ALLERGIC HYPERGLOBULINOSIS AND HYALINOSIS (PARAMYLOIDOSIS) IN THE RETICULO-ENDOTHELIAL SYSTEM IN BOECK'S SARCOID AND OTHER CONDITIONS

A Morphologic Immunity Reaction *

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Numerous investigations have shown a close relation between plasma cells and the pathologic globulins included in the gamma-globulin fraction and consisting chiefly of antibodies against different agents of the nature of antigens (Ranström). It may be stated here briefly that as early as 1913 Hübschmann made the supposition that plasma cells are able to produce antibodies; also, that Bing and Plum (1937) first emphasized the regular occurrence of plasma cells and other reticulo-endothelial cells in and outside the bone marrow in disorders associated with hyperglobulinemia, concluding that plasma cells are able to produce globulin themselves as has also been supposed more recently by a number of investigators.

A parallelism between hyperglobulinemia and accumulation of plasma cells in different organs, in particular in the spleen, has been demonstrated by investigations carried out by Björneboe and Gormsen (1943) on immunization of rabbits by means of polyvalent pneumococcal vaccine. These authors did not find an increase in plasma cells in hyperglobulinemia caused by injection of globulin. That hyperglobulinemia and increase of plasma cells should both be produced by the same cause, but should not otherwise be associated with one another, must be considered improbable after the demonstration by Bing, Fagraeus, and Thorell of the abundant content in the protoplasm of the plasma cell of ribose nucleotide. This substance is considered characteristic of the formation of proteins in cells, presumably giving rise to the basophilia of the cells and to their characteristic staining according to Unna's method. It has been supposed by Magnus-Levy and numerous other investigators that plasma cells in plasma cell myeloma produce the proteinic substances giving rise to hyperglobulinemia in myelomatosis.

In respect to many infections by well known bacterial agents, associated with hyperglobulinemia, it has been well established that the globulin is identical with antibody. It also has been possible during

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recent years to demonstrate hyperglobulinemia as a frequent and characteristic symptom in pathologic conditions of a more obscure nature. This applies to Boeck's sarcoid and to lupus erythematosus disseminatus. The cause of the hyperglobulinemia, its nature, and its relation to morphologic reactions have been unknown in these conditions. R. A. Moore in 1944 (page 545) stated that: "An unexplained increase of plasma globulin to 3 to 6 gm. per 100 cc. is a useful diagnostic sign" (in Boeck's sarcoid), and A. F. Coburn and D. H. Moore, in 1943 (page 213), said that "Hypergammaglobulinemia of unknown cause is a constant characteristic of disseminated lupus erythematosus."

In comparative pathologic-anatomic studies of Boeck's sarcoid, lupus erythematosus disseminatus, and other conditions, I have demonstrated, as a common feature in such disorders of different causation, a coincidence of hyperglobulinemia, paramyloidosis, or hyalinosis in the reticulo-endothelial system which is often decisive as a morphologic specific character, and is sometimes found in direct relation to an accumulation of plasma cells. In the fresh stages, precipitates of a homogeneous paramyloid substance are found, displaying transitional forms to hyaline deposits, frequently arranged in periarterial rings in the lymph nodes and the spleen. According to my observations, these changes must be considered phases of *an elementary morphologic immunity reaction with an underlying allergic hyperglobulinosis in the reticulo-endothelial system* .

The relation between these reactions in lupus erythematosus disseminatus will be described in a separate paper, while the findings in Boeck's sarcoid in particular will be discussed here. The elementary reactions, however, will be described first on the basis of a case of Letterer-Siwe's disease.

Case 1

Letterer-Siwe's Disease with Hyperglobulinemia, Paramyloidosis, and Accumulation of Plasma Cells in the Reticulo-Endothelial System

A boy, 9 years of age, was admitted to the Pediatric Ward of the University Hospital of Copenhagen (service of Dr. P. Plum) on May 6, 1946. He had had morbilli, pertussis, varicella, and rubeola. Following vaccination against smallpox at 2½ years of age, attacks of fever developed, with a rise of temperature to 41° C. of a few days' duration, the temperature then becoming normal; after a few months there was a constant increase of temperature, being normal in the morning but 38° to 39° C. in the evening. When he was 3 years old his mother observed a swelling of his right cheek and also swollen lymphatic nodes on the right side of his neck; he was found to be anemic at the same time (40 per cent hemoglobin). Since that time he had been constantly febrile, with a poor appetite and in bed for certain periods. The swelling of his cheek and of the lymphatic nodes persisted but varied much in size. In October, 1945, he had been admitted for 5 months to "Kronprinsesse Louises Barnsjukhus" in Stockholm, where a histologic examination of the enlarged lymphatic node from the angle of the jaw

gave a picture which most resembled that which is seen in eosinophilic granuloma of the bones or Letterer-Siwe's disease. Moreover, the serum albumin was found to be 1.92 per cent (the normal being 3 to 5 per cent); globulin, 6.26 per cent (the normal being 1.5 to 3 per cent); total protein, 8.18 per cent (the normal being 6.5 to 7.7 per cent); albumin/globulin ratio, 0.3 (normal, 1.5 to 2).

On examination in the Pediatric Ward of the University Hospital in Copenhagen the patient's face was found to be highly asymmetric, with considerable lateral swelling of the right cheek corresponding to the zygomatic bone. The infiltration was firm, not tender, measuring about 5 cm. in the vertical direction. Below the edge of the jaw there were lymphatic nodes. The skin showed nothing abnormal. The liver and spleen could not be palpated.

Roentgenograms of the skull showed considerable swelling of the soft parts on the right and a corresponding defect of the zygomatic arch posteriorly. There were no other alterations. The thorax, the extremities, and the pelvis displayed no abnormal signs roentgenologically. The sedimentation rate varied from 33 to 123 mm., being most frequently about 50; hemoglobin, about 60 per cent; leukocytes, 11,600 to 21,000; differential count, normal; eosinophils, 1 to 2 per cent; thrombocytes, 515,000. The Mantoux (Mendel) test was negative. No abnormal constituents were found in the urine. Total cholesterol was 175 mg. per cent; serum albumin, 3.78 mg. per cent; serum globulin, 5.11 mg. per cent; total protein, 8.89 mg. per cent.

