STUDIES ON LEPROSY. II. FORMATION, DISTRIBUTION AND DIAGNOSTIC SIGNIFICANCE OF PIGMENT

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LITERATURE

The development of pigment in leprosy attracted the attention of Danielssen and Boeck, who noted ‘brownish’ cells in leprous tissues in cases of the ‘nodular’ form of the disease. Hansen described them as ‘brown bodies,’ in which he was the first to perceive the presence of bacilli, without the use of a stain. About forty years ago Ivanovsky found in the lymph nodes in two cases of nodular leprosy an accumulation of pigment which he considered hematogenic, although no microchemical tests were made to ascertain its nature.1

In the literature on leprosy that has appeared during recent years, I have found no reference to the presence of the pigment in the skin or in internal organs. Herxheimer (1923), who carefully studied the skin and internal organs in one case, does not mention pigment. The same is true of Cedercreutz (1921), who published a detailed description of the histologic changes in the skin. A long list of other authors who do not mention pigment could be cited: Askanazy (1912), who studied the histology of the skin; Deycke (1916), who described the changes in the cutaneous nerves and internal organs; Chuma and Gujo (1923), and Melik-Sultanov (1927), who took up the question of the genesis of the lepra cell; Riecke (1929), who made a histological study of one case of nodular leprosy that was autopsied; Rogers and Muir (1925), and Wade and Rodriguez (1928), who give histologic descriptions of the changes in the skin and internal organs on the basis of personal observations and data found in the literature; Kobayashi (1929), who published a monograph on his findings in sixty necropsied cases; Stein (1929), who studied the nature of the lipoids in four necropsied cases; Jeannet (1923), who gave a de-

1 Jadassohn disagreed with Ivanovsky’s opinion that the pigment found in the lymph nodes was of hematogenic nature.
tailed description of one nodular case; Friedheim (1930), who studied the lepra cells; Pambri Hélène, Puis-Gagliari and a number of others.

In the handbook of Klingmüller (1931), which covers the world literature on leprosy, there is a chapter on pigmentation, but it refers only to the skin pigment, melanin. In only a few isolated works have I found brief references to iron-containing pigment in the affected organs. Henke and Lubarsch’s handbook on pathologic anatomy and histology, in the chapter on the spleen (Lubarsch), mentions hemosiderin in that organ in leprosy. Devjikov (1929) noted a hematogenic pigment in the endothelium of the sinuses of the lymph nodes and spleen. This completes the information on the subject.

**NODULAR LEPROSY**

In the cases of nodular (cutaneous-type) leprosy that I have autopsied I nearly always found in the skin, the peripheral nerves, the testicles and especially the lymph nodes of the affected regions a peculiar pigmentation of the tissue, varying from yellowish to a dark brownish tinge. This pigmentation in most cases was so marked that, on section, some of the organs looked spotted. This picture was seen most distinctly when the organ was examined with a magnifying glass, and it varied with each organ.

When the skin was cut in the region of a ganglion or an infiltration, the entire area was of brown color, and against that as a background there were well-defined, isolated, darker spots. This picture was especially clear in cases of severe nodular leprosy, in which the skin is affected over a large area; on cutting through one element after another the same brownish pigmentation was observed, with great constancy, deep down in the skin where there were lesions.

The same color was observed in the peripheral nerves at the places where they were thickened. The extent of the pigmentation varied in different cases. In the early stages of the disease, when the nerve involvement was not very great, only careful examination revealed the presence of brownish or yellowish streaks among the nerve bundles. In more advanced cases, or in those in which the course of the disease had been more "toxic" and the pathological process more rapidly progressive, the changes were more conspicuous. Where the nerve was thickened there were found well-defined brownish streaks among the separate nerve bundles, giving the tissue a striped appearance.

The lymph nodes had a still more characteristic appearance. In some cases there were small, yellowish or brownish foci distributed...
to a greater or lesser extent in the normal tissue; in other cases the entire cut surface was of a yellowish tint, which served as a background against which there were light- and dark-brown islets. In both cases the surface of the node looked variegated, but this was most marked in cases of the second category—to which belong all the protracted and neglected cases of nodular leprosy—in which the nodes are usually enlarged, up to the size of a pigeon's egg or a walnut.

