POLYARTERITIS NODOSA AND THE "RHEUMATIC" DISEASES

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Polyarteritis nodosa has been the subject of comprehensive reviews covering most of its clinical and histological aspects (Smith and Zeek, 1947; Miller and Daley, 1946; Davson, Ball, and Platt, 1948). There are, however, four points which require clarification, and they are discussed in the present paper: (1) the early changes and the question of the so-called "fibrinoid" substance; (2) some histological criteria reputed to distinguish polyarteritis nodosa from the rheumatic and "pararheumatic" diseases, including "temporal arteritis" ("pararheumatic" is used in the sense defined by Teilum, 1946); (3) polyarteritis nodosa as the basis of "Löffler's syndrome" (eosinophil-celled alveolitis) associated with dermatoses; (4) the factor of bacterial hypersensitivity in the causation of polyarteritis nodosa.

The material consists of 18 cases, 13 men and five women. Their ages ranged from 38 to 69, one-third of the subjects being between 46 and 48 years.

Eight biopsies were taken: four from muscle, two from skin nodules, one from sympathetic ganglion, and one from the temporal artery. Ten necropsies were performed.

The following are the preferential sites in which polyarteritis lesions were found post mortem.

Kidney	..	..	..	..	..	..	..	..	6
Myocardium	..	..	..	..	..	..	..	..	2
Tongue	..	..	..	..	..	..	..	..	4
Gut and gall bladder (1 case?)	..	..	..	..	..	..	..	..	2
Brain	..	..	..	..	..	..	..	..	2
Lung	..	..	..	..	..	..	..	..	2
Periadrenal fat tissue	..	..	..	..	..	..	..	..	6
Probable connexion with sulphonamides	..	..	..	..	..	..	..	..	3

The Early Changes

It is generally agreed that the basic change in polyarteritis nodosa is the increased permeability of the vascular wall. If this is mild, fluid penetrates the intact endothelium and causes subendothelial oedema. In more severe cases fibrinogen also escapes and the subendothelial material stains as for fibrin. In the still more severe case, there is actual necrosis of the vascular wall. A patch of fibrin may lie in the necrotic vascular wall, extending into the surrounding tissues, or give the appearance of a solid plug of fibrin filling the breach (Fig. 1) P. As a rule, the subendothelial swelling is patchy or eccentric, but in severe cases it affects the entire circumference (Fig. 2) F. An early fragmentation and later disappearance of parts of the internal elastic lamella is characteristic (Fig. 2a),

FIG. 1.—Section of tongue of male aged 47 years (P.M. 50/66) with polyarteritis nodosa. Haematoxylin and eosin. Breach in arteriolar wall plugged by fibrin (P). Two extra-mural foci of conglomerated collagen (EMF) $\times 120$. Inset left (P) $\times 250$. Inset right (EMF) $\times 250$.

FIG. 2.—Section from same subject as in Fig. 1 stained with phosphotungstic acid-haematoxylin. Fibrinoid necrosis and fibrin deposition along the vascular circumference. Fibrinoid replacing original vascular wall (F). Fibrin deposited inside vascular wall (I.F.). Fibrin deposited outside vascular wall (E.F.) $\times 100$.

FIG. 2

FIG. 2a

FIG. 2a.—Section from same subject as in Figs. 1 and 2 stained with Weigert's elastica stain. Peripheral muscle. "Hair-pin" artery. Gap in the internal elastic lamella caused by fresh fibrin necrosis $\times 120$.

FIG. 13.—Section from Case 1 stained with haematoxylin and eosin. Myocardium (top) eccentric fibrin infiltration in vascular wall (F). Aschoff body (bottom) developing around a vascular lumen showing small patches of fibrin and large cells with fragmented nuclei ($\times 350$).

and the finding of such gaps is helpful in the diagnosis of polyarteritis nodosa scars (Bauke and Kalbfleisch, 1934 ; Ball and Davson, 1949 ; see also page 149).

The degenerative changes in the vascular wall are usually followed by the perivascular collection of inflammatory cells. Among the latter, eosinophil cells may be predominant, but they are not invariably present during the destructive phases of the disease and, as shown below, may occur at a late stage when the acute changes are burnt out.

Deposition of fibrin is conspicuous in the early stages and, to a lesser degree, in the later changes in polyarteritis nodosa, but, as Fishberg (1923) noted, the material deposited in the vascular wall does not entirely consist of fibrin. A

FIG. 4

FIG. 4.—Section from Case 2 stained with haematoxylin and eosin. Subcutaneous nodule. Patch of fibrin bordering a vessel ($\times 85$ and $\times 300$).

FIG. 5.—Section from Case 2 showing patches of fibrin scattered in connective tissue. Most of the cells are eosinophils. Top: $\times 85$. Bottom: $\times 250$. Haematoxylin and eosin.

