is suspected, there are certain other special examinations which may prove the diagnosis. These are:

(1) Examination of a skin nodule - nodules showing the lesion of periarteritis nodosa are said to be present in the skin in about twenty five per cent. of cases. These nodules lie in the subcutaneous tissue close under the skin and have a firm shotty feel. They lie along the course of an artery such as the brachial, and have been got on the extremities most commonly, but also on the face, neck, thorax and abdomen. Usually they are painless, but may be tender and have a small area of inflammatory reaction around them as in Manges and Baehr's[17] case. The nodules are really small aneurisms, but very seldom pulsate as thrombosis takes place within them very rapidly. Where there are no nodules apparent, it may even be advisable to examine a piece of excised muscle as happened in one of Kussmaul and Maier's[1] cases, where the diagnosis was made by excising a piece of gastrocnemius. The muscle showed Zenker's degeneration and on the minute arteries were localised dilatations with marked infiltration of the adventitia.

(2) Ophthalmoscopic examination - the retinal vessels are really the only ones of small size which are open to direct examination by the physician, and as they may show the lesions of periarteritis nodosa, an ophthalmoscopic examination of the fundi should be carried out in every suspected case, and either the tubercle-like nodules of the early stage, or the aneurisms of the later stage, looked for. Unfortunately in the few cases in which this examination was performed the results have

not been encouraging. Albuminuria retinitis was found in the patients of Sacki[60], Manges and Baehr[17], Lamb[8] and Wever and Perry[49]. Grüber[30] has tabulated thirteen cases with ophthalmoscopic examination. In eight of these the fundi were normal, and in three the appearances were those of albuminuric retinitis. Friedenwald and Rones[61], made a pathological study of the retinae in periarteritis nodosa and found that the vessels showed simply extreme arteriosclerosis, differing in no way from that of ordinary albuminuric retinitis. In a case described by Goldstein and Wexler[62] the fundi were reported as normal during life, but the authors found the typical lesions in the retinae post mortem. In Müller's[38] case the typical changes of periarteritis nodosa were found in the retinal vessels. It is interesting to note that in this case the typical lesions were present in the pial vessels so that it is possible that the retinal form of the disease depends upon its presence in the cerebral circulation and is therefore just as uncommon as this is. These reports are rather disappointing, but suggest that positive changes may be occasionally found in the fundus, and then be of great value in diagnosis; but also that a negative result is of no value in disproving the disease.

(3) Laparotomy - a nodule may be excised from the mesentery and examined for the typical histology. The final diagnosis of periarteritis nodosa was thus made in Manges and Baehr's[17] case by examination of a mesenteric nodule during the laparotomy for a supposed acute abdominal lesion.

THE RELATIONSHIP OF PERIARTERITIS NODOSA TO RHEUMATISM.

A resemblance between periarteritis nodosa and rheumatic fever has for long been noted. Both conditions have the appearance of an infectious disease with a long febrile septic course, marked by severe sweating, the development of secondary anaemia, and with persistently negative blood cultures. Both diseases are, moreover, frequently preceded by some bacterial infection such as streptococcal sore throat. Joint pains, with sometimes an effusion of fluid, are present in thirty nine per cent. of periarteritis nodosa cases (Lamb[8]). These pains are often very severe like those of acute rheumatism. A purpuric condition resembling Schönlein's purpura has been found in certain cases of periarteritis nodosa (Zimmermann[21], Schreiber[22], Lamb[8], Frommel[23], Hutinel and his co-workers[24]). Subcutaneous nodules may be found in both conditions. A history of rheumatic fever is not infrequently found in the past history of periarteritis nodosa cases. The Aschoff node also bears some resemblance to the periarteritic nodule. It is usually related to a blood vessel which, at a late stage, shows marked thickening of its wall. There is an area of hyaline necrosis in the Aschoff node, and in a large nodule the arrangement of the cells suggests a granulomatous like lesion. Giant cells like those found in rheumatism are occasionally found in periarteritis nodosa (Haining and Kimball[13]), and were present in the lesion of one of our cases (figs. 96-98).

Friedberg and Gross[63] have brought forward more con-

clusive evidence of a relationship between the two conditions. Taking the presence of Aschoff bodies in the myocardium as a criterion for the diagnosis of rheumatic fever in suspicious cases of periarteritis nodosa, they have shown that four out of eight cases which they published gave evidence of rheumatic heart disease. Of five other records of periarteritis nodosa in their department, they showed that two gave clinical evidence of acute rheumatism and had a verrucose endocarditis of the mitral valve in each case, although no Aschoff bodies were found in the myocardium.

We admit that the arterial lesions of rheumatism in certain cases bear a marked resemblance to those typical of periarteritis nodosa. This was noted by Aschoff as far back as 1904[64] and 1906[65] in his discussion of Lupke's paper on periarteritis nodosa among stags. He mentioned that nodular thickenings might be got on small branches of the coronary arteries in rheumatic cases and that these were due to circumscribed periarterial inflammatory changes with medial destruction; and that these nodules bore a marked resemblance to those of periarteritis nodosa.

Carey Coombs[66] in 1911, in a description of the vascular lesions of rheumatism, also drew attention to the nodular periarteritis sometimes got in the smallest branches of the coronary arteries. More recently Pappenheimer and Von Glahn[67] have described the lesions of the smaller arteries in rheumatism. The changes were found in over twenty per cent. of

the cases examined. They were found in the vessels of the kidney, ovary, testes, lung, pancreas, and the perirenal and periadrenal fat. As a rule, only a few isolated vessels were affected. Much of the wall of the vessel in such cases becomes necrosed, infiltrated with fibrinous threads, and at a late healed stage the muscle of the media may disappear so that the internal elastic lamina comes to lie close to the external elastic lamina, giving an appearance very like that of healed periarteritis nodosa. Unlike periarteritis nodosa, however, thrombosis is said not to occur at any stage of the arterial lesion. Around the vessel granulation tissue is formed and in it there are large numbers of leucocytes, many being of the polymorphonuclear type. The vessels attacked are the small arteries, arterioles and capillaries. Von Glahn emphasises that the lumen of the affected vessel remains open, and that a remarkable and characteristic feature is the formation of new endothelial lined channels in the fibrinous mass and that these communicate with the original lumen and contain circulating blood. He emphasises that these are not canalised thrombi.

We cannot but admit that this description of rheumatic arteritis bears a very marked resemblance to that of periarteritis nodosa. It differs however in some very obvious ways. Thrombosis is said to be absent in rheumatic arteritis, but is a very marked feature of periarteritis nodosa. The lesions are very sparsely found in rheumatic arteritis, but are very widespread in the systemic circulation in periarteritis nodosa.

We have examined the organs from many acute rheumatism cases, but have been unsuccessful in finding the gross arterial lesions mentioned by the above workers. The only cases in which we did find such lesions were those two which we shall later describe, and which show a necrotising arteritis in the pulmonary circulation. In these cases, however, the systemic vessels showed no vascular abnormality in spite of careful histological examination. We shall discuss these cases later as we feel that the lesions here have a very special etiology which is probably not connected with the organism of rheumatism.

