HYPERGLOBULINEMIA, PERIARTERIAL FIBROSIS OF THE SPLEEN, AND THE WIRE LOOP LESION IN DISSEMINATED LUPUS ERYTHEMATOSUS IN RELATION TO ALLERGIC PATHOGENESIS *

GUNNAR TEILUM, M.D.

(From the Institute for Pathological Anatomy, University of Copenhagen, Copenhagen, Denmark)

As a common feature of Boeck's sarcoid and a number of other conditions associated with hyperglobulinemia, I have described in the preceding article (1948) the precipitation, especially in the reticuloendothelial system, of a homogeneous amyloid-like substance, passing on to hyalinosis, which, in the spleen and in lymphatic nodes *inter alia*, frequently occurs in the form of concentric rings. This is apparently an elementary morphologic immunity reaction with *an underlying allergic hyperglobulinosis in the reticulo-endothelial system*. That study emphasized the importance of this reaction in Boeck's sarcoid as an essential alteration pathogenetically related to the experimental "amyloidosis" observed after immunization. Those findings will be applied to lupus erythematosus disseminatus in the present study.

Investigations of recent years have shown that lupus erythematosus disseminatus very often is associated with hyperglobulinemia (Coburn and Moore, 1943, Thyresson, 1944) of unknown nature. Coburn and Moore (page 213) stated: "Hypergammaglobulinemia of unknown cause is a constant characteristic of disseminated lupus erythematosus."

In this disease the spleen, moreover, is the seat of a peculiar periarterial fibrosis confined to the central and penicillary arteries, which was first observed by Sacks (Libman and Sacks); it was described later by Klemperer, Pollack, and Baehr (1941) and Kaiser (1942), among others. This periarterial fibrosis, although not specific for lupus erythematosus, nevertheless is known to occur with a high frequency in this disease, as stated by Kaiser, who (page 38) further adds: "The connection between the periarterial fibrosis and the other lesions of disseminated lupus erythematosus is obscure."

It will be shown in the following study that the hyperglobulinemia and periarterial fibrosis occurring in the spleen in lupus erythematosus disseminatus are identical, pathogenetically and morphologically, with the alterations in Boeck's sarcoid and the atypical amyloidosis described in the preceding article (1948), having allergic hyperglobulinosis as a common primary foundation.

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Allergic Pathogenesis and Morphogenesis of Lupus Erythematosus Disseminatus

The nature of the hyperglobulinemia and the periarterial fibrosis in the spleen in lupus erythematosus disseminatus must be considered in connection with the pathogenesis, which will therefore be mentioned here briefly. A discriminating survey of the different views of the nature of the disease, from 1872 to 1942, has been given by Libman who, in 1924, together with Sacks, described its special form of valvular and mural endocarditis. In a very thorough morphologic description by Klemperer, Pollack, and Baehr (1941), the alterations observed in lupus erythematosus disseminatus are considered "local manifestations of the widespread damage of collagen." These authors dissociated themselves from a concept of allergic pathogenesis, as they wrote: "Furthermore, the classic clinical evidences of hypersensitivity so frequently observed in periarteritis nodosa are lacking in disseminated lupus erythematosus. It would be a mistake, therefore, to speak glibly of lupus erythematosus disseminatus as an allergic disease—at least in the narrow sense of the term." The slight cellular reaction and the absence of a specific granulomatous phase are also stressed as contrasting with the ordinary findings in acute or granulomatous inflammation.

However, the miliary granulomata and nodular necrosis of focal occurrence in the serosa (parietal and visceral pleura), macroscopically visible as clustered grayish white nodules resembling miliary tubercles and described in my previous publications (1945, 1946), afford proof of the *allergic* nature of the disease; these alterations have to be interpreted as special phases of an allergic morphologic tissue reaction in conformity with the typical localization of the disease to the serous membranes. The focal allergic pneumonia described (1946), the endocarditis and the alterations in a number of other organs, such as lymph nodes, kidneys, vessels, and connective tissue, must henceforth also be regarded in the same way and may, in certain of their phases, be completely parallel with Arthus' allergic necrosis (1946). With regard to the Arthus phenomenon, reference may be made to Culbertson's demonstration (1935) of the fact that it is clearly dependent on the occurrence of circulating antibody, thus being of the same nature as anaphylaxis. After neutralization of the circulating precipitin, the phenomenon could no longer be elicited. Apart from all differences, I now see obvious pathogenetic points of resemblance with the conditions dealt with more fully in the preceding article (1948), Boeck's sarcoid and the morphogenetically related experimental atypical amyloidosis, in which "persistent or repeated stimulation of immune mechanisms is a fundamental factor in genesis."

Hyperglobulinemia in Lupus Erythematosus Disseminatus

Both in the conditions mentioned above and in lupus erythematosus disseminatus an increase of the serum globulin is found. In the latter disease, this is a characteristic symptom of frequent occurrence. It was first pointed out by Coburn and Moore (1943), who found an inversion of the albumin/globulin ratio in 15 patients, all of them being females between 6 and 36 years of age. In most of the cases the total protein was within normal limits. Each albumin determination was below the normal (mean value, 3.1), whereas each patient had a total globulin above the normal (mean value, 3.8) and each euglobulin value was found to be considerably increased (mean value, 1.0).

