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THE SIGNIFICANCE OF THE VACUOLE IN THE VIRCHOW LEPRA CELLS, AND THE DISTRIBUTION OF LEPRA CELLS IN CERTAIN ORGANS [1]

By Kensuke Mitsuda

Aisei-En National Leprosarium, Okayama-ken, Japan.

INTRODUCTION

In 1902 the author reported (in the *Tokyo Iji Shinshi*, No. 1240), that in staining leprous tissues with Sudan III he had observed that, while the leprosy bacillus itself became only slightly stained, the vacuolar substance in the lepra cells was remarkably well stained. This was thought to be an interesting matter for special investigation.

For some time after Virchow described the lepra cell its vacuolization was regarded as due to edema, and to be one of the characteristics peculiar to leprous tissues. Unna, however, by staining the leprosy bacillus black by means of osmic acid, demonstrated the existence of fat, not only in the bacilli themselves but also in the gloea that surrounded them. His latest published study seems to show that what he calls the globus corresponds to Virchow's or Neisser's vacuoles. In the author's opinion this body is nothing but a lipoid substance in the cell.

In Japan, Sekine studied the effect of Sudan III on sections of leprous skin, and published a detailed description of his findings (*Hifuka Hitsunyokika Zasshi—Journal of Dermatology and Genito-*

[1] The original of the present article was published in 1918, in the Japanese language, in the *Tokyo Iji Shinshi* (*Tokyo Journal of Medical Affairs*). Because leprosy of the internal organs has been given considerable attention in recent years, and because this original article was accessible to few persons outside of Japan, arrangements were made for its translation into English, with the aid of a grant made for the purpose by the Leonard Wood Memorial. A number of alterations from the original have been made in the translation, partly in connection with classification.

Urology—Vol. 3, Nos. 1, 2 and 5). The author himself had employed this stain, not only for microscopical preparations but also for macroscopical ones, and had obtained very satisfactory results.

Generally speaking, lepromatous lesions of the viscera (exclusive of the lymph gland and testicle), being less than 1 mm. in size, are not infrequently overlooked by inexperienced workers, though no possible mistake can be made by one who is skilled. Thus the suprarenal gland, although it usually contains nodules in lepra nodosa (C type leprosy), is generally regarded as rarely affected. Furthermore, in the spleen it is difficult to tell the follicles or miliary tubercles from the lepromata, and in an infected spleen it is difficult to tell whether lepromata are present or not.

In the preparation of gross visceral specimens of leprosy, if a formalin or Kaiserling specimen is placed in a saturated alcoholic solution of Sudan III for an hour or more, and, after washing in half-strength alcohol, is stored in Kaiserling III solution, a splendid specimen will be obtained that keeps its color for a long time. By this method the dust-like or dendritic lepromata are stained red, so that they can be distinguished from splenic follicles and miliary tubercles. It is true that fatty degeneration sometimes occurs in tuberculous lesions, but as it is always of very slight degree it can be easily told from the lepromatous condition. The method can also be applied to the skin, mucous membrane, and testicle, where leprous infiltrations are stained more clearly.

The general process of leprosy, when the infiltrations are generalized, is such as to permit naked-eye determination of whether a lesion is old or recent. For example, when a skin leproma is new, its surface will present a pale, pearly color, while old lepromata or infiltrations are dark gray, or yellow, or yellowish brown.

That such a change and variety of color is related to the age of the lipoid substance may be demonstrated by microscopical specimens. When the lipoid vacuolar substance in the lepra cell is produced rapidly it causes the cell to expand, and in consequence the nucleus becomes deformed, so that its edges may appear milled or saw-toothed. On the other hand, when the growth of the vacuoles is slow and gradual the nucleus is not deformed, but the cells are stimulated so that they produce multiple nuclei, thus becoming the so-called vacuolate giant cells; in size the cell becomes several times the normal. With the ganglionic cells there is no increase of the

nuclei—they are injured and disappear, and the cell body becomes merely a network bordered by the membrane; but the condition is different from the typical leprous vacuolization.