There was also rather marked pigmentation of the testicles in nodular leprosy. Here again the gross appearance was variegated. In the early stages there were separate yellowish-brown foci on the cut surface. In advanced cases the organ acquired a firmer consistency, and on section the cut surface was of a dark brownish color, against which strands of connective tissue were clearly seen passing in all directions.

The constancy of the color changes in the leprotic tissues attracted my special attention, particularly since the records found in the literature were few and brief. In unstained sections from leprous foci of the above-mentioned organs I found under the microscope large numbers of granules and clumps of light- and dark-brown material that looked very much like hemosiderin. Various chemical tests (Nishimura, Hueck and Perls) fully confirmed this likeness; the granules and clumps reacted by forming Prussian blue.

By study of a large quantity of material I found, first, that the amount of pigment is closely related to the progress of the disease. In the early stages, with fresh manifestations, the quantity is small; in more advanced stages the amount increases and sometimes reaches a very high degree. The amount of pigment also varies with peculiarities in the course of the disease in different cases. Cases of toxic course with frequent exacerbations and comparatively early lethal end show the largest amount of hemosiderin; cases of chronic course, with very few or no exacerbations, do not show abundant accumulations. In the second place, I found that the hemosiderin is mainly deposited in the foamy lepra cells. In some instances it causes only a diffuse, uniform blue staining of the cytoplasm; in other instances it is distributed in the form of a fine dust; a third variation is the deposit of granules and clumps of moderate extent; and finally there are found cell elements loaded with maximum quantities of large clumps.

Histological study of skin macules in the early stages of nodular leprosy (as opposed to those of the anesthetic form of the disease,
which are always of a brownish tint), shows a very small amount of hemosiderin in the cytoplasm of the foamy cells. In such ease the Prussian blue reaction either gives the cells a diffuse blue color or reveals only isolated granules of pigment. In the larger infiltrations the amount of hemosiderin increases greatly, and dense collections of granules and clumps may be seen in the lepra cells. Some clumps can also be found in the connective tissue that surrounds the infiltrations. In old nodules the amount of pigment is exceedingly large. Some of the lepra cells are crowded with pigment granules, others are less full, but taken together their mass forms whole beds of hemosiderin in the skin (Plate 43, fig. 1). In the nodules of the skin that have undergone retrogression, or in scarred areas at the sites of former nodules, there is also a large collection of the pigment. Here the hemosiderin is distributed in the connective tissue and forms streaks and trabeculae and small deposits, depending upon the arrangement of the former lepra-cell infiltrations. If the pathologic process is not limited to the skin, but extends into the subcutaneous tissue, pigment storage can also be observed there.

In the nerves the pigment is deposited in the regions of leprous infiltration, i.e., mainly between the fibers and under the nerve sheaths. Lepra cells are also often found in the cellular tissue surrounding the nerve, and in such cases deposits of hemosiderin are found there. The amount of the pigment depends entirely upon the chronicity of the disease and its course.

As for the degree of pigment storage in the other organs, first place is held by the lymph nodes and spleen, which are relatively rich in endothelium and reticulocytes (Plate 43, fig. 2). Those cells which, on account of "lipoid degeneration," are transformed into "foamy" cells, are loaded with pigment to such an extent that in some instances the sinuses are completely blocked by it, and in consequence have completely lost their normal structure. Large deposits of hemosiderin are also to be found in reticular cells that do not contain lipoids, which in their mass sometimes completely supplant the lymphoid tissue. In the end the entire node is converted into a mass impregnated with iron-containing pigment. This condition occurs chiefly in the peripheral subcutaneous nodes (inguinal, axillary, cervical, epitrochlear, etc.) but it was found with even more constancy in the periporal nodes. In the other internal lymph nodes that are situated far from the skin (mediastinal, mesenteric and peritoneal), I found only single small conglomerates of granules or large clumps
located in the reticulo-endothelial apparatus. But in these nodes, in which the structure is better preserved than in the subcutaneous groups, there was seen evidence of erythrophagocytosis which could not be found in the latter.

The spleen contained large deposits of hemosiderin, usually with no discernable macroscopic changes, though in a few uncomplicated cases there were yellowish-brown and dark-brown nodules that gave these spleens the same appearance as that of the affected lymph nodes. The pigment is deposited as large clumps around the trabeculae and large vessels. In the capillary endothelium and the reticular cells the cytoplasm was either diffusely blue or filled with sometimes quite large clumps of the pigment. There was a considerable amount in the so-called splenocytes, which in such cases become large, almost gigantic. Frequently in these cells phagocytosed erythrocytes were also found. In the bone marrow the pigment is met with in either the lepra cells or the free-lying reticular cells.