Electrophoretic analyses showed that this increase of globulin was to be found chiefly in the gamma fraction with an abnormally low albumin/globulin ratio. The other globulin fractions were approximately normal. Among other conditions in which such abnormally large quantities of gamma-globulin have been demonstrated, mention is made of the serum of hyperimmune antipneumococcal horses, Boeck's sarcoid, lymphogranuloma venereum, and certain cases of plasma cell myeloma.

Periarterial Fibrosis of the Spleen in Lupus Erythematosus Disseminatus

The high frequency of periarterial fibrosis of the spleen in disseminated lupus erythematosus is apparent from the literature (see Kaiser, page 31). Klemperer, Pollack, and Baehr (1941, 1942) ascertained its presence in 19 of 20 cases; Kaiser, in 15 of 18 cases.

Klemperer, Pollack, and Baehr (1941, 1942) described this lesion as a special periarterial fibrosis confined to the central and penicillary arteries, which in cross sections display concentric rings consisting of thick collagenic fibrils produced at the sacrifice of periarterial lymphatic tissue. In one of their cases many of the newly formed collagenic fibrils showed signs of fibrinoid degeneration, eosinophilic swelling and homogenization, and even basophilia.

Kaiser found macroscopic perisplenitis in 10 of 18 cases and considered periarterial fibrosis present when the periarterial collagen of the follicular and penicillary arteries, which normally is closely packed and without evidence of hyalinization, was found to be present in at least three layers, around at least half the circumference of the vessels, producing the appearance of concentric rings. Kaiser stated that this collagen was hyaline in most cases, and in others it was partially broken down to granular eosinophilic material. In most instances the majority of the smaller arteries were affected, whereas periarterial fibrosis was not found in relation to the medium or large arteries, or

around any of the venous structures. As a consequence of the fibrosis, the average diameter of the follicular vessels was found to have increased to about 125 μ in the cases affected, as compared to the normal average of 60 to 75 μ.

Periarterial Hyalinosis in Allergic Conditions Associated with Hyperglobulinosis

After the demonstration of similar hyaline periarterial alterations in the spleen in lupus erythematosus disseminatus and in various other disorders, I have arrived at the view that the periarterial fibrosis in lupus erythematosus disseminatus is not specific; it is essentially different from the focal allergic reactions with necrosis and granuloma formation described in the latter disease. It is a lesion of the spleen which is common to a number of different disorders which have in common the feature of displaying an *allergic hyperglobulinosis* of the reticulo-endothelial system with persistent or repeated stimulation of immune mechanisms as the fundamental factor in the genesis.

a. Lupus Erythematosus Disseminatus

In my previous description (1945, 1946) of the allergic lesions in the narrowest sense of the term (miliary granulomata and nodular foci of necrosis) which occur in lupus erythematosus disseminatus, the alterations of the spleen were not mentioned. Both of the cases reported (1945), however, displayed a typical periarterial hyaline zone with concentric rings. In *case 1* (no. 366/44) the follicular and penicillary arteries of the spleen were thus found to be surrounded by concentrically arranged hyaline bands (Fig. 1) forming up to five lamellae which caused the external diameter of the vessels to be more than twice normal. The individual rings were composed of large and small, often slightly wavy, disconnected hyaline lumps which assumed a red color when stained according to the van Gieson-Hansen method, and a deep blue color with Mallory's stain. When the latter staining method was employed, the vascular wall itself was seen to contain an intensely red-colored substance, and in the parts peripheral to the latter a few coarse, red, Mallory-stained filaments could be observed in relation to the blue hyaline bands, small red bands also being seen peripherally or between the hyaline rings. In the circumference and scattered between the hyaline rings numerous reticulo-endothelial cells were seen, including a few plasma cells which assumed an intensely red color when stained according to Unna's method. The hyaline substance did not give an amyloid reaction with Jürgens' methyl violet or Congo red staining.

Case 2 of lupus erythematosus disseminatus (no. 447/44) displayed

a similar picture (Fig. 2). Here, too, scattered reticulo-endothelial cells were observed around and between the hyaline rings. With regard to the structure of the periarterial fibrosis of the spleen in lupus erythematosus disseminatus, reference may also be made to the more detailed descriptions in the articles by Klemperer, Pollack, and Baehr and by Kaiser.

b. Periarterial Hyalinosis of the Reticulo-Endothelial System Associated with Allergic Plasma Cell Reaction

In various previous observations (Bing and Plum, Björneboe and Gormsen) a connection between an accumulation of plasma cells and other reticulo-endothelial cells and hyperglobulinemia in different pathologic conditions and immunization has been demonstrated, a fact greatly supporting the supposition that these cells are themselves able to produce globulin. The allergic hyperglobulinosis and hyalinosis (paramyloidosis) described in the preceding article (1948) as occurring in the reticulo-endothelial system and which I have considered as the basis of the alterations dealt with here must, however, be associated with this property of the cells. It now appears that whereas large accumulations of plasma cells do not seem to be of common occurrence in the reticulo-endothelial system in lupus erythematosus disseminatus, a periarterial fibrosis of the spleen and of lymph nodes, completely corresponding to the alterations in lupus erythematosus disseminatus, may be accompanied in other conditions with allergic hyperglobulinosis and hyperglobulinemia by a marked accumulation of plasma cells. In some cases an *allergic plasmacytosis* of this nature may dominate the clinical and the pathologic-anatomic pictures and may in a number of cases give rise to confusion with plasma cell myeloma or aleukemic plasma cell leukemia.