FIG. 5

characteristic finding in the material here presented was the deposition of fibrin rings inside as well as outside the "fibrinoid" necrotic part of the vascular wall (Fig. 2) EF and IF. The latter shows gaps through which the internal and external fibrin deposits appear to communicate. The fibrin-negative central part (Fig. 2) F seems to be quite different in structure from the frank fibrin that is deposited inside and outside it. On the other hand, in the polyarteritic lesion fibrin-negative material is found more commonly at the periphery than in the centre of the deposit. This ill-defined homogeneous substance remains unstained by Weigert's method for fibrin, phosphotungstic-acid haematoxylin, and the acid picro-Mallory method recommended by Lendrum (1949). All this seems to favour retaining a special term to describe it. As it has neither the staining reactions nor the morphology of fibrin, the use of the term "fibrinoid" may raise objections. "Hyaline" may be preferable in view of its homogeneous "glass-like" appearance.

The subendothelial deposition of "hyaline" is not in itself indicative of early polyarteritis nodosa. It has been described as a change preceding "arteriolar and capillary platelet thrombosis" (Gore, 1950). On the other hand it can be secondary to capillary thrombosis and form a certain stage in the organization of a fibrin thrombus. This has been shown in "acronecrosis" following subacute bacterial endocarditis and in platelet thrombosis (Pagel, 1949). There is no evidence of any primary thrombosis in early polyarteritis nodosa, and, moreover, subendothelial hyaline deposition, without thrombosis, can also be observed in various other conditions, for example in dermatomyositis, fulminant tuberculous septicaemia, and in the response to intradermal injection of heat-killed streptococci in patients with rheumatic fever (Pagel, 1949; Pagel, Woolf, and Asher, 1949; Humphrey and Pagel, 1949).

The Polyarteritis Nodosa Changes in Rheumatic and "Pararheumatic" Conditions

The histological changes in polyarteritis nodosa are reputed to be typical of this disease and to be distinguishable from the lesions of rheumatic and "pararheumatic" conditions (lupus erythematosus disseminatus, dermatomyositis, scleroderma, "arteritis granulomatosa allergica," temporal arteritis, etc.). It is probably true to say that the basic changes in all these diseases are closely similar, if not identical, although there are differences in the frequency and distribution of the lesions in the different diseases.

Fibrinous Infiltration of the Vascular Wall.—This change, which is virtually a *sine qua non* of the early phase of polyarteritis nodosa, is in fact a common finding in "rheumatic arteritis." It has even been said that "the picture of vascular damage in rheumatic disease recalls polyarteritis nodosa so clearly that one has to ask if this is not the same disease or, at least, their morbid anatomy leads to the same result" (Klinge and Vaubel, 1931; VonGlahn and Pappenheimer, 1926). Two examples of this change have been seen.

Case 1.—A boy, aged 16, had had recurrent rheumatic myocarditis for four and a half years, with mitral and aortic stenosis. Repeated blood cultures were sterile. At necropsy (P.M. 1945/2) a large, elongated heart was seen. There were many partly calcified vegetations on the mitral valve, and aortic stenosis due to scarring of the valves. The lungs were rubbery, showing histological changes typical of so-called

"rheumatic lung." Histological examination of the myocardium showed (a) patches of fibrin and fibrinoid matter in the interstitial tissue and in the intima of arterioles (Fig. 3 F), with or without peripheral cell collection ("early rheumatic infiltration"); (b) multiple "Aschoff-bodies" of the spindle as well as of the coronal type; some of these developed around patches of fibrin in the vascular wall (Fig. 3).

Case 2.—A boy, aged 14 years, had had chorea and rheumatic fever seven years previously. He was admitted with a history of 14 days' pain in both shoulders and knees. He had atactic speech and occasional facial twitching. He had had a few subcutaneous nodules on the right olecranon for some time. Six days after admission a fresh crop of nodules developed on the hands, wrists, and around the ankles. One of these (biopsy S.D. 1602) showed patches of fibrinoid matter, with cores of fibrin, scattered in the connective tissue in typical rheumatic fashion (Fig. 5). But the vascular changes (Fig. 4), which showed in addition widespread infiltration with eosinophils, were characteristically those of polyarteritis nodosa. Clinically, however, the diagnosis seemed to be clearly that of acute "rheumatic fever."

In the "pararheumatic conditions"—lupus erythematosus disseminatus (see especially Figs. 8–10 in the paper by Klemperer, Pollack, and Baehr, 1941) and dermatomyositis (Fahr, 1921; Pagel *et al.*, 1949)—vascular changes occur which are indistinguishable from those of polyarteritis nodosa.