During his stay in the hospital the patient was subfebrile for certain periods. He was discharged on June 30, 1946.

Histologic Examination

Histologic examination was based on the lymph node that had been excised in Stockholm and on subsequent biopsies of a lymph node of the neck and of the tumescence on the right cheek.

In a rather well defined area in the central part of a lymph node there was an accumulation of large, pale reticulum cells with abundant cytoplasm (Fig. 1), resembling the epithelioid cells of the granulomata in Boeck's sarcoid, but without tuberculoid structure. Especially in the peripheral parts of this area were found wide, very coarse bands of a homogeneous, partially hyaline substance, surrounded by a wide border of plasma cells which also passed in dense swarms between the individual bands (Fig. 2). As already mentioned, the latter were partially hyalinized, but in other parts they were of the nature of paramyloid and did not assume a blue but a red-violet color when stained according to Mallory's method. In the more peripheral parts of the lymph node there were finer trabecular and reticular homogeneous deposits in direct relation to plasma cells and reticulum cells. The vessels also contained a precipitate of homogeneous substance in many instances, the larger and smaller vessels being surrounded by concentric homogeneous rings (Fig. 3, for comparison with the alterations in the spleen in lupus erythematosus disseminatus), between which a few plasma cells and other reticulo-endothelial cells were observed.

There were no foam cells, nor giant cells. Microscopic examination of tissue of the tumescence in the right zygomatic region showed a

uniform structure with diffuse reticulum cell proliferation with close-set cells, not especially rich in protoplasm. Reticulin staining was positive; sudan staining, negative. No necrosis, eosinophilia, foam cells, or giant cells were found.

Histologic Diagnosis. Letterer-Siwe's disease.

Summary of Case 1

Letterer-Siwe's disease with a protracted course in a 9-year-old boy began with attacks of fever following vaccination against smallpox when the boy was 2½ years old. Microscopic examination of tissue from a focus in the zygomatic region showed diffuse reticulosis, while in the enlarged lymph nodes a large central accumulation of large, pale reticulum cells, rich in protoplasm, was found. The reticulum cells resembled the epithelioid cells in the granulomata in Boeck's sarcoid, circumscribed in the peripheral parts by coarse bands of homogeneous substance, in some parts hyaline, in others of the nature of atypical amyloid and surrounded by dense swarms of plasma cells. In addition, homogeneous precipitates were found around the vessels in the form of concentric homogeneous rings resembling the periarterial alterations in the spleen in lupus erythematosus disseminatus. There was also a marked hyperglobulinemia.

On close examination of the morphologic lesions in *Boeck's sarcoid,* all of the reactions described above can be found. However, while in the case of Letterer-Siwe's disease described here they reflect only the immunity conditions in this particular case, the analogous reactions in Boeck's sarcoid form the basis of the morphologic characteristics of this disease, illustrating the different phases of their development and explaining the nature of the hyperglobulinemia.

It has been established that cases of Boeck's sarcoid generally display an increase of the serum globulin. Salvesen (1935) first drew attention to this fact. He found an increase of the total protein content in the blood in 3 cases of Boeck's sarcoid owing to an increase of the globulin fraction with an albumin/globulin ratio of 0.86 to 0.51. Harrell and Fisher (1939) and Harrell (1940) found the total proteins to be over 8 gm. per cent in all but 3 of 11 cases which they studied, and the albumin/globulin ratio was reversed in all 8 cases during the active stage. Normal values were found in one of these after recovery. Bing (1940) found an increase of the serum globulin in 2 of 4 cases of Boeck's sarcoid. Fisher and Davis (1942) presented electrophoretic patterns for the sera of 12 cases of sarcoid, all of which had been proved by biopsy. In 4 cases which showed no clinical signs of activity

the sera were almost normal, there being only a slight decrease of albumin and increase of alpha globulin. Those with active lesions were found to have a marked elevation of the gamma globulin at the expense of the albumin, frequently with moderate hyperproteinemia. This electrophoretic pattern was similar to that which has been observed in association with the formation of antibodies in response to an infectious agent.

The morphogenesis and the phasic development of the characteristic lesions occurring in Boeck's sarcoid will be considered more fully in connection with the following case, partly on the basis of findings in post-mortem material and partly on the alterations of common occurrence in material taken for biopsy.

CASE 2

Boeck's Sarcoid with Marked Paramyloidosis

A woman, 28 years of age, was admitted to Medical Ward B of the University Hospital in Copenhagen (service of Dr. E. Warburg) on December 7, 1944. Her brother had died of pulmonary tuberculosis 9 years previously. The patient previously had been in good health. She was taken ill 1 year before admission with fatigue, loss of weight (15 kg.), functional dyspnea, and perspiration. She had not felt febrile and had had no pain in her side.

Examination. The patient was pale and lean. She had dyspnea when resting. Her tonsils were small. There was no glandular swelling in her neck, but one small gland was found in her left axilla and small glands were found in both inguinal regions. The thyroid gland was not enlarged. Upon examination of the heart, the apex impulse was felt in the fifth intercostal space inside the midclavicular line; there was no murmur; the 2nd pulmonal tone was extremely accentuated. Fine moist râles and crepitation were heard almost everywhere.

Roentgenologic examination of the lungs disclosed a large cavern in the left apex, passing through almost the entire depth of the lung. Below this there were a number of smaller caverns surrounded by fibrous adhesions. In the right lung also a large cavern was observed in the apex. On the whole, the lung was heavily infiltrated.

The temperature varied from 38° to 39° C. Hemoglobin was 95 per cent; sedimentation rate, 27; erythrocytes, 4.87 millions; leukocytes, 6,120; blood pressure, 90/40 mm. Hg. Urine: no albumin. Wassermann test of the blood, negative. No tubercle bacilli were found in repeated examinations of sputum. Direct microscopy and cultivation disclosed no tubercle bacilli. The Mantoux (Mendel) test was negative (all strengths, in repeated examinations).

On December 8 the serum protein was 7.1 per cent. Fractional determination of protein was not made.