Also we have not been so fortunate as Friedberg and Gross[63] in finding evidence of rheumatic disease in our cases of periarteritis nodosa. In only one was there an endocarditis which could have been of the rheumatic type.

Taking all the available evidence, we feel that a fair statement of the similarity between the diseases might be summed up thus: periarteritis nodosa and acute rheumatism are two very distinct diseases, each running its own course and having very definite pathological appearances. Certain cases of rheumatic infection show evidence of a necrotising arteritis which bears a very close resemblance to that of periarteritis nodosa. Certain cases of true periarteritis nodosa show evidence of old rheumatic infection, either clinically or pathologically. This evidence suggests that there is some connection between the two diseases but certainly not enough to signify that both diseases are varieties of the one underlying pathological process.

THE RHEUMATIC LUNG.

The rheumatic pneumonias were written about many years ago by Fuller[68] in 1854, Cheadle[69] in 1888, and Garrod[70] in 1890. Garrod very rightly mentioned the transient character of the physical signs but stated that the post-mortem appearances of the lung were the same as in ordinary pneumonia. Pulmonary lesions in rheumatic fever are certainly not uncommon and have in recent years been reported by Thayer[71] in 1925, Swift[72] in 1920, Rabinowitz[73] in 1926, Paul[74] in 1928, and Gouley and Eiman[75] in 1932.

There appears to be great diversity of opinion as to the exact lung lesion got in the acute rheumatic infections. According to Paul[74] the organ shows no specific lesion, and the oedema, congestion and haemorrhagic lobular pneumonia are all due to the failing heart. Naish[76] has described what he looks upon as a specific type of pneumonia. Unlike ordinary pneumonia the lung is tough and non friable, while histologically the essential feature is a marked proliferation of the endothelium of the capillaries in the alveolar wall. These cells grow outwards in all directions so that finally it is difficult to distinguish wall from cavity. Fraser[77] and Gouley and Eiman[75] have described Aschoff nodules in the connective tissue stroma of the affected lung.

Specific vascular lesions are described in the pulmonary artery and its branches, especially the arterioles. These lesions have a focal necrotic character and are somewhat similar to the

arterial lesions occasionally found in other organs in acute rheumatism.

Naish[76] and Gouley and Eiman[75] point out that the acute pulmonary lesion of rheumatic fever is an interstitial inflammation having as its basis the vascular damage and the perivascular infiltrations common to all acute rheumatic lesions. Unlike the acute streptococcal interstitial pneumonias of epidemic influenza or occasionally of measles, rheumatic pneumonia is almost completely non suppurative. In the most acute stages scanty polymorphs are present and found in the areas of acute focal necrosis.

Naked eye the lesion in the lung varies from dark blue to rusty brown in colour and there is said to be a very typical delicate white tracery under the pleura from interstitial exudate.

Naish[76] and Gouley and Eiman[75] also believe that the acute necrotic vascular lesion with perivascular cellular infiltration is followed by an epithelioid cell proliferation and still later by the appearance of the Aschoff nodule. They believe that this last stage is characteristic and establishes the rheumatic origin; and that the significant histological picture is therefore an interstitial perivascular infiltration of large cells, some of which are multinucleated. Important features about the vascular destruction, they believe, are an endothelial hyperplasia with rupture of capillaries, haemorrhage and fibrin liberation. The blood and fibrin pour over into

the alveolar spaces. The typical colour depends upon a blending of the interstitial inflammatory process and the alveolar haemorrhage. If the former be marked, the colour is bluish; if the latter, it is red and more like infarction.

Clinically the lesions of rheumatic pneumonitis usually appear insidiously without much fever or respiratory distress and a lung lesion may not even be suspected. A scanty tenacious sputum is often present and occasionally is blood stained. Dulness is present on percussion and bronchial breathing is usually got. The areas of dulness are found in rather irregular sites and a very characteristic feature is the transient nature of these consolidations which flit from place to place as does the polyarthritis of rheumatism.

The following are two cases of rheumatic pneumonia which we have been fortunate enough to study:

Case 1. Clinical Study. M.G., female, aged 20 years, was admitted to hospital complaining of cough and breathlessness. The patient had suffered from pain in the limbs for many years and two years before had been in hospital suffering from mitral stenosis.

Upon admission marked breathlessness was present and this appeared to be due to a lung lesion rather than the cardiac disease. A week later oedema appeared in the feet and legs and this gradually became worse until the whole of the dependent parts of the body was oedematous. Signs of cardiac dilatation also appeared. Moist crepitant râles were got all over the chest and the patient developed a scanty muco-purulent spit with occasional blood staining. The breathlessness gradually became more urgent and death took place six weeks after admission.

Pathological Study. A post mortem was performed twelve hours after death. The body was that of a rather poorly developed girl. The heart was enlarged, weighing 310 gm. Marked hyper-

trophy of the right auricle and ventricle was present. The mitral valve showed very advanced stenosis, admitting only the tip of the little finger. Associated with this the left auricle showed marked hypertrophy and dilatation and the left ventricle appeared smaller than normal. The aortic cusps showed thickening from old endocarditis and some recent rheumatic vegetations were found on the cusps. A few vegetations were seen on the tricuspid valve. The myocardium showed white streaking from old myocarditis.

Each pleural cavity contained 500 c.c. of clear fluid. The lungs were both heavier and firmer than normal. The surface was on the whole a pale bluish colour but a reddish mottling was present throughout. Incision into the organ disclosed the presence of many small irregular areas which varied in colour from dark bluish to reddish grey. These areas were very numerous, the lung tissue between being pale and well aerated. No pus was seen. A definite infarction the size of a marble was found in the lower part of the left organ. The appearances suggested a broncho-pneumonia of rather unusual type. The other organs showed nothing of note.

Pieces of lung were stained by haemalum and eosin, Gram's stain for organisms and Mann's method for inclusion bodies. The changes in the vessels were first studied and were found to be both acute and chronic in character. The chronic changes consisted of marked endarteritis, in most cases of the concentric type, the media being well seen (fig. 142). Fibrosis was also present around these vessels (fig.143). In other cases the endarteritis was more eccentric and consisted of looser and more nucleated fibrous tissue of fairly recent origin (fig. 144). In other cases two vascular channels were present at the site of the former lumen (fig. 145). The vessels affected were the medium sized and small arteries. Many of the arterioles also showed some thickening of their walls. The acute process consisted of a necrotising arteritis which involved the medium sized and smaller arteries and also, in many cases, the arterioles. In certain vessels the process appeared to affect the media mainly (fig. 146); in others, it affected the tissue immediately around the lumen and spread irregularly outwards (fig. 147). In vessels showing older endarteritis the fibrous tissue immediately around the lumen was that involved (fig. 148). In other sections necrosis appeared less acute, the muscle being damaged at various points and acute endarteritis being present. The marked similarity of these changes to those of true periarteritis nodosa should be noted. The arterioles when involved showed a homogeneous appearance due to their walls being oedematous or necrotic (fig. 150). A perivascular infiltration of polymorphs was obvious in many of these (fig. 151), although others showed little reaction. The arterial process was again found, as in the arteritis of periarteritis nodosa, to be very commonly

related to the beginning of a branch arising from a larger vessel. This was true for both the chronic arterial lesion (fig. 152) and for the acute one (fig. 153), and also for the smaller and medium sized arteries (figs. 154, 155) and the arterioles (fig. 156). The process was very widespread throughout the lung and the appearances suggested that the bronchial arteries, which of course arise from the systemic circulation, were not involved in the process (fig. 157).