"Collagen Disease."—This is a degenerative and exudative change affecting the collagen fibres, which become waterlogged, conglutinate, and lose their normal staining affinities. There is also exudation of fibrin in the collagen tissue.

This alteration of collagen is found in lupus erythematosus disseminatus (Klemperer *et al.*, 1941) and in dermatomyositis (Pagel *et al.*, 1949). It is also present in the "early rheumatic infiltration" in the two cases described above. Indeed, there does not seem to be any *structural* difference between "early rheumatic infiltration" (Klinge, 1933) and this so-called "collagen disease." It is not mere coincidence that when the relationship of these collagen changes to the argyrophil reticulin is studied, it is found to be identical in rheumatic disease (Klinge, 1933), polyarteritis nodosa, and the "pararheumatic" diseases. In all there is a *peculiar resistance of the argyrophil reticulin* even in the middle of a zone of gross change, as is shown in Fig. 6. This section is from the tongue of a male aged 47 with classical polyarteritis nodosa terminating in cerebral haemorrhage (P.M. 1950/66), and shows a typical patch of vascular fibrin-necrosis in which the silver impregnated reticulin fibres remain intact. The abnormality of the collagen fibres of the vascular wall is clearly shown in other sections by their peculiar staining reactions with Van Gieson's and Mallory's methods.

A further point of similarity between polyarteritis nodosa and the rheumatic and "pararheumatic" conditions is that paravascular foci occur in all. An example is given in Fig. 1 from a case of polyarteritis nodosa. In all these varied diseases the paravascular lesion also shows an intact reticulin, and thus conforms to the early rheumatic lesion (*Frühinfiltrat* of Klinge or "reticular Aschoff body" of Gross and Ehrlich, 1934). I have confirmed this similarity in polyarteritis nodosa and in dermatomyositis.

Occasionally, in polyarteritis nodosa, the *paravascular* lesion, especially if cutaneous, goes on to necrosis. The area of necrosis is full of chromatin debris

FIG. 6.—Section of tongue of the same subject as in Fig. 1 showing a trellis of preserved reticulin fibres in an area of perivascular fibrin necrosis. Wilder preparation ($\times 200$).

and is surrounded by epithelioid cells and Langhans giant cells, and thus resembles a tuberculous lesion (Fig. 7). No acid-fast bacilli were found. Similar tuberculoid skin nodules have been mentioned in a case with transient infiltrations of the lung with pleural effusion described by Livingstone (1943-4). Structurally they seem to be identical with focal lesions observed in the upper respiratory tract (Howells and Friedmann, 1950), in the lung (Banowitch, Polayes, and Charet, 1942; Baggenstoss, Bayley, and Lindberg, 1946; Bergstrand, 1946; Smith, 1948), in the heart muscle (Rose, Littmann, and Houghton, 1950), and in the liver (Zuelzer and Apt, 1949), in cases with a variety of clinical symptoms but all showing excessive eosinophilia. It is therefore perhaps significant that the following case with tuberculoid lesions had gross eosinophilia.

Case 3.—A woman, aged 49, with a history of bronchitis and asthma for 20 years, was admitted with indefinite gastric complaints, and on examination showed a leucocytosis (14,500-18,000) of which up to 63% of the white cells were eosinophils. Five weeks before admission she had had an irritating rash on the legs, extreme sweating at night, weakness of the hands and slight weakness of the rest of the body, numbness in the feet up to the knees, foot drop, complete loss of sensation for some time, and transient tender lumps, reaching the size of peas, in the legs and forehead. She showed

FIG. 7

FIG. 7.—Section of skin nodule of woman aged 49 years (S.D. 2564 and 2682) with polyarteritis nodosa, showing granuloma with central necrosis and giant cells of the Langhans type in the periphery. Haematoxylin and eosin ($\times 350$).

FIG. 8.—Same section as Fig. 7. A Wilder preparation for argentaffine reticulin fibres, which are preserved ($\times 100$). Inset is high-power ($\times 200$) photomicrograph.

FIG. 8

irregular pyrexia and a persistent eosinophilia, which gradually came down to 12%, with a total white count of 6,500 per c.mm. The results are tabulated.

Date	White Blood Cells	Eosinophils
13/9/43	18,000 per c.mm.	48% = 8,640 per c.mm.
16/9/43	14,500 " "	63% = 9,135 " "
27/10/43	13,500 " "	33% = 4,500 " "
1/2/44	10,500 " "	46% = 4,830 " "
7/3/44	19,000 " "	30% = 4,700 " "
24/3/44	6,000 " "	16% = 960 " "
16/5/44	7,000 " "	26% = 1,820 " "
16/7/44	6,500 " "	12% = 760 " "

Occult blood in the stools was strongly positive.