Case 3

The patient was a man, 69 years of age, who previously had been in good health, but was admitted to the hospital because of an affection of the skin resembling psoriasis. It was of 1 year's standing and, after admission, appeared as a typical lupus erythematosus. Otherwise there were no special findings in the objective examination. Sedimentation test: 104, 110, 100 mm.; Takata's test, positive; serum protein, 9 per cent; albumin/globulin, 2.2 per cent/6.8 per cent = 0.32; thrombocytes, 150,000; hemoglobin, 70 per cent; erythrocytes, 3.8 millions; color index, 0.83; leukocytes, 3,000. Differential count: segmented forms, 44 per cent; lymphocytes, 32.5 per cent; monocytes, 20 per cent; eosinophils, 2.5 per cent; basophils, 1 per cent. Urine: 1 plus albumin; Wassermann's test on blood, negative; blood pressure, 140/70 mm. Hg; blood urea, 67 mg. per cent increasing to 331 mg. per cent. Temperature up to 37.6° C. The patient died in uremia.

Post-mortem examination (no. 204/42) revealed, in addition to a right-sided lobar pneumonia and fibrinous pleuritis, alterations of the

kidneys with rough, flat depressions on the surface and irregular narrowing of the tissue border. The consistence was increased; the vessels were gaping. The right kidney was slightly larger than the left.

Histologic examination showed a chronic pyelonephritis and an extremely marked periarterial fibrosis in the spleen (Fig. 3), all follicular and penicillary arteries being surrounded by very broad, concentric, hyaline rings. In contrast with the usual findings in lupus erythematosus disseminatus, extraordinarily well defined plasma cell infiltrates (which stained according to Unna's method) were found around the hyaline rings and between the single lamellae of the latter. When Mallory's staining method was used, red lamellae were observed here and there between the others that had been stained blue. Jürgens' methyl violet stain and Congo red staining for amyloid each gave negative results.

A coincidence of hyperglobulinemia, periarterial fibrosis of the spleen, and marked plasmacytosis in the spleen was thus found in this case. There were no findings in support of a diagnosis of plasma cell myeloma or aleukemic plasma cell leukemia, in which periarterial fibrosis of the spleen is not seen either. Consequently, I considered this case to be one of allergic plasma cell reaction in the reticulo-endothelial system, with hyperglobulinosis and periarterial hyalinosis in the spleen, also with hyperglobulinemia.

The reactions in this case are similar to those of case 1 of *Letterer-Siwe's disease* reported in the preceding article (1948). The findings in that case were simultaneous hyperglobulinemia and hyalinosis (paramyloidosis). The concentric homogeneous rings surrounding the vessels (see Fig. 3) and marked accumulation of plasma cells are also similar.

In conformity with the common features of a number of conditions with stimulation of immune mechanisms, the periarterial fibrosis of the spleen observed in lupus erythematosus disseminatus can be considered morphogenetically parallel in all respects to the alterations found in Boeck's sarcoid, in so-called genuine amyloidosis (and paramyloidosis), and also in experimental amyloidosis after immunization; *i.e.*, it is a morphologic immunity reaction in the reticulo-endothelial system.

Examination of preparations from the case of *Boeck's sarcoid* in which post-mortem examination was made and which was reported in the preceding article (1948) revealed a marked periarterial fibrosis of the spleen (Fig. 4), in many places in close relation to the hyalin (paramyloid) developed around the epithelioid cell granulomata. In this case, too, numerous plasma cells and other reticulo-endothelial cells were observed between the lamellae. The hyaline deposits did

not stain like amyloid with Congo red, but with Mallory's staining method numerous fine and coarser red bands were found in the hyaline tissue that had been stained blue. Another striking feature is the resemblance between the concentric paramyloid rings in the peripheral parts of the granulomata in Boeck's sarcoid (Fig. 4 of the preceding article) in which numerous plasma and reticulum cells were embedded and the hyaline periarterial rings found in lupus erythematosus disseminatus.

Pathology of Lupus Erythematosus Disseminatus

The periarterial hyalinosis referred to here takes a position of its own among the pathologic-anatomic alterations in lupus erythematosus disseminatus, partly owing to its constant localization, partly because of the sclerosing nature of the process. In these respects it is in contrast to the local changes observed in such cases in which there is evolution by stages with total, possibly fibrinoid, allergic necrosis, development of miliary granulomata, and secondary fibrosis (1945, 1946).

Another lesion of frequent occurrence and constant localization in lupus erythematosus disseminatus is the special alteration of the glomerular coils of the kidneys which has been previously characterized as "wire loops" because of the resemblance of the coils to bent wire (Baehr, Klemperer, and Schifrin). This is generally considered the most striking alteration of the kidney in this disorder. According to Klemperer, Pollack, and Baehr (1941, 1942), the coils are irregularly thickened and rigid, and are strongly eosinophilic. The thickening is found between the endothelium and the epithelium, apparently in relation to the basal membrane, resembling amyloid but failing to respond to all staining reactions for amyloid. In other cases, as in my case 1 (1945), there is *focal* fibrinoid necrosis of part of the glomerular coils, the others remaining unaffected. There seems to be no gradual transition between these two forms of alteration.