The lung tissue itself showed three groups of changes. Interstitial fibrosis was noted and this corresponded to the old arterial lesion. In such areas, which were seen in the paler and bluish parts of the lung, the alveoli were separated by fibrous stroma and their linings were columnar or cubical (figs. 158-161). Their lumina contained desquamated epithelial cells, some of these being of the heart failure type got in the red induration of chronic venous congestion. Other areas showed infiltration by polymorphonuclear cells, the appearances suggesting a broncho-pneumonia, although the localisation around a bronchus was not present. Such areas appeared to be specially associated with the necrotising arteritis and were as a rule quite small in size. Certain of the bronchi contained collections of polymorphs (fig. 162). Still other areas of lung tissue had the appearance of acute haemorrhagic infarction, the number of red cells being less than is usually found in an infarction. These areas were specially related to vessels showing necrotising arteritis with some degree of closure of their lumina (fig. 163). In other parts the alveolar walls showed moderate thickening and in their interiors was serous fluid containing so many red and white corpuscles (fig. 164). In certain of the areas showing the interstitial fibrosis the bronchi had desquamated epithelium present (fig. 165). No Aschoff bodies were seen. By Mann's method of staining no inclusion bodies were found. No specific organisms were got by Gram's staining method.

Sections of ovary, kidney, liver, perinephric fat, pancreas, heart, showed no evidence of necrotising arterial disease.

Case 2. Clinical Study. P.B., age 27 years, typist, was admitted to hospital complaining of breathlessness. The patient had suffered from rheumatic fever at the age of 21 years and again at 25 years. Since the last attack she had become breathless upon exertion and for the year before admission she had been unable to exert herself at all because of the dyspnoea. One week before admission she developed oedema of the legs.

On admission auricular fibrillation was found to be

present and oedema was apparent in both legs and extended up to the abdominal wall and lumbar region. There was slight improvement under treatment. Cough was present during most of her stay in hospital, and with it there was a mucoid spit. on the day of her death, three weeks after admission, she suddenly became breathless and cyanosed, lapsed into unconsciousness and died.

Pathological Study. A post mortem was performed six hours after death. The body was that of a moderately well-nourished young woman. Marked oedema of the legs, abdominal wall and back was present. The heart was markedly enlarged and weighed 450 gm. The mitral valve showed marked stenosis and admitted only the little finger, the cusps being thick and fixed. The right ventricle showed marked hypertrophy and dilatation. The right auricle showed hypertrophy and dilatation. The left auricle showed moderate dilatation. The left ventricle showed hypertrophy and dilatation. The aortic valve was competent and showed an incomplete row of small firm rheumatic vegetations. The tricuspid valve showed a few vegetations. The myocardium showed a few scattered fibrotic areas.

Both lungs were firmer than normal and had the reddish appearance of chronic venous congestion. Some pale and red mottling was observed scattered throughout the organ. A small firm area like old partial infarction was found on the lower edge of the right lung. The pulmonary arteries were generally thickened and showed slight atheroma. The other organs showed nothing of note.

Sections of lung were stained by haemalum and eosin, Mann's method and by Gram's stain. The lesions found were essentially the same as in the last case, but less diffuse. Endarteritis of the medium sized and smaller arteries was noted and was frequently more eccentric than in the last case (figs. 166-167). In the smaller arteries, concentric endarteritis of more recent origin was frequently noted (fig. 168), and in some of these, one or two new channels could be made out in the fibrous tissue which occluded most of the lumen of the original vessel (fig. 169). The necrotic process was found mainly in the smallest arteries and arterioles (figs. 170-173). Again in this case the necrotic process was at times found to involve a branch as it arose from its parent vessel (fig. 174). The marked interstitial fibrosis seen in the last case was not prominent in this one although the alveolar wall showed slight thickening in many places (fig. 175). No specific organisms or inclusion bodies were got by Gram's or Mann's methods of staining.

Discussion.

From our study of these two cases we feel that our outlook on the pathology of rheumatic pneumonitis has become much simplified and, while we agree with the earlier workers as to the naked-eye appearances, we differ somewhat in the histology and also, as we shall later show, in our view as to the etiology of this very characteristic lesion. The vessels affected appeared to be the medium sized and especially the smaller arteries and the arterioles. Two processes were visible. There was a chronic one marked by endarteritis and an acute one - a necrotising arteritis - marked by death of the wall of the vessel with perivascular polymorphonuclear infiltration. In the case of the chronic lesion some of the vessels appeared to have become closed completely and later recanalised, there being small new channels in the fibrous tissue filling the lumen. In the case of the acute lesion, the appearances were in most cases exactly the same as those of the necrotising arteritis of periarteritis nodosa, it being impossible to distinguish the conditions from an examination of the affected vessels alone (figs. 176-177). Thrombosis did not appear so frequently in the rheumatic arteritis as in true periarteritis nodosa.

The lung appearances were secondary to those of the vessels. Slow closure of pulmonary radicals caused a replacement fibrosis of the area of lung supplied and this was seen by a decrease in the number of alveoli, those remaining

developing a high cubical epithelium and being separated by fibrous stroma. Where the acute lesion was present in a vessel, an overflowing of the leucocytes associated with it took place into the surrounding lung tissue, giving the localised broncho-pneumonic like areas. Most of these leucocytes were polymorphs and they were even seen occasionally in the related bronchi. Where thrombosis was superadded to the necrosis or where the lumen was narrowed, infarction of the corresponding area of lung ensued, giving haemorrhage into the alveoli. No Aschoff nodules were seen in either of our cases.

An important feature, and one which was got also in true periarteritis nodosa, was the presence of the necrotic lesion in many cases in the vessel at the point where it left its parent trunk.

It should be noted that both of these cases had a very marked degree of mitral stenosis with back pressure on the pulmonary circulation which might explain some of the chronic arteriole thickenings present. We shall refer to this later when we are discussing the etiology of periarteritis nodosa, and the relation to this lung condition.

Thus, summarising, we might also say that in our experience the so-called rheumatic lung has the appearances of "periarteritis nodosa" localised to the pulmonary circulation; and the lung appearances are secondary to these arterial changes.

RELATIONSHIP OF PERIARTERITIS NODOSA AND NEPHRITIS.