Polyarteritis nodosa was diagnosed, but it was noted that the fever and pulse were not typical and that the patient was not as ill as might be expected. Herpes zoster affecting the seventh and eighth dorsal segments appeared shortly after admission. Biopsy of skin from a foot (10/10/43) showed extensive perivascular, perifollicular, and periglandular infiltration with eosinophil leucocytes and a few plasma cells and mononuclear cells. The same changes were present in the subcutaneous adipose tissue.

Biopsy from skin and deltoid muscle (23/10/43) showed no appreciable changes in the skin except subpapillary oedema with smoothing out of the corpus papillare. A few plasma cells were scattered in the layers of the cutis. There were no vascular or perivascular changes, or changes in muscular tissue. Biopsy from skin of a foot (1/4/44) showed that the dermis contained a well-defined nodule with central necrosis and a number of giant cells of the Langhans type in the periphery (Fig. 7). A ring of lymphocytes and thickened connective tissue surrounded the focus. Wilder preparations showed the reticulin fibres to be occasionally fragmented but preserved (Fig. 8), although collagen fibres seemed to have disappeared. Some arterioles in the periphery showed fibrinoid necrosis in the intima.

The patient improved considerably and, although she was still well when seen four years later, it is considered that this was, in fact, a case of polyarteritis nodosa.

Granuloma.—The initial vascular changes in polyarteritis nodosa, the fibrinoid necrosis in the subintimal layers, are soon followed by cellular aggregation, and in some cases go on to frank granuloma. One type of this is rather in the nature of an extension of the necrotic region described above (Fig. 7). The other type of tuberculoid granuloma in polyarteritis nodosa occurs in the affected vascular wall itself (Fig. 9).

Case 4.—A man, aged 47, had classical polyarteritis nodosa in all stages, and the sections were taken from a branch of the tibial artery. The granuloma with prominent giant cells (GC), both of the Langhans and foreign body type, had developed around a patch of fibrin (FP), adherent to the intima. This parietal fibrin-thrombus, together with the granuloma, filled a gap in the vascular structure which was outlined by a defect of the internal elastic lamella. Elastic debris acting as foreign bodies may possibly explain the granuloma and the presence of giant cells.* No such debris was found, however, in the present case.

* The connexion of giant cells with elastic debris is clearly seen in "temporal arteritis" (Harrison, 1948), and in the lung of pulmonary haemosiderosis (Lendrum, Scott, and Park, 1950).

FIG. 9

FIG. 9.—Section of the tibial artery of same subject as in Fig. 1 showing, left, tuberculoid granuloma in the intima filling a gap in the internal elastic lamella with patches of fibrin inside. Giant cells=G.C. Fibrin patch=F.P. Haematoxylin and eosin ($\times 120$). Section on the right shows gap in internal elastic lamella (arrows). Weigert's elastica stain. ($\times 120$).

FIG. 10.—Section from same subject as in Fig. 1 showing granuloma (G) developing along both sides of a thrombosed artery (W) in the myocardium in polyarteritis nodosa ($\times 100$). This granuloma is not tuberculoid, but somewhat resembles a rheumatic nodule. See particularly the inset ($\times 350$). Haematoxylin and eosin.

FIG. 10

The vascular granuloma in polyarteritis nodosa may thus resemble the histological picture of Buerger's disease and "temporal arteritis." Gordon and Thurber (1946) and Harrison (1948) suggest that temporal arteritis has many points in common with polyarteritis nodosa. A less tuberculoid form of granuloma may also be seen in the vessel wall, resembling more closely a rheumatic granuloma with predominantly mononuclear cells and "giant cells" with hyperchromatic nuclei. Fig. 10 shows a section of a vessel wall from a case of polyarteritis nodosa demonstrating the resemblance to the more localized rheumatic granuloma.

Discussion

It seems clear that on microscopical grounds an identical vascular lesion occurs in polyarteritis nodosa, in acute rheumatic disease, and in the pararheumatic diseases as defined above. The focal lesions outside the vessels, referred to as paravascular foci, which occasionally occur in polyarteritis, are closely similar to, if not identical with, the "reticular Aschoff body" (Gross and Ehrlich, 1934), which is probably the lesion described by Klinge as "early infiltrate." Whether or not the coronal Aschoff body (Gross and Ehrlich, 1934) arises at the site of a resolving reticular Aschoff body is still a matter for argument, as is also the question of its specificity (Siegmund, 1931). What is important for present purposes is the similarity of the paravascular focus of polyarteritis nodosa to the "early infiltrate" (reticular Aschoff body) of acute rheumatic disease.

If it be accepted that the coronal Aschoff body be different, then acute rheumatic disease has all the components which characterize polyarteritis nodosa, plus an additional lesion. Similarly, a pararheumatic disease, such as acute disseminated lupus erythematosus, may show vascular changes which resemble those of polyarteritis, with certain additional features which are specific for disseminated lupus erythematosus, if we accept the views of Klemperer (1950) and Klemperer, Gueft, Lee, Leuchtenberger, and Pollister (1950).