On December 14, biopsy of the tonsil showed a tuberculoid structure (Boeck's sarcoid ?). On December 19, biopsy of an inguinal gland showed a tuberculoid structure as in Boeck's sarcoid. The patient died on January 3, 1945.

Post-mortem Examination

Post-mortem examination showed the *bone marrow* of the vertebral column to be macroscopically unaltered. There were no alterations of

the *skin*. The *tonsils* were not enlarged and their cut surface was uniform. No ulcerations of the *larynx* or of the *trachea* was found.

The *pleurae* displayed extensive fibrous adhesions.

In the apex of the *right lung* a cavern was seen, measuring 3 to 4 cm. in diameter. Its walls were discolored, with irregular trabeculae and cords. The pulmonary tissue below was of nodular consistence and grayish red. The *left lung* also displayed a large cavern superiorly, measuring 6 cm. in diameter, with firm solidified areas in the walls. No miliary tubercles or peribronchitis were seen. The *bronchial glands* showed a large conglomeration of firm, only partially necrotic lymph nodes of a grayish red color, measuring 4 cm. in diameter.

The *heart* presented some hypertrophy of the right ventricle. Otherwise the myocardium was without alteration. The *lymph nodes* around the aorta formed large conglomerations of a firm consistence, having a pale grayish red cut surface. No necrotic areas were seen.

The surface of the *liver* was smooth; it was not enlarged and the cut surface was unaltered. The *suprarenal glands* showed no signs of tuberculosis. The *spleen* was enlarged, measuring 6 by 10 by 16 cm., with a dry cut surface and no tubercles. Its consistence was not so firm as in amyloidosis. The *ovaries and tubes* showed no signs of tuberculosis. The *brain* and *kidneys* were normal.

A *bacteriologic examination* was made (at the State Serum Institute) of a necrotic gland and the cavernous tissue of the right lung, of other tissue of the right lung, the spleen and a lymph node from the hilus. By this examination (comprising cultivation and inoculation into guinea-pigs) no signs of tuberculosis were demonstrated.

Histologic Examination

The *spleen* was permeated, as were the *lymph nodes,* by masses of typical epithelioid cells displaying a tuberculoid structure which was well defined. In most areas giant cells were few or absent. The picture was characteristic of Boeck's sarcoid. A very extensive hyalinosis (paramyloidosis) was especially remarkable, however, being localized partly to the peripheral parts of the epithelioid-cell granulomas, in which broad, homogeneous, concentric rings, often two to four, were found (Fig. 4), and partly to certain diffuse areas in the tissue (Fig. 5). The hyaline substance extended from the periphery into the individual granulomas, which were thus in many parts wholly replaced by hyaline masses. Around these more or less transformed cell accumulations, isolated homogeneous bands and clumps were found (Fig. 6), representing a more advanced phase of hyaline or paramyloid develop-

ment from the homogeneous "extragranulomatous precipitates" outside the tuberculoid structure, which in my remaining material of Boeck's sarcoid was a characteristic finding (Fig. 8).

In their central parts the tuberculoid structures contained typical double-contoured and stratified, often calcified corpuscles, described by Schaumann, among others, as being present in tonsils and lymphatic nodes in Boeck's sarcoid. A strikingly great number of plasma cells, in addition to other reticulo-endothelial cells, were found around the epithelioid cells. There was no necrosis, but in the central parts of the granulomas a precipitate of a homogeneous substance without cellular structure was observed in several spots. In the parts of the *spleen* in which the lesions were less extensive, the follicular arteries were found to be surrounded by broad rings of a hyaline substance resembling the typical lesions in lupus erythematosus disseminatus. In the peripheral parts of these rings granulomata often were found, surrounded by hyaline bands displaying a direct continuity with the periarterial rings. The concentric rings in the transformed granulomata also bore a close resemblance to the periarterial lamellae. Staining according to Mallory's method gave very fine pictures with rings of an intense blue from which a blue network passed between the intensely red epithelioid cells and into the reticulum tissue. Just as in case 1 of Letterer-Siwe's disease, red lamellae were found scattered among the blue bands of hyaline substance, such lamellae also being conspicuous in the deep part of the splenic capsule which displayed a high degree of hyaline thickening.

Jürgens' methyl violet reaction for amyloid and Congo red staining were negative.

Tubercle bacilli could not be demonstrated.

The *lymph nodes* also displayed typical Boeck granulomata with marked hyalinosis (paramyloidosis). Here, too, concentric homogeneous rings could be demonstrated around the smaller vessels (Fig. 7), reminiscent of the periarterial lesions in the spleen in lupus erythematosus disseminatus and of the alterations in a lymph node in case 1 of Letterer-Siwe's disease with hyperglobulinemia.

The *liver* contained scattered typical granulomata with a few giant cells. No necrosis was present.

The *lungs* displayed a highly variegated picture with well defined epithelioid cell granulomata surrounded by lymphocytes and in most instances by a hyalinized tissue, in some parts passing on to large structureless masses containing epithelioid cells and giant cells, a number of which resembled Langhans' cells. Others resembled regular

giant cells of foreign body type, frequently containing the stratified, often calcified, corpuscles referred to in the description of the spleen, which were stained a deep blue by hematoxylin and eosin. Some of the granulomata resembled those of Boeck, while others could not be distinguished with certainty from tuberculosis. In the walls of the cavern an even transition from a peculiar homogeneous necrosis to hyalinosis was observed. No tubercle bacilli were found on microscopic examination. Sudan staining showed no lipoid content in the granulomata.

The kidneys, suprarenal glands, thyroid gland, intestines, appendix, and the pituitary gland displayed no alterations, especially no tuberculoid structure.

Summary of Case 2

Case 2 thus was noteworthy especially for the following reasons:

1. The combination of marked changes, like those seen in Boeck's disease (sarcoidosis), in the spleen, lymph nodes and lungs, with alterations in the lungs which, as far as the clinical features and the macroscopic picture are concerned, bore a close resemblance to tuberculosis (caverns), but without any tubercle bacilli being found on cultivation or microscopic examination, the tuberculin reactions also being negative. These findings may be made to correspond perfectly well with the prevailing Scandinavian view of Boeck's sarcoid as a form of tuberculosis with a high immunity (positive anergy, discussed later).