In studying this question there are four important features for consideration:

(1) In certain cases of hyperacute nephritis or nephritis acris, changes in the vessels of the kidney almost identical with those of periarteritis nodosa are found. The following is a typical case:

J.M., a boy aged 8 years, died after five weeks of obscure illness which became acute with abdominal pain and rigidity the day before death. At the post mortem there were marked signs of rickets present. There was an acute peritonitis due to streptococci. No local origin for this was found. The kidney showed marked congestion with prominence of the glomeruli, and microscopically the appearances were those of nephritis acris with necrosis of arteries, marked polymorphonuclear infiltration and death of areas of renal tissue (fig. 178). Necrosis of arterioles where they branched from the parent vessel was apparent in sections (fig. 179) and also of branches as they left their parent trunk (fig. 180). The smaller arteries also showed necrosis with marked leucocytic reaction.
Those appearances are almost identical with those seen in certain cases of periarteritis nodosa as they affect the kidney except that the smaller vessels are affected as a rule in nephritis acris. Nevertheless if solitary fields of such a kidney be examined, it is frequently very difficult if not impossible to differentiate the two conditions. Otherwise they are of course very easily distinguished, for in nephritis acris the rest of the kidney substance shows evidence of the hyperacute process, the glomeruli, tubules, and interstitial tissue all showing marked acute inflammatory changes with necrosis; whereas in periarteritis nodosa the vessels show the damage and the rest of the kidney tissue is relatively much less affected. Moreover periarteritis nodosa is a generalised disease, affecting more or less all the systemic arteries.

(2) In certain malignant hypertension cases a varying number of vessels frequently show necrotising arteritis. The following cases illustrate this:

G.S., male aged 52 years, was admitted with marked breathlessness which had been slowly getting worse for the past two years. His heart showed marked hypertrophy and the blood pressure was 220/120. Death took place from uraemia. At the post mortem the kidneys showed the changes of malignant hypertension, having the appearances of the genuine Schrumpfniere of the German workers. Necrosis of many of the arterioles (fig. 181) and of some of the smaller arteries (fig. 182) was seen. The very marked resemblance of the lesion of fig. 182 to that of genuine periarteritis nodosa of the smallest arteries should be noted.

P.C., aged 43 years, a surfaceman, was admitted with swelling of the face and failing vision. The blood pressure was 210/120 and the blood urea 343 mgm. per cent. While in hospital the patient's blood pressure slowly fell but his general condition deteriorated and death took place a week after admission from uraemia. Post mortem the kidneys were small and showed an uneven granularity of the surface. Histologically the appearances were those of chronic vascular nephritis. A necrotising arteritis (fig. 183) and arteriolitis (fig. 184) were seen here and there and thrombosis had taken place in certain of the damaged arterioles.

It will be noted that these individual lesions are the same as those which are found in certain cases of periarteritis nodosa of the kidney although they are much fewer in number in malignant hypertension and are, of course, accompanied by the very typical arterial and arteriolar lesions of this condition, so that no real confusion could exist between the two conditions. Fahr suggested that the necrotic arterial changes are got in the most severe types of malignant hypertension. It is interest-

ing to note that cases of true generalised periarteritis nodosa are sometimes got in which the kidney also shows the lesion of malignant hypertension such as interstitial fibrosis, hyperplastic changes in the smaller arteries and hyaline thickening of the afferent glomerular arterioles. This was so in Kountz's[33] case. This suggests that there may be some association between the two conditions so that true periarteritis nodosa may at times follow malignant hypertension, although it has been suggested by others that malignant hypertension may follow periarteritis nodosa of the kidney.

(3) The changes of acute nephritis are got during the acute stage of periarteritis nodosa and those of chronic interstitial nephritis or so-called vascular nephritis at the healing of chronic stages of the condition. This has been well illustrated in our series of cases (Nos. 1, 2, 3 and 5). These appearances suggest that a certain degree of vascular narrowing may be at the root of even the acute stage of nephritis, vascular narrowing caused perhaps by spasm.

(4) The kidney is the organ by far the most commonly involved in periarteritis nodosa - in 80 per cent. of cases according to Arkin[12].

All these observations suggest that there is at least some relationship between periarteritis nodosa and nephritis. We shall refer to this later and suggest a possible explanation when we are discussing the mechanical view of the etiology of periarteritis nodosa.

IS THERE A LOCALISED FORM OF PERIARTERITIS NODOSA?

We have seen necrotising arteritis in a wide variety of conditions including anthrax (fig. 185), ulceration of the colon in uraemia (fig. 186), and locally in streptococcal infection (fig. 187). In all these the arteritis was obviously secondary to the primary condition. Is there however a localised primary form of necrotising arteritis which may not prove so fatal as the usual diffuse periarteritis nodosa? We have seen one interesting case which suggests that the answer may be 'yes'.

Mrs C., aged 30 years, was admitted to the surgical wards complaining of abdominal pain which had come on during the previous day and become gradually worse. On examination there was some diffuse swelling of the abdomen. Tenderness was found to be most marked in the right iliac fossa but to be present to a lesser degree elsewhere in the abdomen. Her temperature was 100.2°F. Acute appendicitis was diagnosed and appendicectomy performed. Following operation she continued to have some abdominal discomfort and a slight remitting temperature which passed off in the course of a week or so. She was discharged feeling well after three weeks.
The appendix histologically showed a necrotising arteritis with marked leucocytic infiltration around some of the smaller arteries, the leucocytes mostly belonging to the mononuclear class (fig. 188). No other evidence of inflammatory disturbance apart from that associated with the vascular damage was seen in the organ. The patient has been well for two years since this time.

The possible explanation of this case appears to be that the patient had a slight attack of periarteritis nodosa affecting only the vessels of the gastro-intestinal tract, and the disease manifested itself histologically in the excised appendix. If this be so, it suggests that the lesser degrees of the condition may pass unnoticed and heal spontaneously.

CAUSATION OF PERIARTERITIS NODOSA.

It is not surprising that a disease like periarteritis nodosa, which may have so many manifestations and which is so unlike other diseases, should raise a host of speculations as to its origin. Kussmaul and Maier[1] and many of the earlier workers thought that the disease had a syphilitic origin. The disease was however described in certain of the lower animals, e.g. stags[78], and it was then believed that it was a specific infectious disease of the arterial system which was caused possibly by a filter passing virus. Others cultured streptococcus from the lesion and suggested that it was caused by this organism. Ferrari[34] believed that the cause was some unknown toxin. He would not admit that it acted on the vessel wall directly, but on the vascular nerve centres, and this view was backed by those who could find no vascular lesion in the nerves concerned in the polyneuritic type of the disease. Allergy was then thought of as a possibility. Grüber[30] says "We regard periarteritis nodosa as the expression of a constant reactive process of the arterial system in the manner of a hyperergic phenomenon during the course of very different infectious-toxic diseases." To-day, pathological opinion seems to favour the view that it is a specific infectious disease, and the work of Harris and Friedrichs[56], who claim to have transmitted the disease to lower animals, suggests that this view may be the correct one. Sir Robert

Muir in his textbook[15] states that it appears certain that the condition is not syphilitic and that no characteristic organisms have been found in the lesions. He suggests that the picture is that of an unknown infective agent spreading along the perivascular lymphatics and producing the characteristic changes. Boyd[16] states that the cause is unknown and adds that syphilis seems to be out of the question but that the streptococcus has been found in a number of cases.