It is likely that the future will show the similarities to be more significant than the differences, but it is already justifiable to say that the polyarteritic lesion is an important part of the morbid anatomy of acute rheumatic disease and of the pararheumatic diseases.

Polyarteritis Nodosa and Löffler's Syndrome.—It does not appear to be certain whether polyarteritis also plays a part in the transitory pulmonary infiltrations with eosinophilia known as Löffler's syndrome. On histological grounds there would appear to be two main types of this disease. The first is the commoner form, which shows focal eosinophil-celled bronchopneumonia with eosinophil-cell infiltration of vascular walls, but without any sign of fibrinoid necrosis (von Meyenburg, 1942a and b; 1944–5), or other evidence of polyarteritis nodosa. The second is the type which shows necrotizing arteriolitis and phlebitis, associated with granulomata, sometimes referred to as "rheumatoid" or "tuberculoid"; these are either necrotic or fibrosing and contain eosinophils or oxyphilic granular debris, and areas of fibrinoid swelling of collagen (Bergstrand, 1946; Baggenstoss *et al.*, 1946; Lumb, 1950). Most of the cases of this type which have been recorded had bronchial asthma during life and showed characteristic anatomical changes.

In sharp contrast to these, two personally observed cases showed not only the concomitant presence of eosinophil-cell granuloma and eosinophil-cell alveolitis, but also vascular changes which, particularly on the basis of the gaps in their elastica, were considered to be examples of burnt-out polyarteritis nodosa.

Case 5.—A man, aged 47, had generalized exfoliative dermatitis and recurrent erythroderma for two years, chiefly involving the feet, legs, arms, and scrotum. An excised inguinal lymph node showed the so-called “lipomelanotic reticulosis.” There was a raised serum globulin and a blood eosinophilia of 9–10%. Death was due to a sudden cerebral haemorrhage. At necropsy it was seen that there was extensive cerebral haemorrhage of the right parieto-occipital region, dermatitis, superficial ulcers on the posterior wall of the larynx, fatty liver, and a few renal infarcts. The lungs were emphysematous with ill-defined areas of lobular consolidation, notably in the lower lobes. No plugging of the bronchi was seen. The naked eye changes of the lung were in no way characteristic.

Histological examination showed that eosinophils were present in many organs. On the tongue they formed small foci eroding the thin epithelial lining from below. They were present in the deeper strata of the laryngeal ulcers, in a post-mortem clot, in myocardial septa, and in the spleen (pulp and centres of Malpighian corpuscles). The main changes were in the lungs, and were as follows.

(a) Multiple *nodules* in the interlobular septa: some of these were purely fibrotic and attached to unchanged vessels, others consisted of soft, oedematous, and fibrosing ground tissue.

(b) Collections of *eosinophil cells*: these were present as collections in diffusely thickened septa around dilated vessels (Fig. 11 EC) and as masses forming the necrotic centres of the soft fibrotic nodules mentioned above (Fig. 12).

(c) Vascular changes: in the larger arteries the intima was generally thickened with *eccentric fibrotic cushions* containing a large number of eosinophil cells, some of which formed a subendothelial fringe. There were definite and fairly extensive gaps in the internal elastic lamella, adjacent to and opposite the intima cushions (Fig. 13). Gaps in the internal elastic lamellae were also found in some completely obliterated arteries (Fig. 14). The hilar lymph nodes contained fibrotic areas with concentric hyaline thickening of small vessels, without distinctive features.

Case 6.—A man, aged 46, had had dyspnoea for eight months, and a scaly, papular rash, not unlike pemphigus vegetans, on face, neck, and one arm, with erythroderma and exfoliation.

At necropsy the lungs were found to be emphysematous, with mucous intrabronchial plugs, associated with gross cyanosis and dilatation of the right heart.

The main histological changes were in this case also found in the lungs.

(a) Intrabronchial changes, typical of bronchial asthma, namely whorled plugs of mucus containing many eosinophil cells and some Charcot-Leyden crystals, were seen. There were also concentric and regular warty thickenings of the bronchial mucosa around cores of conglomerated elastic fibres.

(b) Necrotizing eosinophil cell alveolitis forming well defined nodules with a well preserved alveolar elastic pattern (Fig. 15) was found. The cells filling both alveolar spaces and septa were almost exclusively eosinophils. Occasionally a fibrinoid-necrotic patch could be seen lining a dilated alveolar duct on one side, with eosinophils and what appeared to be desquamated and confluent alveolar epithelium (Fig. 16).

(c) Vascular changes affected small arterial branches, and included fibrous intimal cushions filled with eosinophil cells and concentric fibrous thickening of the walls with gaps in the internal elastic lamellae (Fig. 16, inset).