2. The combination of typical Boeck granulomata with paramyloidosis (hyalinosis), especially in the spleen, in which, in this connection, the close relation between the hyalinized border zone of the granulomata and the periarterial hyalinosis was noted in particular. This must be considered identical with the findings described above in Letterer-Siwe's disease with hyperglobulinemia, and with the lesions occurring in atypical and experimental amyloidosis, and in lupus erythematosus disseminatus.

Discussion

The paramyloidosis in Boeck's sarcoid must be considered a definite phase of the development of the lesions, with an allergic hyperglobulinosis in the reticulo-endothelial system as the underlying primary cause. The paramyloid phase and the hyperglobulinemia in Boeck's sarcoid as well as in the other conditions mentioned must be considered an elementary immunity reaction in the reticulo-endothelial system.

In preparations from a number of other cases of Boeck's sarcoid, chiefly from lymph nodes, tonsils, and skin, I found good conformity with the view advanced here concerning the nature and phasic develop-

ment of the Boeck lesions, the morphologic structure of the lesions on the whole showing that a gradual development takes place from precipitate (Figs. 8, 9, and 10) to hyalinosis. The following features may be stressed in this connection:

1. Granulomata with large, pale epithelioid cells with *complete absence of necrosis;*

2. Outside the actual tuberculoid structure, precipitates of a homogeneous substance (*i.e., extragranulomatous precipitates*) of the same nature as that observed in the granulomata, staining in the same manner and forming homogeneous bands or clumps between the typical granulomata (Fig. 8);

3. A central homogeneous area in the granuloma, which is sometimes interpreted as slight or early necrosis, represents a similar precipitate, corresponding alterations also being observed in some instances in the walls of the vessels;

4. Preparations from cases of Boeck's sarcoid in the different phases of the disease show all transitions, from the precipitation of homogeneous eosinophilic substance (Figs. 8, 9, and 10) to marked *paramyloidosis* as in case 2, with broad concentric hyaline rings beginning peripherally in the individual granulomata (Fig. 4), which are gradually replaced by clumps of hyaline tissue (Fig. 6);

5. In most cases plasma cells in strikingly great numbers are found in direct relation to these paramyloid rings;

6. A marked periarterial hyalinosis in the *spleen* was localized to the follicular and the penicillary arteries, resembling the alterations in the spleen in lupus erythematosus disseminatus which will be dealt with in a subsequent publication.

Considering lastly the conformity with the findings in case 1 of Letterer-Siwe's disease (large, pale epithelioid cells without any necrosis; depositing of paramyloid beginning in the peripheral parts and in relation to the accumulation of plasma cells; extensive homogeneous and paramyloid deposits independent of the granulomata and giving the same staining reactions as the latter; vascular rings and hyperglobulinemia, which is a characteristic symptom in Boeck's sarcoid), I consider it highly probable that *the morphologic lesions in Boeck's sarcoid represent a serologic hyaline (paramyloid) precipitation, having as its starting point a globulin-precipitate, especially in the reticuloendothelial system.*

In a number of preparations from different cases of Boeck's sarcoid stained according to Unna's method, the epithelioid cell granulomata and homogeneous precipitates during the active stage assumed a deep

red color, in contrast with the granulomata in tuberculosis. This must be considered as a further support of the view that a hyperglobulinosis is present.

The combination of Boeck's sarcoid and paramyloidosis, so conspicuous in case 2, requires special comment. This is not, as in tuberculosis with amyloidosis, a special complication but *a phasic development of the typical morphologic lesions* characteristic of Boeck's sarcoid. It now appears that the reactions described in Boeck's sarcoid and in case 1 of Letterer-Siwe's disease, like the increase of globulin in these conditions, are quite similar to the reactions previously demonstrated in "experimental amyloidosis" after immunization, so that the view of Boeck's sarcoid advanced above as an immunity reaction in which a *hyperglobulinosis* in the reticulo-endothelial system forms the basis of the morphologic lesions (reticulosis ending in paramyloidosis) as well as of the hyperglobulinemia, can easily be made to correspond with previous findings in such immunization experiments.

Hass, Huntington, and Krumdieck, in 1943, stressed that: "It seems, therefore, that persistent or repeated stimulation of immune mechanisms is a fundamental factor in the genesis of amyloid disease." The only exception stated is the type seen in plasma cell myeloma.

Loeschcke (1927) carried out sensitization experiments in rats with a 5 per cent solution of casein sodium and, soon after the first intraperitoneal injection, found a considerable increase in the volume of the spleen, with enlarged reticulum cells which were constantly increasing in number. He presumed that antigen-antibody reacted with one another, with the formation of an insoluble precipitate. All that is termed hyalin was said by him to be the morphologic expression of such antigen-antibody fixation, whereas amyloid was perceived as a special case of the serologic precipitation of hyalin, which is present primarily only at the place of formation of the antibody, *i.e.*, in the reticulo-endothelial system. Just as the specificity of the formation of antibody against different proteins is stressed, we must, according to Loeschcke, recognize specific forms of hyalin, of which, however, only amyloidosis is open to a histologic characterization. Still, it also applies in part to the atypical amyloidosis (paramyloidosis) described here and also to the depositing of amyloid in plasma cell myeloma, termed paraproteinosis (Apitz).

As early as 1926 Letterer pointed out hyperglobulinosis, *i.e.*, the increased liberation of globulin from the cells to the tissue sap and to the blood, as the primary basis of amyloidosis (*i.e.*, experimental amyloidosis), stating that it may be caused both by the known fundamental disorders and by protein therapy, and also emphasizing the

absolute, or at least relative, increase of serum globulin in such conditions. Lastly, mention may be made of the atypical amyloidosis in serum horses described by Arndt, and others, in which "the reticulo-endothelial cell reaction" seems to be of constant occurrence. Reticulo-endothelial reactions were present at all stages, when the animal had been immunized once, while amyloidosis occurred only when the animal had been used for the production of serum for 8 months at the earliest, and was fairly constant after 16 months. According to Arndt, such reticulo-endothelial alterations may appear as a precursory stage of amyloidosis, having in the spleen a typical *perinodular* localization in the splenic follicles; the serum horse also frequently displays very marked hyperglobulinemia.