We shall discuss the main suggested causes in some detail:

(1) Syphilis. Although discredited by most workers nowadays, syphilis was thought by the earlier investigators to be the cause of the condition. Amongst those who held this view were Kussmaul and Maier[1], Chvostek and Weichselbaum[37], Graf[79], Müller,[38] and Versé[45]. The vascular lesions in both tuberculosis and syphilis bear some resemblance to periarteritis nodosa. Versé showed the similarity between syphilitic arteritis and periarteritis nodosa, and pointed out that in both conditions there were (a) aneurism formation, (b) necrosis involving the arterial wall, (c) giant cell formation. He suggested therefore that periarteritis nodosa was simply a very virulent or acute form of syphilitic arteritis and that the lesion started in the adventitia and outer media as an inflammatory process with fibrinous exudate and spread from here inwards to destroy the muscle of the media. The original case of Kussmaul and Maier was thought

by the authors to be a rare form of syphilis, and Virchow, after examining the material, agreed with them. Since that time however there has been a slow but definite change of opinion for, although most of the recorded cases have been thoroughly investigated for evidence of a luetic origin, the presence of syphilis has only very occasionally been proved and even in such cases has been taken as a concomitant rather than a causative factor. In most of the cases the Wassermann reaction has been negative. Moreover, in spite of Versé's original suggested resemblance between the two conditions, the histological pictures really differ quite widely. Admittedly in both syphilitic arteritis and periarteritis nodosa there is an endarteritis and a periarteritis. In both there may be necrosis of the vessel wall. In syphilitic arteritis however the periarteritis and endarteritis are important and primary features and are constantly present by themselves, whereas in periarteritis nodosa, as has been shown by our serial sections, the necrosis of the media is the all important feature and the endarteritis and periarteritis are secondary to this and fade off as the sections of the diseased vessel go further and further from the point of necrosis. Necrosis of the vessel wall in syphilis when it occurs, as it does only rather infrequently, is associated with gummatous formation in the adjacent tissue and is in fact really part of a general necrosis of the tissue at one side of the vessel. In the acute necrotising stage of periarteritis nodosa, there is an

abundant infiltration by polymorphs, although in the later stages the cellular reaction becomes of the mononuclear and plasma cell type. In syphilitic endarteritis there is the formation of new elastic fibrils which is entirely unlike the typical fracturing of the internal elastic lamina got in periarteritis nodosa. Giant cells, although not uncommon in syphilitic arteritis, are very rare in periarteritis nodosa; and in one of our cases where they were seen in the arterial lesion, they were entirely unlike those of syphilis and resembled rather the Dorothy Reed cell of lymphadenoma or that of the Aschoff node. Spirochaetes have never been demonstrated in periarteritis nodosa. The occurrence of the affection in certain of the lower animals such as the calf, swine, dog and deer, in epidemic form (78)(12), is against a venereal origin.

The distribution of the lesions in periarteritis nodosa differs from that of syphilis. In the latter disease the aorta and cerebral vessels are said to be most commonly involved although occasionally vessels elsewhere are affected; but if one scrutinises the literature carefully, one must agree that there appears to be a fairly diffuse syphilitic affection of the vessels of the body resembling true periarteritis nodosa quite closely. Before the publication of Carnegie Dickson's paper many such cases appear actually to have been recorded as cases of true periarteritis nodosa. The condition is said to start as a proliferation of the intima followed by an increase of tissue around the vessels and, as in Baumgarten's (80)

case: "Later, when the proliferation reaches a certain degree, the tissue undergoes caseation as it would in any other syphilitic proliferation." A case of so-called diffuse syphilitic arteritis has recently been reported by Derrick and Hess (81). The lesions of their case resemble very markedly those of periarteritis nodosa. They consider that the condition they describe is of syphilitic origin because this disease had been contracted some months before. The histology of the vascular lesions appears to be identical with that of the healed stage of periarteritis nodosa, there being cicatrisation of the media at parts, which is very characteristic of true periarteritis nodosa. Two other features strongly suggesting true periarteritis nodosa to me are firstly, the localisation of the lesion to the systemic circulation with non involvement of the pulmonary circulation, and secondly, non involvement of veins, even those adjacent to the affected arteries. I am therefore not satisfied that their vascular lesion is of syphilitic origin. Although over sixty blocks were examined from various parts of the body, spirochaetes were demonstrated in one section only and then in an area of necrosis and inflammation in the submucosa of the duodenum. I feel therefore that the lesion is a true periarteritis nodosa which, from the histology, has been present for some months. It is to be noted in this case that the blood pressure at the time of the illness was 230 mm. whereas it had been 110 mm. some months before. I shall later suggest that a certain

rise of blood pressure is possibly a very important feature in the causation of periarteritis nodosa. In this present case therefore I shall go no further than suggest that this fairly sudden rise of blood pressure was quite possibly the cause of the periarteritis nodosa, and that the raised pressure may have been caused by the syphilitic virus or, perhaps more likely, by hypersensitivity to the drugs used in treating the disease. In connection with this the authors themselves admit that both arsphenamine and mercury are toxic to the walls of blood vessels.(82)

(2) Periarteritis Nodosa as a Specific Disease. According to this view the condition is a specific infection caused by a bacterium or by a virus with a peculiar affinity for the vascular system. Culture or inoculation of material from cases of periarteritis nodosa have unfortunately only rarely been performed. The main results of these experiments may be summarised:

(a) Babes and Mironescu(83) described diplococci and streptococci in the arterial lesions, but they report also a case of syphilitic arteritis where a diplococcus was also found. It is doubtful too whether periarteritis nodosa was actually present in their specimens.

(b) Longcope(39) found "a few groups of cocci in chains" in specially stained preparations of the kidney tissue distinct from the nodules; these were absent in the other organs uninvolved by the disease.

In the next set of cases, blood cultures were made during life and cultures at the autopsy from the heart, pericardium, peritoneum, gall-bladder and from the nodules themselves.

(c) Beitzke's (84) blood cultures during life were negative.

(d) Oberndorfer (85) cultured staphylococcus aureus from the liver and spleen.

(e) Datnowski (28) - a streptococcus was cultured from the heart blood at autopsy, but as a peritonitis was present, this should probably be discarded as being of little value.

(f) Veszprémi (86) - cultures were sterile.

(g) Jonas (87) cultured streptococcus from the kidney and the influenza bacillus from the adrenal.

(h) Lamb's (8) first case - a streptococcus was got from the heart blood along with a colon bacillus. A streptococcus was got from the peritoneal exudate. These bacteriological findings are again unreliable, because there was also present a vegetative endocarditis and a terminal peritonitis.