FIG. 11.—Section of lung from Case 5 showing cuffing of pulmonary vessels by eosinophil cells EC ($\times 100$). Inset: high-power view ($\times 350$).

FIG. 12.—A second section of lung from Case 5 showing eosinophil-cell nodule in an interlobular septum of the lung ($\times 120$), and necrotic centre full of eosinophil cells and scattered eosinophil granules ($\times 300$).

FIG. 13

FIG. 13.—Section from Case 5 showing eccentric fibrotic cushion of the arterial intima in the lung. Elastic stain showing gaps in the internal elastic lamella at A and B ($\times 120$).

FIG. 14

FIG. 14.—This section also from Case 5 shows the gap (G) in the elastic lamellae of the wall of an obliterated branch of the pulmonary artery (arrows). Elastic stain ($\times 80$).

These two cases show the unusual combination in the lung of eosinophil-cell granuloma with healed polyarteritis nodosa, associated with bronchial asthma in one patient and with a dermatitis in both patients. Histologically, the picture may be described as a "dissociation" of vascular changes and eosinophilia. Eosinophil-cell infiltration appears to be an independent phase rather than a reactive by-product of polyarteritis nodosa.

The definition of Löffler's syndrome is rather vague, but the observations made on these cases certainly indicate that they belong to the group described by Baggenstoss *et al.* (1946). The early polyarteritis present in the group of cases of pulmonary eosinophil granuloma following asthma suggests that the aetiology of the condition may be associated with polyarteritis nodosa. It may be recalled that polyarteritis with dermatitis or eosinophilia has been reported in association with hypersensitivity to iodine (Rich, 1945) and to dilantin sodium (van Wyk and Hoffmann, 1948). An example of fatal iodine sensitivity following bronchography (to be published by Sumner, Lichter, and Nassau) showed extensive exfoliative and bullous dermatitis with ulcerative bronchitis and gastritis. The arterioles related to the areas of ulceration, and a few arterioles elsewhere showed foci of eccentric mural necrosis with gaps in the internal elastica, a picture very like that of polyarteritis nodosa.

Pathogenesis and Aetiology of Polyarteritis Nodosa.—The disease is histologically characteristic, especially when taken as a whole. It is true that some of its features can be seen in essential hypertension, but in this disease the usual change is concentric hyaline swelling of the arterial wall, with fibrosis, in contrast to the eccentric swelling, fibrinoid necrosis, and perivascular collection of cells, notably eosinophils, seen in polyarteritis nodosa. Hypertensive changes tend to show a predilection for certain organs; those in polyarteritis nodosa do not. The changes in vessels involved in a chronic inflammatory or ulcerative process can, at a certain stage, resemble polyarteritis nodosa, but the lesions are restricted to the vessels in the affected area.

There are a number of conditions in which the changes of polyarteritis nodosa do not appear to be accidental or secondary but form an essential component. This fact alone suggests that the changes are indicative of a tissue response to a variety of stimuli rather than to one single agent. Evidence has been adduced, both in man and the experimental animal, that a hyperergic antigen-antibody reaction may produce the characteristic lesions. Such observations have been made in allergic persons (asthmatics) suffering from serum sickness or reacting to a course of chemotherapy, notably with sulphonamides (Rich, 1942; Rich and Gregory, 1943; Black-Schaffer, 1945; Rosenak and Maschmeyer, 1945; van Rijssell and Meyler, 1948). In the experimental animal the changes at the site of local serum hypersensitivity (Arthus phenomenon) typically include eccentric fibrinoid necrosis of vascular walls with cell collections (Pagel, 1939). In the experimental reproduction of polyarteritis nodosa serum-antigens are normally used (Rich and Gregory, 1943; More and McLean, 1949).

The natural history of polyarteritis nodosa and related diseases justifies the search for bacterial antigens. Experiments have been carried out in human volunteers with intradermal injections of heat-killed streptococci (Humphrey and Pagel, 1949). At the site of injection in normal persons there were minimal changes after 10 to

FIG. 15

FIG. 15.—Section of lung from Case 6 showing nodular eosinophil-cell alveolitis with the alveolar elastic pattern preserved. Left: haematoxylin and eosin ($\times 80$). Right: elastin ($\times 120$).

FIG. 16.—Second section from Case 6 showing fibrinoid patch bordering the wall of dilated alveolar duct (F.P.) haematoxylin and eosin ($\times 120$). Inset (top): The fibrinoid patch ($\times 350$ haematoxylin and eosin). Inset (bottom): Arteriole with gap in internal elastic lamellae. Elastic stain. ($\times 350$.)