The liver stores pigment, in lesser but still considerable amounts (Plate 43, fig. 3). The Kupffer cells contain large quantities of it, and when tested for iron they appear as small blue bodies of various forms. The pigment is also present in the hepatic cells, but here it occurs as separate granules of different sizes. The lepra cells that are always found along Glisson's capsule also contain pigment, sometimes in large amounts.

The testicles contain a considerable quantity of the pigment, which occurs as elsewhere mainly in the lepra cells situated near the blood vessels. It is also found with constancy in the dense connective tissue around the greatly changed tubules where the lepra-cell infiltration is undergoing organization. Here it is found either in the lymph spaces or in the remnants of the leprous tissue. It is easily discovered in the walls and lumina of the ducts, depending on the presence there of lepra cells.

MACULO-ANESTHETIC LEPROSY

The picture observed in cases of maculo-anesthetic (neural type) leprosy is quite different. In view of the slow and relatively slight development of the process in this form of the disease it might be expected a priori that the blood pigment is stored to a very limited extent, if at all. This proved true; in the organs of the two cases studied the amount was so small that attempts to reveal it were un-
successful until I modified the technique slightly, whereupon it was demonstrated with some frequency.

In the skin the pigment occurs in the "epithelioid" cells as limited quantities of small granules and dust that are seen with difficulty under low magnification but are clearly discernible under high-power lenses (Plate 43, fig. 4). It does not occur in the round cells. In the peripheral nerves (which though thickened remain white in color) no pigment was found, though a large number of sections were examined.

The lymph nodes in this form of leprosy, if they enlarge at all, do so to only a very small extent. On section they are of a grayish-white color, without yellowish or brownish tinge. Microscopically the structure is usually unimpaired, except that in the sinuses there is a limited hyperplasia of the endothelium. In the cytoplasm of these cells the special technique reveals small clumps of blood pigment. Sometimes evidence of erythrophagocytosis is also noted here.

The spleen contains a comparatively large amount of hemosiderin, collected along the course of the vessels, in the endothelium of the capillaries, and in the reticular cells. It occurs as small clumps and granules but is never as abundant as in nodular leprosy. Erythrophagocytosis also takes place here, but only to a very limited extent. In the bone marrow the pigment is found in the reticular cells, in some of which the cytoplasm is packed closely with it.

In the liver there are small foci of round cells, distributed along the course of the capillaries and in the Glisson capsule. Pigment in small granules is found in the Kupffer cells, as in the nodular form, but in considerably smaller amounts.

In some of the other organs I succeeded in finding hemosiderin, not even in the testicles, which undergo quite considerable changes in this form of the disease. To some extent these changes are similar to those occurring in nodular leprosy. There is thickening and hyalinization of the walls of the seminal ducts, with atrophy of their epithelium and complete absence of spermatogenesis, even in comparatively young patients. In the intertubular connective tissue, mainly along the course of the vessels, there are small islets of round-cell infiltration (Plate 43, fig. 5), very similar to that seen for
example in the liver. Search of these inlets for pigment was unsuccessful. Small groups of round cells were also found in the stroma of the adrenals, but no pigment was found in them.

**Tuberculoid Leprosy**

Recently attention has been turned to the so-called tuberculoid form of leprosy. In the main it is the same as the 'macular' variety, though it differs from the latter in some of the peculiarities of the clinical course, but mainly with regard to its pathologic-anatomical substratum. Histologically the tuberculoid lesions show changes that are so typical of tuberculosis that for a long time there was doubt as to whether they were due to leprosy. These doubts have now been dispelled to such an extent that there is a tendency to distinguish tuberculoid leprosy as a special 'variant' or 'form' of the disease. Because of the very peculiar pathological changes in these cases it has seemed to me of interest to ascertain whether or not blood pigment is stored in the lesions. I have had twelve cases of this condition at my disposal, from eleven of which biopsy material was obtained while the twelfth came to autopsy. These cases are being studied and will be reported in due course; at present I shall only take up the question of pigment.

Using the modified test, I found hemosiderin in the skin in all of these cases, but in very small quantities. It was found in the epithelioid cells in the tuberculosis-like areas, diffusely throughout the cytoplasm, which was stained blue, or concentrated in vacuoles.