While the foci of necrosis of the glomerular coils are naturally considered analogous to the other scattered, allergic, in the narrowest sense, lesions, the "wire loop lesion" seems to be essentially different and its nature can probably be explained on the basis of the above-mentioned observations. For, if we grant that in such disorders as lupus erythematosus disseminatus, Boeck's sarcoid and atypical (genuine) amyloidosis there is, at any rate at certain stages, a hyalinosis of the reticuloendothelial system (especially of the spleen), in addition to a stimulation of immune mechanisms with hyperglobulinemia, it seems natural to accept the "wire loop lesion" as a hyalinosis analogous to the deposition of amyloid in the kidneys. Like Loeschcke, we may here reckon

with specific forms of hyalin, of which only the amyloid is open to a histologic characterization. In "paramyloidosis" the amyloid reactions are not constant either.

A relation between the wire loop lesion and the changes in so-called genuine amyloidosis may be illustrated by the following case.

Case 4. Polyarthritis Chronica with Atypical Amyloidosis

The patient was a woman, 63 years of age, who had been admitted several times to Department A of the University Hospital of Copenhagen, service of Professor C. Sonne, for polyarthritis chronica rheumatica. She had never been affected with rheumatic fever, but had had angina tonsillaris several times a year and also recently. The onset of the patient's rheumatic disorder, in 1922, was associated with angina tonsillaris in the course of which she developed pain and swelling of the ankle joints, later spreading to other joints. About 18 months previously, she had had angina, fever, and albuminuria. Since then her condition had varied, but albuminuria had been present constantly. About 1 month before admission she had articular pain with increase of temperature to 39° C., in connection with influenza.

On examination a systolic murmur was found over the entire precordium in addition to swelling and tenderness of the joints. Blood pressure was 140/110 mm. Hg; hemoglobin, about 70 per cent; erythrocytes, 3.60 millions; leukocytes, 7,800; differential count, 61.5 per cent segmented forms, 4 per cent eosinophils, 1.5 per cent basophils, 25 per cent lymphocytes, 8 per cent monocytes. Wassermann test of the blood, negative; complement deviation reaction for gonococcal antibodies, negative.

On her first admission in 1942 the sedimentation test was from 34 to 91 mm. in 15 examinations made at regular intervals. On her second admission (from February 6 to May 1, 1946) it was found to be increasing evenly: Feb. 7, 82; Feb. 11, 91; Feb. 23, 92; March 2, 117; March 9, 107; March 13, 117; April 3, 144; April 13, 154; April 20, 140 mm. At the same time there was increasing *albuminuria* (up to 20 gm. per liter), increasing *blood urea* values (Feb. 7, 23; April 3, 82; April 13, 90 mg. per cent), and increasing *serum globulin* values:

	Total protein *per cent*	Albumin *per cent*	Globulin *per cent*
2/11/46	6.0	3.2	2.8
3/13/46	6.4	2.9	3.5
3/16/46	6.0	2.7	3.3

On her first admission, in 1942, the antistreptolysin titer was found to be increased (200); later it was normal.

Post-mortem examination (no. 212/46) showed pronounced brownish pigmentation of the skin, especially of the parts normally exposed to light. The *liver* was of normal size, with slightly increased consistence and giving a faintly positive amyloid reaction (iodine-potassium iodide). The *spleen* measured 15 by 8 by 4 cm., weighed 280 gm.; the cut surface was firm, elastic, and translucent. The *kidneys* were of normal size, displaying a slight granulation of the surface. The cortex had narrowed, and was pale. Spleen, kidneys, and suprarenal glands gave an intense amyloid reaction. Post-mortem diagnosis: Progressive polyarthritis; amyloidosis, marked in spleen, kidneys, and adrenals,

and mild in liver and small intestines; emaciation; melanoderma; bilateral hydrothorax; Addison's disease due to amyloidosis(?).

Histologic examination. In the periarterial zones to which the fibrosis is localized in lupus erythematosus, the *spleen* displayed homogeneous rings which assumed a purple-red color when stained according to Jürgens' method for amyloid. A similar substance was demonstrated in the intima, and in homogeneous clumps surrounding the vessels. There were numerous plasma cells.

The *kidneys* displayed marked glomerular alterations, with deposits of homogeneous substance between endothelium and epithelium in the coils, not so massive as they are normally seen in amyloidosis, but bearing a close resemblance to the wire loop lesion (Fig. 5). The substance assumed a blue color with Mallory's stain. With Jürgens' method it gave a faintly positive amyloid reaction. Congo red staining was negative. The amyloid and numerous casts in the tubules assumed a red color when stained according to Unna's method. The walls of the arterioles also contained large deposits.

In the course of a comparatively short time this patient presumably developed an atypical amyloidosis simultaneously with a highly increasing sedimentation reaction and an increase of the serum globulin. The spleen contained homogeneous deposits around the follicular arteries, in the kidneys deposits were found bearing a close resemblance to "the wire loop lesion" in lupus erythematosus disseminatus, and numerous homogeneous cylinders were present in the tubules staining in the same manner and presumably representing deposits of a globulin-like substance.