FIG. 16

14 days, with perivascular collection of a few lymphocytes and macrophages. Numerous cocci were seen in the macrophages, indicating the disposal, via the lymphatics, of the bacterial foreign body. The results were quite different in patients with rheumatic fever and subacute bacterial endocarditis. In these diffuse oedema was prominent in the early stages, and later, in the more severe type of response, oedema was patchy and focal with fibrin exudation, conglutination of collagen fibres, and loss of staining affinities. Pictures thus obtained were indistinguishable from the infiltrative changes characteristic of early rheumatic fever (Figs. 4 and 5) and lupus erythematosus disseminatus. Figs. 17 and 18 compare the changes following intradermal injection of heat-killed streptococci in a rheumatic fever patient, aged 21, with those of an early rheumatic nodule in the skin of the hand of a patient aged 33 years. Focal oedema and fibrinous conglutination of collagen fibres are present interstitially (Fig. 17) and the cells are swollen and vacuolated. There is a tendency for the cells to group themselves around patches of fibrin and conglutinated ground substances, which act as foreign bodies and produce a surrounding granulomatous reaction, with the formation of giant cells. There is eccentric fibrin infiltration and necrosis of the vascular intima (Fig. 18). No cocci were seen

in any of these lesions.

An example has therefore been shown of the production of the so-called "anaphylactic" type of hypersensitivity with oedema and fibrinoid necrosis of vascular walls following the injection of a bacterial antigen. This anaphylactic type of hyperergic response is usually attributable to serum hypersensitivity and distinguished from the delayed necrotic changes of the "tuberculin type" observed in bacterial hypersensitivity. It is probable that the bacterial antigens produce a "trigger action," and the results may possibly be due to antigens which are common to bacterial and serum proteins.

FIG. 17.—Top: Section of acute rheumatic skin nodule from male aged 33 years showing focal oedema and fibrin infiltration of collagen. Phosphotungstic acid-haematoxylin stain. Bottom: Section from human volunteer aged 21 years with rheumatic fever showing focal oedema and fibrin infiltration of collagen 18 days after intradermal injection of heat-killed streptococci. Haematoxylin and eosin ($\times 250$).

FIG. 18.—Same subject as top Fig. 17 showing eccentric oedema and fibrin infiltration of intima. Haematoxylin and eosin ($\times 450$). Bottom: Same subject as in Fig. 17 (bottom) showing the same change induced by intradermal injection of heat-killed streptococci. Haematoxylin and eosin ($\times 450$).

These experimental results in the animal and in human volunteers suggest a multiplicity of aetiological agents which may produce polyarteritis nodosa and the related conditions, the common pathogenic factor being antigenic hypersensitivity which is expressed in common tissue changes.

Summary and Conclusions

The early changes in polyarteritis nodosa appear to be subendothelial swelling due to permeation of fluid, followed by fibrinogen exudation with subsequent—mostly eccentric—necrosis of the vascular wall. A breach in the latter can be plugged by fibrin, or fibrin may be found both inside and outside the breached and necrotic vascular wall. The term “fibrinoid” should be restricted to the deposited material that fails to stain like fibrin.

The differences between polyarteritis nodosa and the rheumatic and “pararheumatic” diseases (lupus erythematosus disseminatus, dermatomyositis, “arteriolitis allergica,” temporal arteritis) concern the natural history of these diseases and the site and distribution of the lesions, but the basic histological change appears to be identical in all. In polyarteritis nodosa, fibrin deposition and necrosis affect the vascular walls mainly, but extramural foci may occur and involve the collagen fibres, with lesions indistinguishable from the acute “infiltrative” changes in rheumatic fever, lupus erythematosus disseminatus, and dermatomyositis. There is characteristic preservation of the argyrophil reticulin within the zone of collagen change. In addition to these paravascular foci, pseudo-tuberculous necrotic lesions may occur in polyarteritis nodosa. Finally, granuloma may develop in the vascular wall, resembling the Aschoff nodule and the changes seen in temporal arteritis. On the other hand, “rheumatic arteritis,” as typically seen in rheumatic fever, can be indistinguishable from polyarteritis nodosa and the vascular changes observed in dermatomyositis and scleroderma.

Two cases are described of eosinophil-celled alveolitis (one form of Löffler's syndrome) in association with exfoliative dermatitis and asthma. In both there is evidence of burnt-out polyarteritis nodosa and of a “dissociation” of eosinophilia and arterial necrosis.

The course of events which leads to the explosive arterial lesion of polyarteritis nodosa is indicative of hyperergy. This hypersensitivity may be to a foreign or modified serum, or to abnormal protein, being comparable to the Arthus phenomenon and of the type generally referred to as the “anaphylactic type of allergy.” On the other hand the hypersensitivity may be to a bacterial antigen, as shown by the use of streptococci in experiments on human volunteers.