With regard to pathogenesis, structure, phasic development (reticulum cell proliferation and precipitation), localization, and alterations in the blood, the points of resemblance between such forms of experimentally produced atypical amyloidosis and the findings in Boeck's sarcoid, as described here, are so striking that we have to reckon with completely parallel processes. The morphogenetic interpretation of the alterations in Boeck's sarcoid given above tells us nothing about the etiology of the disease; it may, however, easily be made to agree with the prevailing view of tuberculosis and Boeck's sarcoid as two phases of the same disease, supported as this view is by a number of publications (Lemming, Kallós, and Warfvinge, and others).

As has been pointed out by Hellerström, a special form of anergy is present in Boeck's sarcoid in all cases, which is fundamentally different from the anergy found in the organism that is not infected by tubercle bacilli. This type of reaction (of positive anergy) is doubtless the outcome of an especially high degree of immunity; "the organism tackles the tuberculin so rapidly that no reaction, or only a faint one, appears" (J. Jadassohn).

That the morphologic reactions dealt with here must be considered allergic immunity reactions is also illustrated by the unquestionable etiologic importance of the vaccination against smallpox in the case of Letterer-Siwe's disease reported as case 1. Also, in a case of typical, histologically verified Boeck's sarcoid, described by Lemming, in which the tuberculin reaction was negative, Boeck's sarcoid developed in the skin at the site of intradermic injection of B.C.G. vaccine, Mendel's reaction remaining negative after the injection.

While the described morphologic immunity reaction (hyperglobulinosis, paramyloidosis) in Boeck's sarcoid constitutes an essential part of the morphologic characteristics of that disease, similar reactions must also be supposed to play an important rôle in a number of other

disorders. This applies to lupus erythematosus disseminatus, which will be dealt with in the article that follows, and also to syphilis, lymphogranuloma inguinale (and certain cases of tuberculosis), in which specific "necroses" and hyalinosis, often in relation to plasma cell accumulation, are of frequent occurrence, hyperglobulinemia having been demonstrated also in such cases (Bing).

In these and in other special disorders associated with hyperglobulinemia, reactions analogous to atypical (and experimental) amyloidosis must henceforward be considered decisive for the morphologic specific pattern.

Summary

As a feature common to Boeck's sarcoid and a number of other pathologic conditions associated with hyperglobulinemia, the reticulo-endothelial system is found to contain precipitates of a homogeneous substance passing on to hyalinosis (paramyloidosis). The alterations with regard to pathogenesis, structure, and phasic development (proliferation of reticulum cells and precipitation), localization, and alterations of the blood (hyperglobulinemia) must be considered analogous to atypical and experimental amyloidosis. The common primary basis is supposed to be an allergic hyperglobulinosis in the reticulo-endothelial system, determined by persistent or repeated stimulation of immune mechanisms.

In Boeck's sarcoid the following points, among others, are thus explained:

1. The localization in the reticulo-endothelial system.

2. The morphologic features (epithelioid-cell granulomata without any tendency to necrosis; the occurrence of "extragranulomatous" precipitates; the paramyloid phase with frequently concentric, hyaline rings in the border zone; the development of a periarterial hyaline zone in the spleen and in other organs, analogous to the periarterial fibrosis of the spleen in lupus erythematosus disseminatus).

3. The occurrence of hyperglobulinemia, which is a useful diagnostic sign in Boeck's sarcoid.

4. The state of immunity, in accordance with the generally accepted view of Boeck's sarcoid as a condition with a high immunity (positive anergy).

Like the different antibodies, various forms of hyalin and paramyloid must also, after these findings, be considered products of plasma cells and other reticulo-endothelial cells.

BIBLIOGRAPHY

Apitz, K. Die Paraproteinosen. *Virchows Arch. f. path. Anat.*, 1940, **306**, 631–699.

Arndt, H. J. Retikuloendothel und Amyloid. *Verhandl. d. deutsch. path. Gesellsch.*, 1931, **26**, 243–250.

Bing, J. Further investigations on hyperglobulinemia. *Acta med. Scandinav.*, 1940, **103**, 547–583.

Bing, J., Fagræus, A., and Thorell, B. Studies on nucleic acid metabolism in plasma cells. *Acta physiol. Scandinav.*, 1945, **10**, 282–294.

Bing, J., and Plum, P. Serum proteins in leucopenia. (Contribution on the question about the place of formation of the serum proteins.) *Acta med. Scandinav.*, 1937, **92**, 415–428.

Björneboe, M., and Gormsen, H. Experimental studies on the rôle of plasma cells as antibody producers. *Acta path. et microbiol. Scandinav.*, 1943, **20**, 649–692.

Coburn, A. F., and Moore, D. H. The plasma proteins in disseminated lupus erythematosus. *Bull. Johns Hopkins Hosp.*, 1943, **73**, 196–220.

Fisher, A. M., and Davis, B. D. The serum proteins in sarcoid: electrophoretic studies. *Bull. Johns Hopkins Hosp.*, 1942, **71**, 364–374.

Harrell, G. T. Generalized sarcoidosis of Boeck; clinical review of 11 cases, with studies of blood and etiologic factors. *Arch. Int. Med.*, 1940, **65**, 1003–1034.

Harrell, G. T., and Fisher, S. Blood chemical changes in Boeck's sarcoid with particular reference to protein, calcium and phosphatase values. *J. Clin. Investigation*, 1939, **18**, 687–693.

Hass, G. M., Huntington, R., and Krumdieck, N. Amyloid. III. The properties of amyloid deposits occurring in several species under diverse conditions. *Arch. Path.*, 1943, **35**, 226–241.

Hellerström, S. Dermatologiska synpunkter pa betydelsen av negativ tuberkulinreaktion. *Nord. med.*, 1942, **15**, 2567–2570.

Hübschmann, P. Das Verhalten der Plasmazellen in der Milz bei infektiösen Prozessen. *Verhandl. d. deutsch. path. Gesellsch.*, 1913, **16**, 110–115.