The underlying common immunity reaction was described in the preceding article (1948). Mention may also be made here of Stoeber's description (1934) of cases of allergic conditions combined with so-called genuine amyloidosis, and of Cazal's case of amyloidosis in a 7-year-old girl with "un état d'anaphylactique" as the only etiologic factor. It appears to me to be natural to associate both the splenic periarterial hyalinosis and "the wire loop lesion" in lupus erythematosus disseminatus with the allergic hyperglobulinosis of the reticuloendothelial system after the analogy of the conditions in atypical amyloidosis and paramyloidosis. In this way "the wire loop lesion" of the kidney would have to be considered a *glomerulonephrosis* like glomerular amyloidosis, consisting in the deposition of a globulin product between the endothelium and the epithelium in the capillary coils. Special immunobiologic conditions as well as the time factor must be supposed to be of importance in the development of the alterations and to their degree in the individual cases. It may be mentioned here that in the case of lupus erythematosus disseminatus previously de-

scribed by me (1945), and not displaying any signs of the wire loop lesion but widespread focal allergic lesions with necroses and development of granulomata, the symptom of hyperglobulinemia was lacking.

A distinction presumably should be made between different phases of the disease. A whole series of lesions which are allergic in the narrower sense (Teilum, 1946) are thus pathogenetically related to periarteritis nodosa, arteriolitis granulomatosa allergica, and to some extent resemble allergic reactions in serum sickness and experimental sulfathiazole intoxication described by Rich (1942) and in allergic syndromes of other nature (Bergstrand). In other cases the deposition of coagulable material resembling amyloid is the predominant feature, especially in the spleen and the glomeruli, but presumably also in the walls of the vessels. These last mentioned cases thus display morphogenetic features in common with "genuine" or atypical, and also experimental amyloidosis, and with the conditions with hyperglobulinemia, in particular Boeck's sarcoid, mentioned in the preceding publication. It is possible that we may in certain cases distinguish between an anergic form (positive anergy), in conformity with the conditions found in Boeck's sarcoid, and an allergic form in the narrower sense of the term, with preponderance of necrosis, possibly with cellular resorption and development of granulomata (Teilum, 1946).

Besides the relation already described between lupus erythematosus disseminatus and other allergic conditions (Teilum, 1946), a certain connection with such conditions as scleroderma, purpura haemorrhagica, and dermatomyositis (see Libman) also has been proposed. The connection between hyperglobulinemia, alterations in spleen and kidneys in lupus erythematosus disseminatus, and genuine and experimental amyloidosis seem to elucidate these conditions.

The occurrence of amyloid nodes in the skin has thus been demonstrated in clinical scleroderma (Lubarsch, case 1). In Goetz' case of generalized scleroderma there was thickening of the intima in the blood vessels with "fibrinoid" material and alterations resembling periarteritis nodosa, a "marked thickening and increase of the perivascular connective tissue" being demonstrated in the spleen. In a case clinically resembling Goetz' and described by Jörgensen, dermatomyositis-like alterations were found to be combined with widespread paramyloidosis and increase of plasma cells in the sternal marrow (20 per cent). The simultaneous occurrence of periarteritis nodosa and atypical amyloidosis has been described by Volland, and in "serum" horses with amyloidosis Doerken often found allergic intimal granulomata in the hepatic veins, resembling the granulomata of endophlebitis hepatica.

With regard to purpura hæmorrhagica, reference may be made to

the clinical picture of "purpura hyperglobulinemica" established by Waldenström, but purpura also has been described several times in atypical amyloidosis (*e.g.*, Lubarsch, case 2) in which many plasma cells were found in the spleen. Like hyperglobulinemia, purpura is also a symptom of frequent occurrence in lupus erythematosus disseminatus. Especially in cases of atypical amyloidosis with hyperglobulinemia the accumulation of plasma cells may be very considerable. Such a case which, like my case 3, might easily be considered one of plasma cell leukemia but for that accumulation, will be reported here.

Case 5. Hyperglobulinotic (Paramyloid) Syndrome Caused by Sulfonamides

A man, 58 years of age, was first admitted to Department A of the University Hospital of Copenhagen, service of Dr. C. Sonne, for examination because of albuminuria, ascertained 1 week before. He had no hematuria, hypertension, or immediately preceding infection. No previous renal disorder had been recognized. He had recently been suffering from fatigue and for the past 3 weeks from edema of the legs. Seven months previously he had had right-sided pneumonia with a protracted course in spite of treatment with sulfonamide (100 gm. in all). Pleuritis developed. When admitted for the second time he had constant albuminuria, about 12 gm. per liter. The blood showed a simple anemia. Hemoglobin had decreased from 96 to 55 per cent, and the sedimentation rate was increasing, from 50 to 100 mm. The formol-gel test was negative. There was no Bence-Jones protein in the urine. On Aug. 7, 1944, the total serum protein was 5.16 gm. per cent, with albumin, 2.36 gm. per cent, and globulin, 2.80 gm. per cent; on Dec. 19, 1945, serum protein was 7.5 gm. per cent, albumin, 3.10 gm. per cent, and *globulin, 4.4 gm. per cent.* Blood pressure varied from 90–125/50–90 mm. of Hg. Blood urea determinations were: Oct. 10, 1944, 40 mg. per cent; Dec. 11, 1945, 144 mg. per cent; Dec. 15, 1945, 156 mg. per cent. The patient died in uremia.