(i) Lamb's second case - streptococcus was got from a cardiac nodule, staphylococcus aureus from the peritoneum, and a colon bacillus from the pericardial fluid. In this case Lamb washed one of the large aneurismal nodules in three changes of sterile saline and then divided it into two by Rosenow's sterile method. Guinea pigs and rabbits were inoculated with the material, but all kept perfectly well and when they were finally killed, no lesions were seen.

(j) Beattie and Douglas (88) - a streptococcus was got from the renal haemorrhage.

(k) Wever and Perry[49] - culture of a smear from a mesenteric nodule taken post mortem showed a growth of staphylococcus albus. The autopsy was done eleven hours after death and it is thus very probable that the organism was a contaminant from the adjacent bowel.

(l) Manges and Baehr[17] - aerobic and anaerobic cultures made from blood during life and nodules excised at operation were negative.

(m) Baehr[89] - toxins were negative.

(n) Klotz[9] - two cases were studied, and he obtained staphylococcus aureus, bacillus proteus, streptococcus and a diphtheroid bacillus from the heart blood, bile, liver and subcutaneous nodules. He injected streptococci into the periarterial tissues or lymph spaces and produced lesions which, he states specifically, were not those of periarteritis nodosa.

(o) Ophüls[11] - blood cultures during life at one attempt showed the presence of streptococcus, but were negative at the second attempt.

(p) Kountz[33] - numerous blood cultures were negative, both under aerobic and anaerobic conditions.

(q) Bennet and Levine's[41] second case - blood cultures were negative. No organisms were recovered on culture from the cerebrospinal fluid which showed a marked increase of cells, mostly polymorphs. At the autopsy blood cultures were made from the heart's blood, spleen and meninges, using blood agar, hydrocele agar and brain broth as culture media. All the original cultures and the subcultures were overgrown with colon bacilli, but no other organisms were found. Sections of organs were stained by Gram's, Giemsa's, Goodpasteur's and Levaditi's method, but no organisms found.

(r) Arkin's[12] first case - blood cultures at the height of the fever were negative.

(s) Von Hahn (90) - the blood from a proven case was injected intraperitoneally into two guinea pigs. The animals died after eight weeks without showing any evidence of the disease. From these animals (i) the heart's blood was injected into other guinea pigs, and (ii) an organ emulsion prepared from them injected into still other guinea pigs. This second series of animals showed microscopical changes in the smaller arteries of organs and a disseminated inflammatory lesion of the adventitia and media of different arteries. Von Haun therefore concluded that periarteritis nodosa was a specific infectious disease due to an unknown factor in the circulating blood which was capable of causing inflammatory lesions in the blood vessels of guinea pigs. From the histology, these lesions do not appear to be very convincing, and are certainly not those of periarteritis nodosa. Von Haun himself doubted their importance and concluded that the guinea pig was an unsuitable animal for the experiment.

(t) Carling and Hicks (91) repeated the experiments of Von Haun and even allowed some of the guinea pigs to live longer than two months. No lesions were found either naked eye or microscopically.

(u) Harris and Friedrichs' (56) experiments have been the most promising of all. The material was derived at the post mortem on a male aged 32 who had been ill for five weeks with periarteritis nodosa. Cultures were taken from kidney lesions and put into plain broth, glycerol potato broth, dextrose agar and Loeffler's blood serum. No growth was got. Pieces of nodule were ground in sterile saline and the emulsion injected into the ear veins of two rabbits. When these animals died, further injections into other rabbits with filtered and unfiltered tissue emulsions were performed. These animals lived for from two to six months. The most typical lesions were seen in the animal which had been inoculated with the filtrate which had been passed through a Berkefeld N filter. The lesions found in the vessels consisted of infiltrations of the media and adventitia with different kinds of cells, such as neutrophils,

lymphocytes and plasma cells. With this, some degree of degeneration and necrosis of the media occurred with dilatation of the vessel lumen and thrombosis. The veins were occasionally affected. This work of Harris and Friedrichs is very suggestive, but has been very adversely criticised by many workers and held to be by no means conclusive. The lesion was seen most typically in the pulmonary arteries, which is unlike that in periarteritis nodosa. Moreover veins are never involved in periarteritis nodosa. Lupke and Jaeger have described a spontaneous disease in stags identical with periarteritis nodosa in man and the possibility of this lesion in Harris and Friedrichs' experiments must be borne in mind. Their work is very promising, however, and should be repeated by future workers.

It will be recognised from the above summary of the bacteriological findings in the cases recorded that the results are rather confusing and indefinite. The presence of organisms is by no means a common feature of the disease, and when found, contamination is frequently a very possible factor. The only organism which seems to show itself fairly consistently is the streptococcus; and when we correlate this with the frequency with which a sore throat or quinsy ushers in many of our cases, we cannot but feel that the streptococcus may play some part in the causation of the condition.

The work of Harris and Friedrichs, as described above, strongly suggests that a filter passing virus which can pass through the Berkefeld N filter plays a part in the etiology of the disease. Leddingham[92] has lately shown that in certain of the virus diseases, notably vaccinia and smallpox, the lesion is essentially an inflammatory one of the vascular tissue of

the dermis, causing an oedema which produces the characteristic vesicle. In experimental typhus fever in the guinea pig, Olitsky[93] described a periarteriolitis nodosa, the causative agent of which is said to be a filterable virus. All this work suggests that a filter passing virus may very likely be the cause of periarteritis and periarteriolitis.

We have already suggested the likelihood of a streptococcus being important in the causation of periarteritis nodosa and the work os Friedrichs and Harris and that of Leddingham and Olitsky also appears to indict a filter passing virus. Our thoughts then at once turn to the work of Shope[94] on swine influenza. He showed that the clinical syndrome of swine influenza could be produced experimentally by a true filterable virus acting in conjunction with an organism. This organism, which was regularly got from the respiratory tracts of swine inoculated from material from clinical cases, was unable in pure culture to reproduce the disease. The filterable virus, which was got by trituration of diseased lungs and lymph nodes, could not by itself produce the typical clinical swine influenza, but nevertheless produced a relatively mild disease called the filtrate disease and characterised by transient fever, slight cough and some leucopenia. This condition was also contagious. The combination of this comparatively innocent filterable virus with the apparently innocuous artificial cultures of the bacterium was capable of producing

the severe lesions of typical swine influenza. Thus, apparently, the presence of a virus may at times confer upon a bacterium powers of invasion not hitherto possessed.

If we carry our analogy to periarteritis nodosa, we may suggest it possible that the disease is caused by the action of both the streptococcus and a virus, the streptococcus gaining entrance by the throat. We also recall those other two diseases which bear some obscure relationship to periarteritis nodosa, namely nephritis and the rheumatic infections. In both of these a sore throat is frequently found and the streptococcus is indicted again and again. The exact part of this organism in the causation of either acute nephritis or acute rheumatism cannot be satisfactorily proved so that most workers agree that it may play some part in the etiology of these conditions, but not the whole part. Carrying the analogy still further, we might suggest that the similarity between periarteritis nodosa, acute nephritis and acute rheumatism was due to the fact that a streptococcus played a part in the causation of all of them. Their dissimilarity and their individualities as separate diseases with a different distribution may be due to the presence, along with the streptococcus, of a virus of specific type for each of the three diseases.