Jadassohn, J. Cited by Hellerström.

Kallós, P. Beiträge zur Immunbiologie der Tuberkulose. Monographie. Stockholm, 1941.

Lemming, R. Development of Boeck's sarcoid at the place on the skin where a BCG vaccination had been made in a case of Schaumann's disease. *Acta med. Scandinav.*, 1942, **110**, 151–160.

Letterer, E. Studien über Art und Entstehung des Amyloids. *Beitr. z. path. Anat. u. z. allg. Path.*, 1926, **75**, 486–588.

Loeschcke, H. Vorstellungen über das Wesen von Hyalin und Amyloid auf Grund von serologischen Versuchen. *Beitr. z. path. Anat. u. z. allg. Path.*, 1927, **77**, 231–239.

Magnus-Levy, A. Multiple Myelome. *Acta med. Scandinav.*, 1938, **95**, 217–280.

Moore, R. A. A Textbook of Pathology. W. B. Saunders Co., Philadelphia & London, 1944, p. 545.

Ranström, S. On the term "essential hyperglobulinemia" and "premyeloma." *Acta med. Scandinav.*, 1946, **124**, 134–147.

Salvesen, H. A. The sarcoid of Boeck, a disease of importance to internal medicine. *Acta med. Scandinav.*, 1935, **86**, 127–151.

Warfvinge, L. E. Boeck's sarcoid, experimentally produced by virulent, human tubercle bacilli in a case of Schaumann's disease. *Acta med. Scandinav.*, 1943, **114**, 259–270.

[*Illustrations follow*]

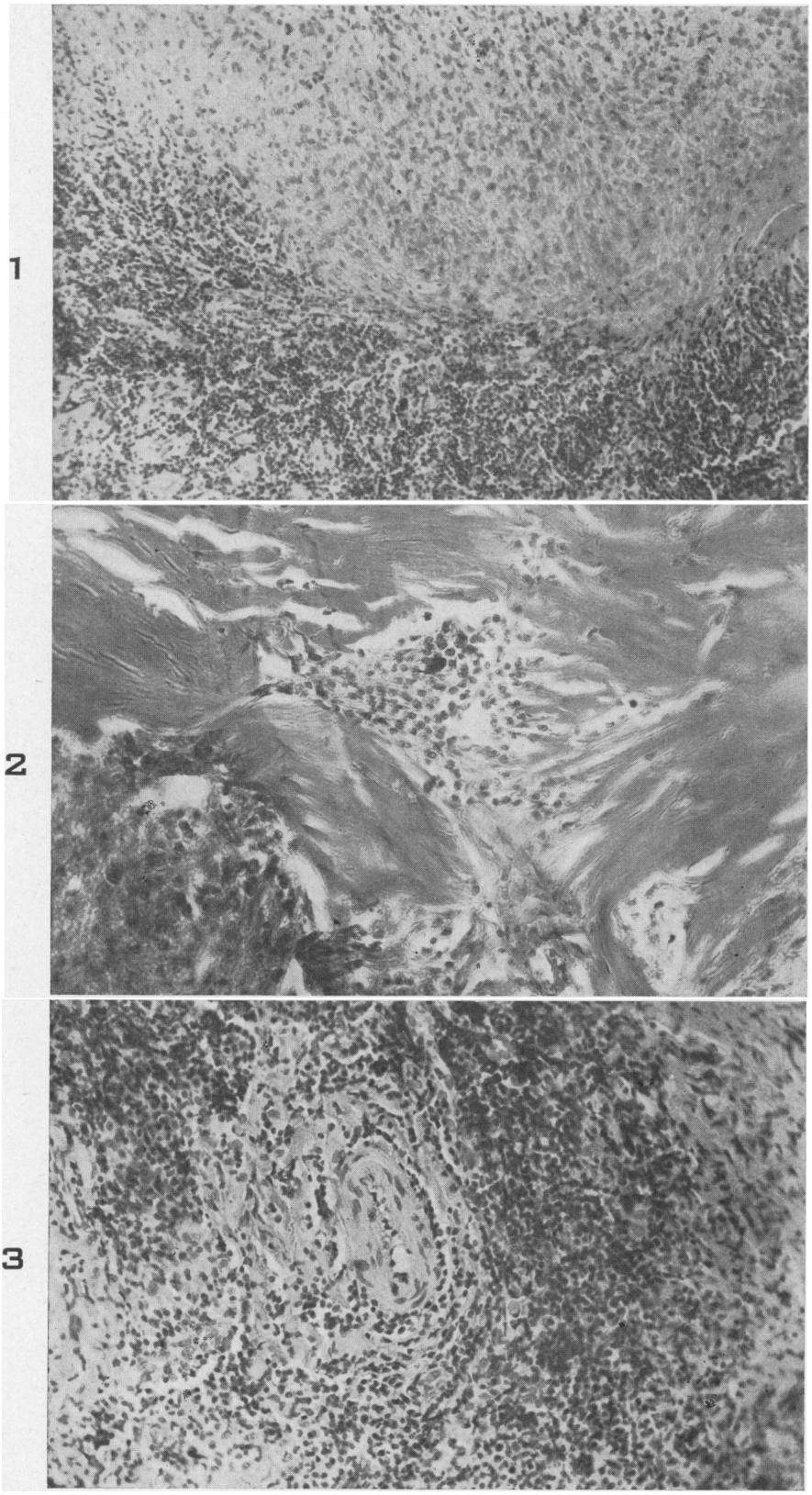
DESCRIPTION OF PLATES

PLATE 77

FIG. 1. Case 1. Epithelioid-cell reaction in a lymph node in Letterer-Siwe's disease with hyperglobulinemia. Hematoxylin and eosin stain. × 135.

FIG. 2. Case 1. Hyalinosis (paramyloidosis) with plasma cell accumulations in a lymph node. Hematoxylin and eosin stain. × 320.

FIG. 3. Case 1. Periarterial hyaline (paramyloid) rings in a lymph node. Hematoxylin and eosin stain. × 220.