As a rule the number of leprosy bacilli in the vacuolate lepra cells decreases, and most of those found among the vacuoles are of granular form, only a minority being typical rods. When such lepra cells have accumulated to form a small localized nodule in a viscus, the vacuolated tissue can be recognized in the microscopical specimen; macroscopically it appears gray or yellowish-brown, the latter color evidencing increase of the lipoid pigment. In the fresh nodule whose cut surface looks pale the vacuoles are not clearly visible; there the bacilli are of rod form and, grouped in bundles, are enclosed in spindle-shaped cells. In a section of such a leproma stained with hematoxylin and eosin we see an arrangement of cells as in sarco-fibrous tissues. When this kind of lesion becomes old, there develops the vacuolar tissue described, though not always from the sarco-fibrous type of lesion.

In the so-called infiltration form of leprosy (a sub-type of cutaneous leprosy), the slow progress of the condition tends to bring about the vacuolate kind of lesion from the beginning, while the nonvacuolate kind is seen in the nodular form (sub-type), which is rapidly progressive. The nature of the lesion also depends on the part affected. The nonvacuolate kind often occurs in the skin, the mucous membrane of the upper air passage, and the testicle, but in the viscera and lymphatic glands the vacuolate kind is generally seen to appear slowly and gradually, as an infiltration. Ultimately, however, the spindle-form cells existing in the nodular, tumor-like lepromata are subject to lipoid degeneration, and the leprous granulomata appearing in various organs of the body are not free from it.

It is more than fifty years since Virchow discovered this tendency to vacuolation of the lepra cell, and notwithstanding the multitude of theories concerning it put forward during that half century, we still call that cell by his name. The present writer has long desired to obtain an accurate knowledge of this lipoid substance in the lepra cells, and when Kawamura published his work on the microchemical classification of fats he saw in it a lead toward the solution of the problem.

Microscopical examination of a frozen section of unstained leprous tissue (from the skin or an internal organ) shows that the lepra cell contains a shiny kind of granule and sometimes in addition minute

crystals of yellowish-brown color. Examined with the polarizing microscope these elements are not doubly refractile. Application of 3 percent potassium hydroxide solution does not cause them to disappear. On the other hand, when such a section is immersed for a few days in a fat solvent, such as absolute alcohol, ether, chloroform, or acetone, a part of the material is dissolved and its stainability by Sudan III is decreased. If this section is then stained with Ziehl's solution and differentiated by Gabbet's, the leprosy bacilli are seen again to be stained. If such a specimen stained by Ziehl's solution and differentiated by hydrochloric alcohol is stained by van Gieson's method, the bacilli are red and the nuclei are stained by the hematoxylin, while fine fibrils are crimson and the vacuoles yellow.

Again, if a section is treated with osmic acid for a few hours it becomes grayish, and with Sudan III or scarlet red takes on an orange color. With Nile blue the vacuole is stained green, and sometimes purplish-red. If Smith's method is employed, the vacuole stains a greenish-black color, the bacilli themselves being black. By the Ciaccio method the lepra cells become light orange-yellow, and by the Fischler method they stain blue-black, while the fresh bacilli are black, as by Smith's method.

Finally, when a specimen with many fresh bacilli is treated with a mixture of equal parts of ether and alcohol, the lepra-cell vacuoles become unstainable, but the bacilli still retain their stainability, showing that the fatty element of the leprosy bacillus contains a strong lipoidal substance which is not easily extracted by the ether-alcohol mixture.