(3) The Condition is a Non Specific Condition. According to this view, periarteritis nodosa is no disease sui generis, but is a non specific form of infective or post-infective mesarteritis. This was the opinion of Spiro[10] and of Grüber[30] who stated that "we regard periarteritis nodosa as the expression of a constant characteristic reactive process of the arterial system in the manner of a hyperergic phenomenon during the course of very different infectious-toxic diseases." It has been shown that small vessels may show a necrotising arteritis in widely different conditions, such as the cerebral vessels in influenza and the skin capillaries in epidemic meningitis.[95] The similarity of the pathological findings to those of Rocky Mountain spotted fever (Wolbach[96]) and typhus fever (Wolbach, Todd and Palfrey[97]) is used as an additional argument as to its non specificity. We do not deny that vascular lesions of a necrotic nature may be got in these affections, but they are very irregular and erratic, both in their distribution and their appearance, unlike the very definite histological lesion and distribution of true periarteritis nodosa.

Klotz[9], who also regards the disease as non specific in character, likens the condition to the spread of organisms in the perivascular lymphatics in other pyogenic infections. "It is not uncommon to observe the advance of infection and inflammation in tissues surrounding the small arteries of the mesentery of the appendix. The thromboses occurring in the vessels of these outlying tissues may possibly have their origin

in the damage induced through infections of the arterial coat arising from the perivascular involvement. Periarteritis nodosa differs from the common periarterial inflammations only in the peculiar manner of the damage in the arterial wall. The distribution and progress of the disease along particular branches of arteries are not unique for this lesion which has received a special name." We have frequently observed the perivascular cuffing at the periphery of an inflammatory lesion to which Klotz refers (fig.189). Klotz however really admits that it is a very specific lesion when he states that the lesion of periarteritis nodosa "differs from the common periarterial inflammations only in the peculiar manner of the damage in the arterial wall." It is this "only" which makes the condition so specific, for in none of the vessels at the periphery of an inflammatory process have I seen appearances which in any way approached those of periarteritis nodosa. Moreover, Klotz speaks of these appearances at the margin of an inflammatory process. Periarteritis nodosa occurs quite unassociated with any neighbouring inflammatory process. It is unnecessary to discuss this view any further for any person who has seen the disease knows from the appearances, which are so typical, that it is a very definite specific entity.

(4) Mechanical Cause. This view has never been a popular one and although held by certain workers in the past, appears to have fallen sadly into disrepute. There are certain facts which suggest that the disease has not an inflammatory origin: (a) The lesions never go on to suppuration: (b) Organisms are not found as a rule in the necrotic lesions: (c) The disease has not been satisfactorily reproduced in animals. It might be suggested by some that the presence of a temperature and of a polymorphonuclear reaction around the arterial lesions and in the blood was evidence of an inflammatory origin. This is not so, for the presence of inflammatory cells around any necrotic tissue is well known as is also the presence of a temperature.

Eppinger[3] held that the disease was one of the media primarily and was due to congenital weakness and spontaneous rupture of the media. Meyer[4] supported this view as did also Schroetter[14] in Nethnagel's Handbuch. Ferrari[34] also seemed to be looking for such an origin and suggested that the lesion was produced by the central or local action of a toxic substance such as alcohol causing a paralysis of the smooth muscle fibres. Wever and Perry[49] more recently also suggested a mechanical origin for the condition.

In studying our own cases and reviewing those in the literature we have been struck by certain features:
(a) Whereas the vessels throughout the systemic circulation are widely affected, those of the lungs are but very rarely involved although they have been examined in a great many of

the cases reported. In one of our cases (Case 5) we found side by side, uninvolved pulmonary arteries and involved bronchial arteries which come of course from the systemic circulation. Why should the pulmonary circulation be so usually uninvolved while the systemic one shows widespread lesions? This is rather difficult to explain on an infective basis. Kountz[33] suggested in his case that the localisation was possible because of a patent foramen ovale but even in the presence of this it is difficult to believe that the infected agent could escape the pulmonary circulation. It is also remarkable that in our rheumatic lung cases the pulmonary circulation was widely involved while the systemic one appeared untouched. Do these two circulations, systemic and pulmonic, differ markedly in any special respect? They are quite independent, or almost so, as regards the pressures in them so that a marked rise of pressure may take place in the systemic circulation without affecting the pulmonic one very much and vice versa.

(b) The process appears to be primarily a necrosis of the media. The infective view of periarteritis nodosa claims that the infective agent spreads along the perivascular lymphatics working further inwards towards the media until it finally reaches it and causes necrosis. This suggests that the most marked polymorphonuclear reaction should lie at the oldest part of the infection, i.e. at a distance from the necrotic media which is, of course, therefore the most recent part of the infective process; and it suggests, moreover, that

the process should cease here as it has now run its course. This is not borne out by serial sections which show that the polymorph reaction is most abundant actually at the site of the necrosis and fades off not in one but in both directions. We have, moreover, demonstrated that necrosis of the vessel wall occurs in channels which are too small to have either a vaso vasorum or perivascular lymphatic channels; and in these the necrosis is frequently found with little or no leucocytic response.

Fishberg (19) studied a case which died after a few days' illness before the polymorphonuclear reaction had time to occur in the necrotic vessels. His opinion was that the lesion was primarily one of the media.

If we refuse to accept the spread of infection from the perivascular area, the natural answer might be that the infective agent comes from the interior of the vessel. If an infective agent were circulating in the blood, it is rather difficult to understand why it would fasten on to the medium sized and smaller arteries and as a rule leave the smallest ones free. If it were of embolic nature, we should expect the arterioles to be the most frequently affected as the emboli would most likely stick here. If it were a virus with a preference for the muscle of the arterial wall, one would expect the veins, which have also a muscular wall, to be affected as well, even if only to a lesser degree; for such an agent is almost certain to be able to pass through into the venous circulation. A characteristic

of the lesion moreover is that the intima is intact and in fact is frequently seen separated as a distinct circle at the site of necrosis by the polymorphs, causing an acute endarteritis These facts suggest that the lesion is a primary non infective one, affecting usually the media of the arterial walls.

(c) The condition or force necessary for the damage appears to come from the interior of the vessel. This is suggested by our studies of cases which show a recrudescence of the disease in vessels which have older and partly healed lesions. In these the media has been partly destroyed and replaced by young fibrous tissue, forming a well-marked endarteritis by delicate tissue. Where a recrudescence of the acute process has taken place, instead of the media, which now lies at some distance from the lumen, being involved, the necrosis involves the fibrous tissue immediately around the lumen. In such cases, moreover, the leucocytic reaction is much less than is got where the process involves a normal vessel, and this may be because the lymphatic channels have been largely obliterated by the older healing lesion. It should also be noted that where the medium sized arteries have thick hyaline fibrous walls due to old disease, the necrotic process falls back on to a smaller series of vessels, the smallest arteries and arterioles (Case 3).