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REFERENCES

- Baggenstoss, A. H., Bayley, E. C., and Lindberg, D. O. N. (1946). *Proc. Mayo Clin.*, **21**, 457.
 Ball, J., and Davson, J. (1949). *J. Path. Bact.*, **61**, 569.
 Banowitch, M. M., Polayes, S. H., and Charet, R. (1942). *Ann. intern. Med.*, **16**, 1149.
 Bauke, E. E., and Kalbfleisch, H. H. (1934). *Frankfurt. Z. Path.*, **47**, 340.
 Bergstrand, H. (1946). *J. Path. Bact.*, **58**, 399.

- Black-Schaffer, B. (1945). *Arch. Path.*, **39**, 301.
- Davson, J., Ball, J., and Platt, R. (1948). *Quart. J. Med.*, n.s., **17**, 175.
- Fahr, T. (1921). *Arch. Derm. Syph., Wien*, **130**, Orig., 1.
- Fishberg, A. M. (1923). *Virchows Arch.*, **240**, 483.
- Gordon, L. Z., and Thurber, D. C. (1946). *Arch. Path.*, **42**, 402.
- Gore, I. (1950). *Amer. J. Path.*, **26**, 155.
- Gross, L., and Ehrlich, J. C. (1934). *Ibid.*, **10**, 467.
- Harrison, C. V. (1948). *Journal of Clinical Pathology*, **1**, 197.
- Howells, G. H., and Friedmann, I. (1950). *Ibid.*, **3**, 220.
- Humphrey, J. H., and Pagel, W. (1949). *Brit. J. exp. Path.*, **30**, 282.
- Klemperer, P. (1950). *Amer. J. Path.*, **26**, 505.
- Gueft, B., Lee, S. L., Leuchtenberger, C., and Pollister, A. W. (1950). *Arch. Path.*, **49**, 503.
- Pollack, A. D., and Baehr, G. (1941). *Ibid.*, **32**, 569.
- Klinge, F. (1933). *Ergebn. allg. Path. path. Anat.*, **27**, 1.
- and Vaubel, E. (1931). *Virchows Arch.*, **281**, 701.
- Lendrum, A. C. (1949). *J. Path. Bact.*, **61**, 443.
- Scott, L. D. W., and Park, S. D. S. (1950). *Quart. J. Med.*, n.s., **19**, 249.
- Livingstone, J. L. (1943-4). *Proc. roy. Soc. Med.*, **37**, 156.
- Lumb, G. (1950). *Brit. med. J.*, **2**, 645.
- Meyenburg, H. von (1942a). *Virchows Arch.*, **309**, 258.
- (1942b). *Schweiz. med. Wschr.*, **72**, 809.
- (1944-5). *Schweiz. Z. Tuberk.*, **1**, 205.
- Miller, H. G., and Daley, R. (1946). *Quart. J. Med.*, n.s., **15**, 255.
- More, R. H., and McLean, C. R. (1949). *Amer. J. Path.*, **25**, 413.
- Pagel, W. (1939). In *Fortschritte der Allergielehre* (vol. 1), p. 73. Basel and New York.
- (1949). *Amer. J. med. Sci.*, **218**, 425.
- Woolf, A. L., and Asher, R. (1949). *J. Path. Bact.*, **61**, 403.
- Rich, A. R. (1942). *Bull. Johns Hopk. Hosp.*, **71**, 123.
- (1945). *Ibid.*, **77**, 43.
- and Gregory, J. E. (1943). *Ibid.*, **72**, 65.
- Rijssel, T. G. van, and Meyler, L. (1948). *Acta med. scand.*, **132**, 251.
- Rose, M. H., Littmann, D., and Houghton, J. (1950). *Ann. intern. Med.*, **32**, 1114.
- Rosenak, B. D., and Maschmeyer, R. H. (1945). *Lancet*, **1**, 305.
- Siegmund, H. (1931). *Verh. dtsch. Path. Ges.*, **26**, 231.
- Smith, C. C., and Zeek, P. M. (1947). *Amer. J. Path.*, **23**, 147.
- Smith, J. F. (1948). *J. Path. Bact.*, **60**, 489.
- Sumner, J. J., Lichter, J., and Nassau, E. (1951). *Thorax*. In the press.
- Sweeney, A. R., and Baggenstoss, A. H. (1949). *Proc. Mayo Clin.*, **24**, 35.
- Teilum, G. (1946). *Acta med. scand.*, **123**, 126.
- VonGlahn, W. C., and Pappenheimer, A. M. (1926). *Amer. J. Path.*, **2**, 235.
- Wyk, J. J. van, and Hoffmann, C. R. (1948). *Arch. intern. Med.*, **81**, 605.
- Zuelzer, W. W., and Apt, L. (1949). *Amer. J. Dis. Child.*, **78**, 153.