Post-mortem examination (no. 481/45) showed a widespread fibrinous pericarditis. The *heart* measured 11 by 11 cm., the weight being 440 gm. The wall of the left ventricle was 17 mm. thick. The myocardium was pale, without any macroscopic signs of fibrosis or myomalacia. Valves and ostia were normal. The *aorta* showed some atheromatosis. There was no ascites. The *stomach* displayed multiple fresh erosions. The *colon* showed no ulcerations. The *liver* measured 24 by 16 by 10 cm.; the surface was smooth and pale, and the cut surface had normal markings. The organ was of normal consistence. The *pancreas* and the *suprarenal glands* were normal. The *spleen* was enlarged, measuring 6 by 9 by 16 cm. Its cut surface was reddish and of a gritty consistence. The *kidneys* measured 3 by 5 by 11 cm., being slightly decreased in size. The surface displayed extensive, irregular, rather coarse depressions. The color was mottled deep red and pale red. On the cut surface the cortex was seen to be narrowed and somewhat spotted, the markings being blurred. The other organs were normal. The central nervous system was not examined.

Histologic examination. The glomerular coils of the *kidneys* displayed large homogeneous masses (Fig. 6) resembling amyloid, in some instances with secondary hyalinization. Similar precipitates were found everywhere in the walls of the small vessels as well as in those of the larger ones, forming thick homogeneous bands of a substance assuming a yellow-brown color when stained according to van Gieson's method. The tubules also contained deposits. Dense plasma cell infiltrates were scattered about and secondary fibrosis had occurred. The amyloid-like substance stained with Jürgens' amyloid stain and with Weigert's fibrin stain, but did not react with Congo red. With Unna's staining method it assumed a deep red color like that of the protoplasm of the plasma cells.

The *spleen* was the seat of diffuse plasma cell infiltration in the pulp. The walls of all vessels contained broad homogeneous bands (Fig. 7) like those of the renal vessels.

The *liver* contained accumulation of plasma cells, partly localized and partly diffusely scattered in the capillaries. The liver cells showed much fatty degeneration, and the vessels contained amyloid deposits which, like those of the other organs, caused a considerable thickening of the walls.

In the *myocardium* the same homogeneous deposits (Fig. 8) were found in the walls of the vessels, but plasma cells were few. There were incipient interstitial fibrosis and some interstitial leukocytic infiltration.

This was therefore a case of paramyloidosis with deposits in the glomeruli and in vessel walls of a number of organs. I have interpreted the alterations in this case as being expressive of a marked positive anergy (plasmacytosis with hyperglobulinosis and atypical amyloidosis). Morphogenetically the paramyloidosis must be considered analogous to the periarterial hyalinosis in case 3 in which there was also an allergic plasmacytosis.

The causal importance of sulfonamides to the paramyloid syndrome in this case (and to the development of allergic hyperglobulinosis in a case later on observed by me) forms a contrast to the well known hypersensitive reactions to sulfonamides. Together they represent reactions of two types which, as described above, form part of the pathology of lupus erythematosus disseminatus.

Summary

Hyperglobulinemia, periarterial fibrosis of the spleen, and the wire loop lesion of the glomeruli in lupus erythematosus disseminatus are all considered to be expressive of a primary allergic hyperglobulinosis in the reticulo-endothelial system, after the analogy of the previously

described (1948) morphologic immunity reaction in atypical and experimental amyloidosis, Boeck's sarcoid, and other conditions.

Periarterial fibrosis of the spleen is thus produced in various conditions with hyperglobulinemia (with or without any demonstrable increase in the number of plasma cells) and displays all transitions to atypical amyloidosis, which, as an underlying cause, also has a stimulation of immune mechanisms with hyperglobulinemia.

Like the periarterial deposits and the collagenic sclerosis (diffuse scleroderma), the characteristic "wire loop lesion" occurring in many cases of lupus erythematosus disseminatus must be looked upon as alterations which are closely related pathogenetically to atypical amyloidosis; whereas focal, and in the narrowest sense allergic, lesions (miliary granulomata in the serosa, nodular necroses, cases of focal allergic pneumonia) are predominant in other cases, or may be present in addition to the lesions first mentioned. From the point of view of immunobiology these two groups of alterations may be considered expressive of a positive anergy and an allergy, respectively.