Of the peripheral nerves of the case that was necropsied, only the ulnar showed any change, this being a spindleshaped thickening at the elbow. Microscopically there was a large caseous necrotic area surrounded by a compact hyalinized capsule. In the peripheral zone of this capsule were seen groups of epithelioid cells, some of which contained clearly distinguishable blue clumps of hemosiderin. In the lymph nodes no macroscopic changes were observed, but microscopically there was slight hyperplasia of the sinus cells, in which sometimes clumps of hemosiderin were seen. None was found in the liver, but in the spleen there were comparatively small quantities. In the bone marrow it was found only in occasional reticular cells. In the testicles it was noted in the cytoplasm of epithelioid cells, which were present among the cells of the round-cell infiltrations. The changes in the testicles in this case were very similar to those in the
cases of the maculo-anesthetic form. In the other organs no pigment was found.

SUMMARY

An iron-containing blood pigment was found in the affected organs and tissues of all cases of leprosy that I examined. In the nodular form of the disease this pigment is deposited in strikingly large quantities, while in the maculo-neural and tuberculoid forms the quantity is very small.

The cause of the pigment formation may be (a) erythrocyte destruction in the general blood stream, or (b) some process of local character. The generally accepted view that the leprosy bacillus does not excrete toxic substances that may act on the cells of the organism seems to be against the first of these theories. However, this view is based entirely on clinical data and not on experimental immuno-biological studies. It seems quite possible that products of bacillary activity may be fixed by the lipoid membrane of the erythrocyte and destroy them. In favor of the second theory, that the pigment is of local origin, is my observation that erythropagocytosis is found with some constancy in the lesions. It is true that in cases of the nodular form phagocytosis is demonstrated with great difficulty, though the pigment is deposited in large quantities. However, in some of the cases in which there were lesser quantities of pigment, that did not interfere with the clearness of the picture, phagocytosis was observed constantly and in a considerable degree. Even in the maculo-neural type both pigment storage and erythropagocytosis could be observed. At any rate, the question must be regarded as an open one, requiring further study.

Though the study of pigment formation in leprosy is only beginning, I would like to call attention to two ways in which this process may have an important practical significance. The initial symptoms of both types of the disease include the appearance of macules. The clinicians point out that in nodular leprosy the macules are elevated above the skin surface, while in the anesthetic form they remain level with the surface; but it is known that this distinction is not always clearly evident. My biopsied material shows that in the macules of the nodular form the appearance and accumulation of the pigment goes on much more rapidly and to a greater extent than in the anesthetic form. Therefore the finding of hemosiderin in the macules in the initial stage of the disease might have practical sig-
nificance as indicating the course which the further development of the disease will take.

Of still greater importance may be the finding of pigment in the macules of tuberculoid leprosy, where it may serve to distinguish the tuberculous-like changes caused by the Hansen bacillus from true tuberculous changes produced by the Koch bacillus. However, this question requires further comparative study.

CONCLUSIONS

1. In the nodular form of leprosy (cutaneous type) the infected organism suffers as a whole. The pathologic process is characterized by marked hyperplasia of the reticulo-endothelial system, with bacilli, lipoids and hemosiderin loading the cells.

2. In maculo-anesthetic (neural type) leprosy the skin, nerves and internal organs (liver, testicles, adrenals) show ordinary round-cell infiltrations containing small quantities of bacilli and hemosiderin. In my material the foamy cells were absent. Bacilli were found in the skin, lymph nodes and spleen in small quantities, in the nerves in larger quantities, but not in the testicles and adrenals. Evidently in this form the involvement of the organism is also of a general character.

3. In all of the cases studied, larger or smaller quantities of hemosiderin were found deposited in the affected areas of the skin as well as in the internal organs. The presence of this pigment in the lesions of leprosy may be of significance in the matter of differential diagnosis.
DESCRIPTION OF PLATE

Plate 4

Fig. 1. Skin lesion from a case of nodular leprosy, showing large deposits of pigment. Prussian blue reaction.

Fig. 2. Lymph node showing deposits of pigment, Prussian blue reaction.

Fig. 3. Pigment in liver, Prussian blue reaction.

Fig. 4. Clumps of pigment in the infiltration of a skin lesion in a case of maculo-neural leprosy. Prussian blue reaction.