(d) Site of the lesion - the smaller arteries are those usually involved. Where the larger ones are affected, it is usually at one side only and in such cases serial sections show that

the process is actually involving a branch coming from the larger vessels. This is a very important feature with regard to the etiology. We have shown it to be present in both the acute necrotic lesions and also in the healed ones, and moreover found that it is commonly present in the rheumatic lung and nephritis acris. The site of the lesion recalls to our mind the work of Forbus (98) who showed that many congenital aneurisms of the circle of Willis occurred at the points of branching from the main vessels and demonstrated in many cases a congenital defect in the elastica and muscularis at this point.

Can we suggest a theory of origin of the process which will satisfy these various facts? It is our belief that periarteritis nodosa is due to a comparatively sudden rise of the circulatory pressure in a system which is unable to withstand this strain. Where the pressure is raised slowly, as in the nephrosclerosses and hypertensions, the medium sized and smaller arteries show an increase of the elastic and muscular elements of their walls, which become greatly thickened in an attempt to withstand the greatly increased strain being thrown upon them. What will happen if the rise of pressure be too quick for these reactive processes to take place? The circulatory system of arteries, arterioles and capillaries will, if the heart stands up to the rise, rupture at any points of weakness. Where are these points likely to lie? There are two important structural features in the circulatory system which are bound

to modify the effect of any increased pressure within it. The first is the tensile strength of the vessel wall. This is of course greatest in the largest vessels and becomes less as we go down the scale to the smaller ones until we reach the thin walled arterioles and capillaries. The second is the pressure within the vessels. This depends largely upon the area of the arterial bed and because this becomes greater as the vessels become smaller in size, so does the pressure within them thus become less. If we take these two features together, at the upper end of the scale we have a small arterial bed and therefore a high pressure, which however is easily withstood by the great strength of the vessel wall. At the other end of the scale we have vessels with very weak walls which are unable to withstand any marked increase of pressure within them; but to more than compensate for this the circulatory bed is extremely wide so that any increase of pressure within them will be more than compensated for by the greater space. Lying in an intermediate position between these two extremes we have the medium sized and smaller arteries in which the arterial bed is only moderately large and in which the tensile strength of the wall is only moderately good, and thus it may be that any sudden increase of pressure within the arterial system will fall most heavily on these and damage them. The reason for the small arteries being commonly involved at the site of origin from the parent trunk and the process fading off a short distance along the branch is now obvious if it be remembered that the

pressure in a branch is greatest at its beginning and fades off in an outward direction. We can also understand why the lesions of periarteritis nodosa should be confined to the systemic circulation for the rise of pressure may be present here and leave the pulmonary one unaffected. The bronchial arteries however will show the lesions because they arise from the systemic circulation. We can also understand why the necrotising arteritis in the rheumatic lung cases should be confined so extensively to the pulmonary circulation and leave the systemic one unaffected. We need only add that the necessary sudden rise of pressure in these cases may have been set up by a relative failure of the left auricle which was working against a very marked degree of mitral stenosis in both cases. The effect of this would be to cause a sudden damming up of blood in the pulmonary circulation by a hypertrophied right ventricle and this might quite readily increase the intrapulmonary pressure to a degree possible of rupturing the arterial walls. This view also explains why, in cases where there is an endarteritis due to an older lesion, the fibrous tissue of the proliferating intima suffers and the damaged media, which is now at some distance from the lumen, is untouched. We can also understand why, in one of our cases (Case 3), the smallest arteries and arterioles were principally affected. This may have been because the medium sized and smaller arteries had their walls too thickened and rigid from old disease to be possibly affected by the increased intravascular tension which therefore acted

upon the next class of vessels which, although they had a wider vascular bed, were now however relatively weaker.

We may add a suggested explanation of the necrotic vascular lesion which we have noted in the kidneys in malignant hypertension. Volhard[99] has suggested that spasm of the branches of the renal artery may play a part in the pathology of the condition, the condition having its counterpart in the spasm of the bronchioles, which is said to occur in asthma. If this were so, contraction of a smaller artery would cause a sudden rise of pressure in the related arterioles and if this were at all marked, it would cause rupture and necrosis of these.

Is there any closer relationship between periarteritis nodosa and malignant hypertension if we accept this pressure view of the etiology? It has been suggested by Kiemmerstiel and Wilson[100] that benign and malignant hypertension are not two different diseases, but really stages in the one process, and that border-line cases do occur. The benign type occurs in the older person, while the malignant type is found in the younger individual; and in certain cases of the latter type they show that Fahr has pointed out that the vascular necrosis with reactive exudative and proliferative changes resembled in its most marked form periarteritis nodosa. We have also shown this to be the case. If we now remember that whereas malignant hypertension occurs between 33 and 48 years, reaching its peak about 42 years, periarteritis nodosa

occurs between 20 and 40 years, reaching its peak about 30 years, we are set wondering if all these vascular diseases are not phases of the one underlying process with a rise in pressure as its main symptom, the young subjects being more reactive and the pressure therefore rising more quickly than in the older ones.

We also suggested in one of our cases (Case 1) that partial closure of the renal arteries might be factor in the causation of the glomerular changes of acute nephritis. If this closure be due to spasm, one can understand how very excessive spasm might cause the necrotising arteritis and arteriolitis of nephritis acris.

Is there any evidence from the literature that high blood pressure is a feature in periarteritis nodosa? In reviewing the cases, and in studying our own ones, we have been very much struck by the number of cases in which the blood pressure is grossly higher than normal. There is also evidence that the blood pressure in these cases was rather irregular, being high at one stage and apparently normal, or almost so, at others, as if the patient had been having paroxysmal rises. Unfortunately, a large number of cases of periarteritis nodosa reported in the literature give insufficient information concerning blood pressure or heart weight. In spite of this, Kiemmerstiel and Wilson[100] in their analysis of periarteritis nodosa found evidence of hypertension in 47 cases from the literature, and of these 18 showed a systolic pressure at or greater than 200

mm. of mercury, thus, to say the least of it, we can state that at least an appreciable number of periarteritis nodosa cases have hypertension.

As to the possible causes of the hypertension, we can only speculate. In a few of the cases where the patient's habits are mentioned, there is a suggestion of excessive tobacco smoking. This was noted in one of our cases and is seen in Teacher and Jack's[48] case where the blood pressure was 230 mm. and the patient smoked very excessively of cigarettes. This suggestion is rather interesting if we consider the recent work done on the relation of tobacco smoking and certain arterial diseases such as thrombo-angitis obliterans (Coller and Maddock[101], Barker[102], Wright and Moffat[103], Lampson[104]). It has been shown by these that there is a definite vaso-constriction produced by smoking with a consequent rise of blood pressure, and Lampson[104] has actually measured this quantitatively.

Thus, to summarise, the histological appearances of periarteritis nodosa lead us to suggest that the cause is a sudden increase of intravascular pressure which causes rupture at points of weakness in the vascular system. The cause of this rise is unknown, but there is a possibility that the unknown toxin may be a product of excessive smoking in individuals who have become super-sensitive to tobacco products.

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