In some cases also, administration of sulfonamides may give rise to a hyperglobulinotic (paramyloid) syndrome (plasmacytosis, hyperglobulinosis, paramyloidosis in different organs, possibly uremia), in contrast to the well known hypersensitive reactions to sulfonamides.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

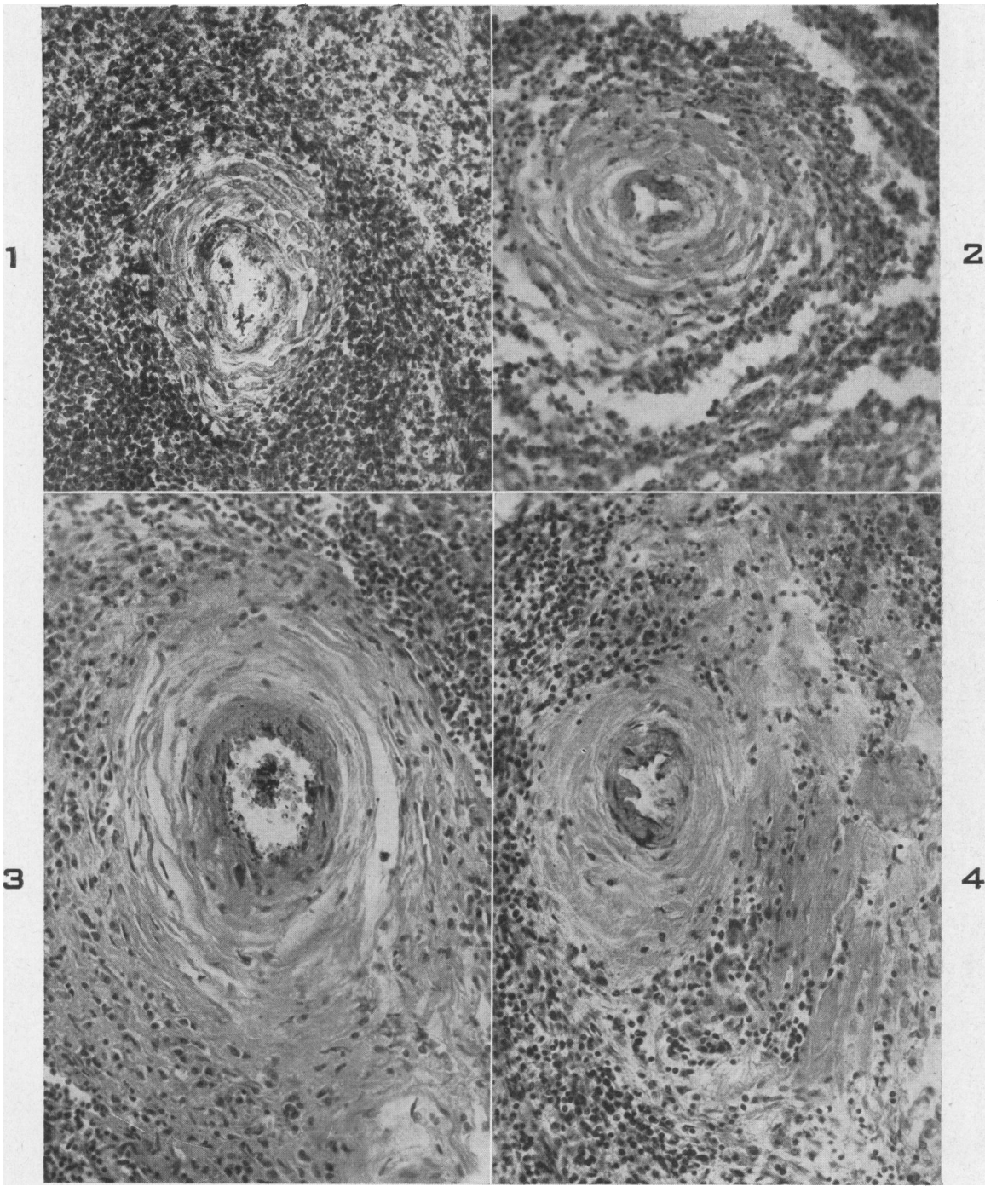
PLATE 80

FIG. 1. Case 1. Periarterial fibrosis of the spleen in lupus erythematosus disseminatus. Concentric lamellar hyaline bands. van Gieson-Hansen's stain. × 220.

FIG. 2. Case 2. Periarterial fibrosis of the spleen in lupus erythematosus disseminatus. Between the rings a few reticulo-endothelial cells are seen. Hematoxylin and eosin stain. × 220.

FIG. 3. Case 3. Periarterial fibrosis of the spleen in allergic plasmacytosis of the reticulo-endothelial system with marked hyperglobulinemia. Marked accumulation of plasma cells in the border zone. Hematoxylin and eosin stain. × 220.

FIG. 4. Periarterial fibrosis of the spleen in Boeck's sarcoid with hyalinosis (paramyloidosis). Epithelioid cell granuloma with peripheral paramyloidosis is seen in the border zone. A number of plasma cells and other reticulo-endothelial cells. van Gieson-Hansen's stain. × 220.