Teilum Allergic Hyperglobulinosis and Hyalinosis

PLATE 78

FIG. 4. Case 2. Lymph node. Boeck granulomata with concentric paramyloid rings in the peripheral parts. Hematoxylin and eosin stain. × 220.

FIG. 5. Case 2. Lymph node. Boeck's sarcoid, passing on to diffuse paramyloidosis. Hematoxylin and eosin stain. × 150.

FIG. 6. Case 2. Boeck's sarcoid in spleen. Paramyloidosis beginning in the peripheral part of a granuloma. In the circumference isolated paramyloid bands and clumps are present. (For comparison with the extragranulomatous precipitates in Fig. 8.) Hematoxylin and eosin stain. × 320.

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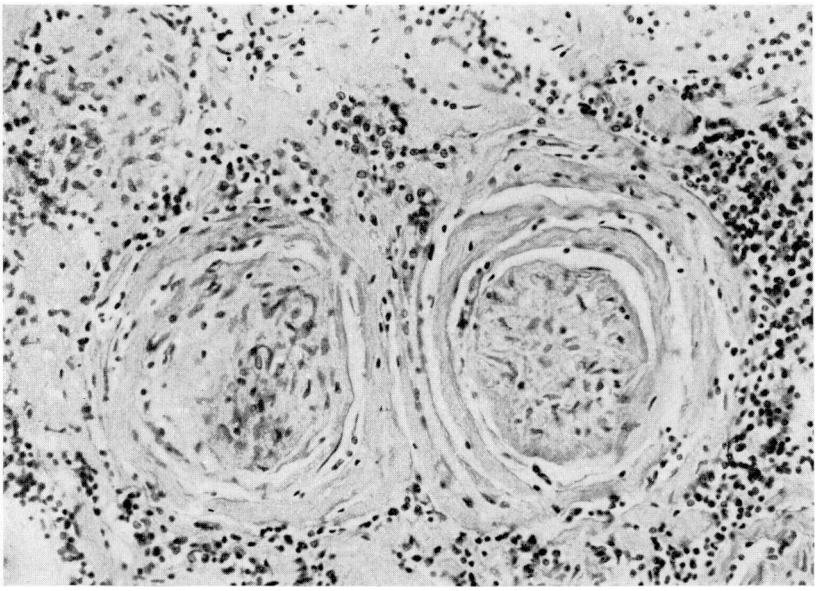

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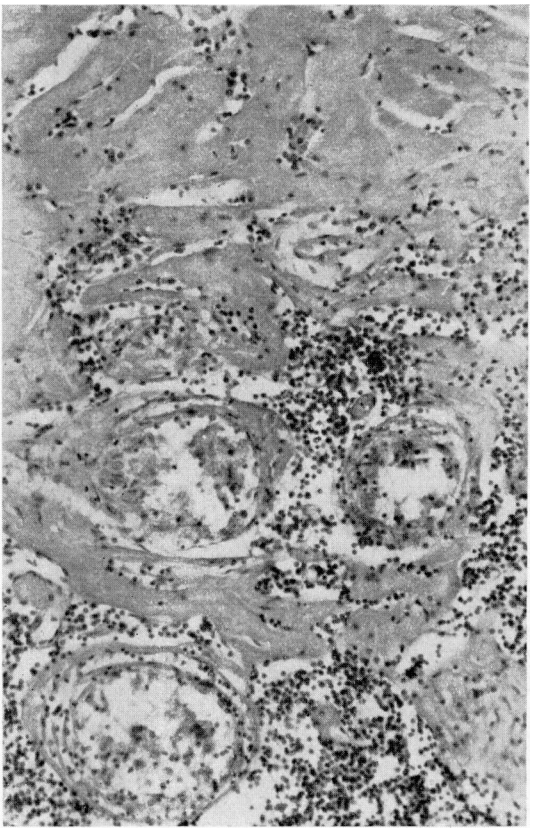

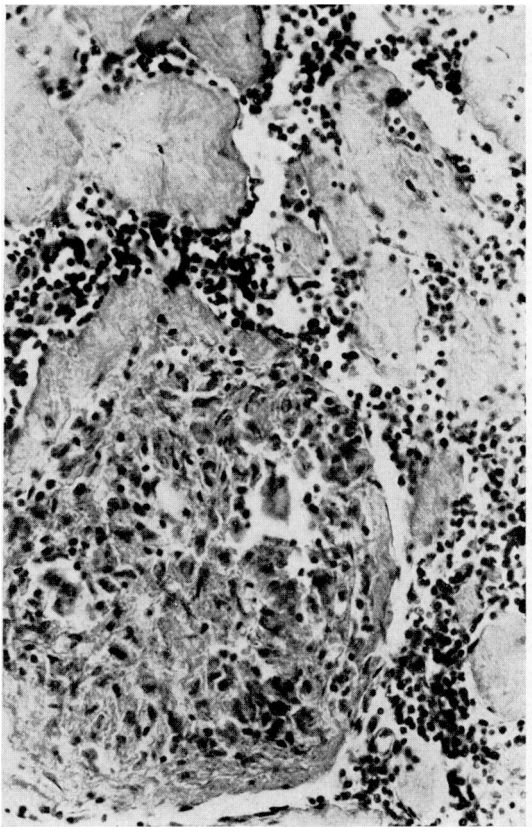

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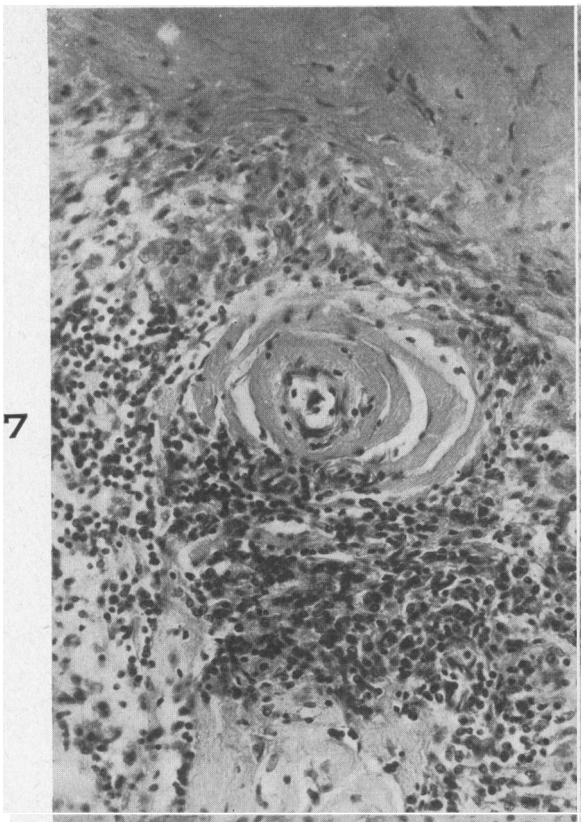
PLATE 79

FIG. 7. Case 2. Periarterial hyaline (paramyloid) rings in a lymph node in Boeck's sarcoid. (For comparison with Fig. 3.) Hematoxylin and eosin stain. × 220.