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Periarterial Fibrosis in Disseminated Lupus

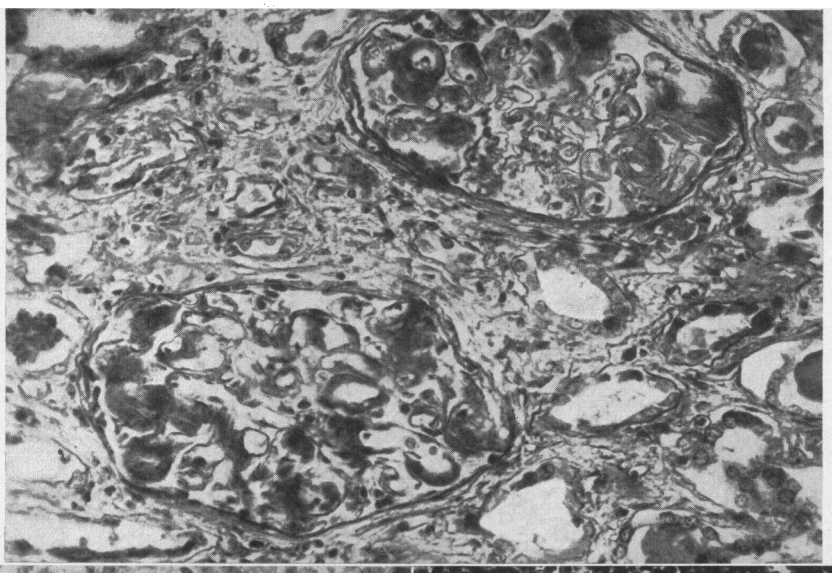
PLATE 81

FIG. 5. Case 4. Glomerular lesions of chronic polyarthritis with atypical amyloidosis and hyperglobulinemia, for comparison with the wire loop lesion in lupus erythematosus disseminatus. Mallory's stain. × 270.

FIG. 6. Case 5. Glomerular lesions in allergic plasmacytosis with paramyloidosis and hyperglobulinemia, for comparison with the wire loop lesion in lupus erythematosus disseminatus. Hematoxylin and eosin stain. × 310.

FIG. 7. Case 5. Paramyloid deposits in the splenic vessels. van Gieson-Hansen's stain. × 220.

FIG. 8. Case 5. Paramyloid deposits in the vascular walls of the myocardium. Hematoxylin and eosin stain. × 120.



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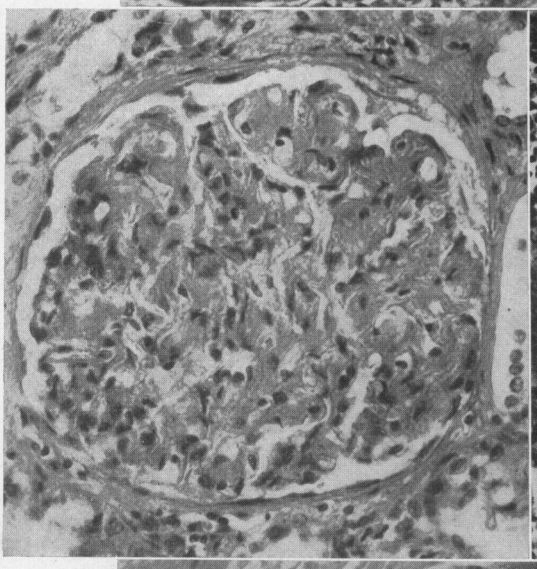

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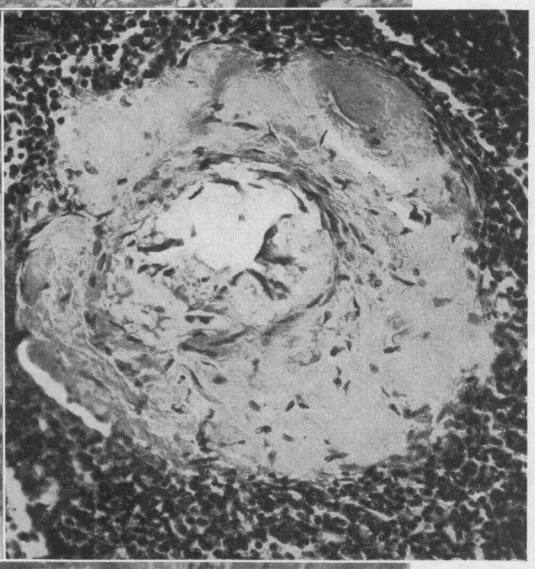

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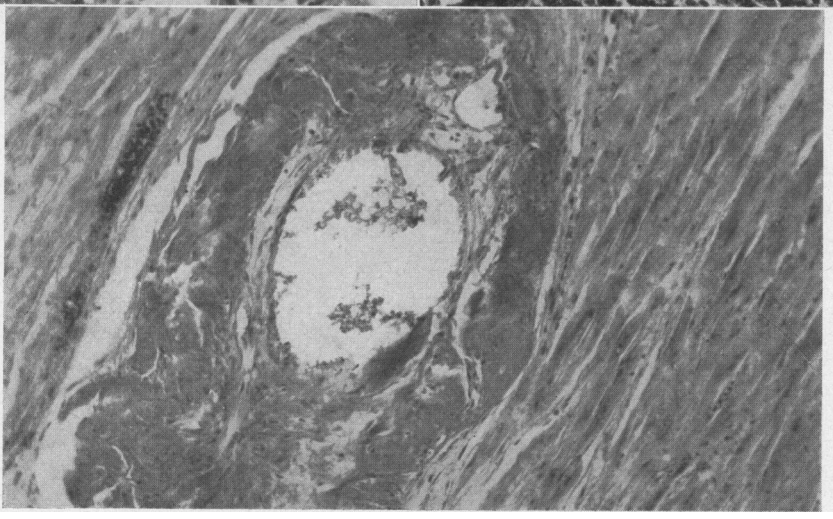

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