FIG. 8. Extragranulomatous homogeneous precipitates (lymph node) without hyalinosis; a common finding in Boeck's sarcoid. (For comparison with Fig. 6.) Hematoxylin and eosin stain. × 200.

FIG. 9. Extragranulomatous precipitates (lymph node, Boeck's sarcoid). Hematoxylin and eosin stain. × 240.

FIG. 10. Lymph node in Boeck's sarcoid. Homogeneous precipitates assuming a red color when stained by Mallory's method. × 240.



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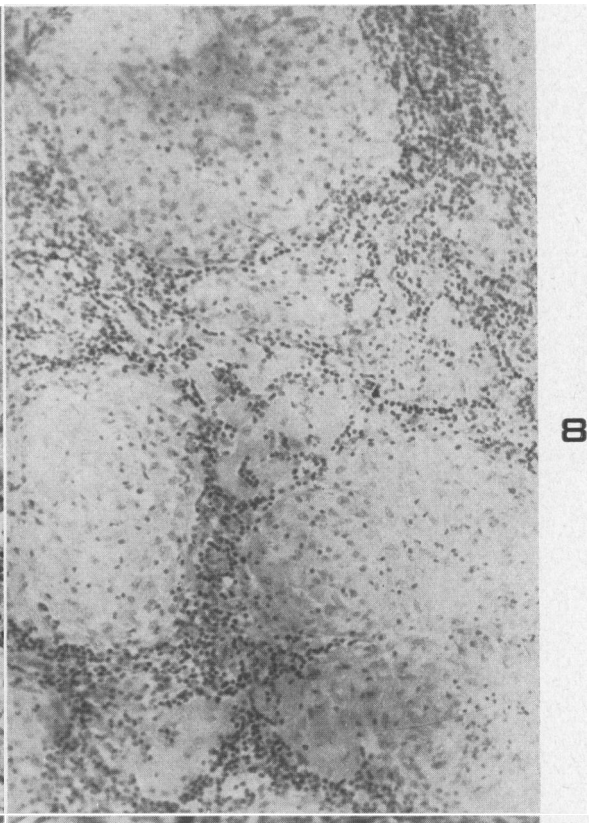

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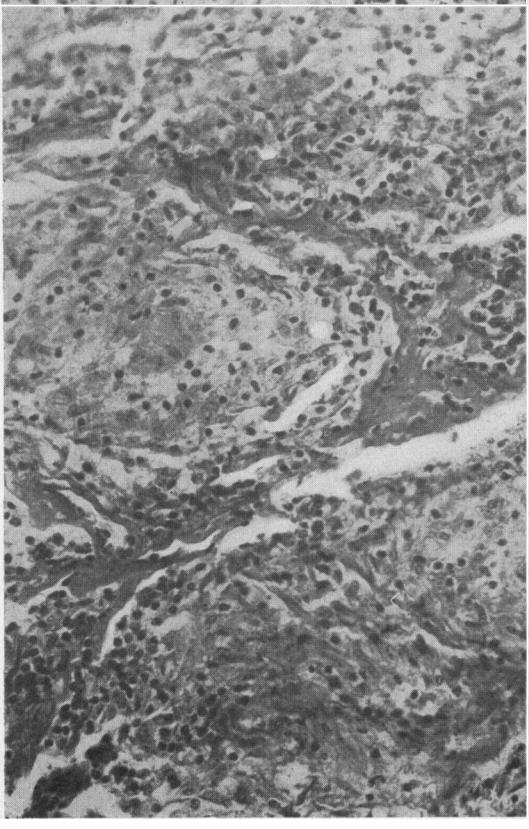

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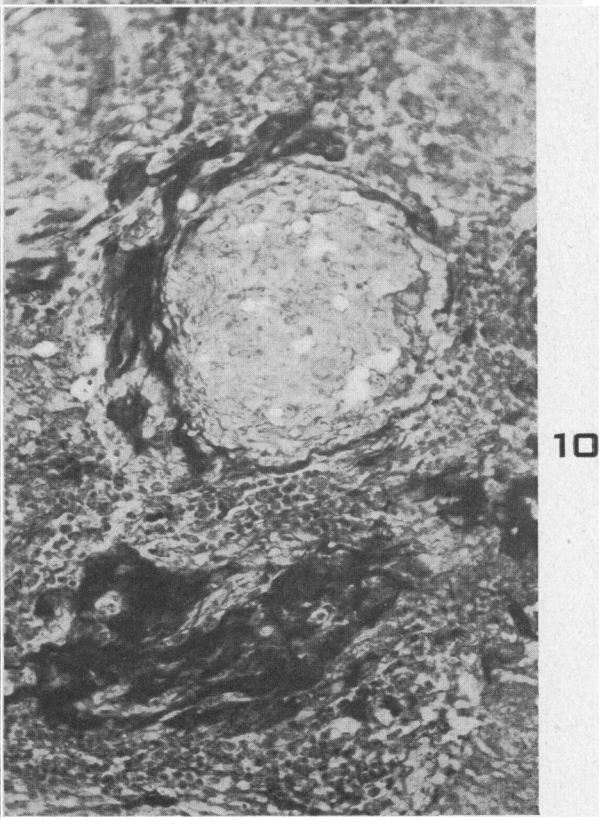

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Teilum

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