To sum up: Since the lipoid substance in the lepra cells stains by either the Smith, Ciaccio, or Fischler method, it cannot be a neutral fat. Because it is not doubly refractile it is not the cholesterin ester. Consequently, it must be one of the so-called lipoid substances. Its chemical formula has not been established, but it may very well be of very complex structure. Since the fresh leprosy bacillus can also be stained with Sudan III or by the Smith and Fischler methods, it also contains a lipoid substance. On the whole the lipoid content of the bacillus is similar to that of the lepra cell, the only difference being that the bacillus resists the fat solvent, and that its acid-fastness is much greater than that of the vacuolar substance; moreover, it is stained more rapidly by osmic acid.

As for the origin of lipoid substance in the lepra cell, we do not know whether it is a product of the cell itself, or is something

that has entered from outside it, or is excreted or secreted by the bacillus. However, its striking similarity to the content of the bacillus, save for certain differences because of its being a fat-like substance, makes one inclined to regard it as the product of, or due to, the bacillus. In this connection note should be taken of the fact that, although the larger globi which are often seen in the skin, mucous membrane and testicle always contain many lepra bacilli crowded together, we no longer find them in the globi in the organs of a patient who has suffered repeated occurrences of erythema nodosum leprosum or has had severe complicating tuberculosis; in such tissues there remains only bacillary debris.

The lipoidal reaction manifested by them gives strong support to the theory that the globi are mostly the product of degeneration of the leprosy bacilli. However, in leprotic lesions of the viscera, particularly such organs as the liver and spleen, there are not produced globi such as are found in the skin, the mucous membrane, the testicle, or the lymphatic glands directly connected with skin leprosy; in these organs the infiltration always takes the form of vacuolate lepra cells. Furthermore, in such organs as the heart, stomach, intestines and uterus, hitherto regarded as free from attack by the leprosy bacillus, there are always seen colonies of lepra cells, notstanding the fact that there is no actual growth of the bacilli and their number in the cells is very small. But this peculiar form of lesion, and its lipoid reaction, are never seen in normal organs or in organs affected by any other disease, and a close search always reveals the existence of a lepra bacillus or two in the lepra-cell colonies. In such cases lipoid transformation from the leprosy bacillus is unthinkable.

LEPROTIC INVOLVEMENT OF THE VISCERA

Here are presented the results of a study, made from the new angles of observation indicated (with special reference to lipoid degeneration), of the distribution of lepra cells in the lymph nodes, liver and spleen, which are recognized to be usually involved in nodular leprosy, and also in other organs that have been generally understood to be rarely affected by leprosy.

1. LYMPHATIC GLANDS

Babes seems to think that the lymphatic gland is a good hiding place for the leprosy bacillus, but compared to such parts as the skin,

mucous membrane, nerve and testicle, where primary infiltrations or nodules appear, the lymphatic gland would seem to be of secondary importance.

The femoral, inguinal, cubital, axillary, submaxillary and cervical glands assume the so-called Virchow suprarenal-gland form in both cortex and medulla; the follicles of the cortex particularly harbor the bacillus in abundance, and here the condition assumes the nodular form. In the serous membrane and directly under it globi are formed, and in the follicle there are produced vacuolate and multinucleate cells, both rich in bacilli. The lymph sinuses, too, contain some pigment granules in their reticulum cells, together with small numbers of bacilli, but no bacillary colonies so large as to clog the sinuses have been observed. In the trabeculae the bacilli are very few, and vacuolar degeneration is rather prominent.

In the iliac, retroperitoneal, mesenteric and bronchial glands the pathological changes are much milder than in the glands closely connected with the skin. In their follicles the reticulum cells are first affected, with the appearance of bacilli and the production of lipoid degeneration, followed by proliferation of the reticulum cells. In the mesenteric glands only the vacuolate reticulum cells are seen, as a rule, and bacilli are rarely found. In the bronchial gland there are sometimes found cells showing vacuolate degeneration and containing a few bacilli, together with coal pigment; the bacilli may be hidden by the pigment, but Sudan III will clearly reveal the leprous degeneration.

When there is leprous infiltration of the liver the portal gland is swollen and presents an appearance similar to that of the suprarenal gland of lower animals. Even when the lepromata of the liver are obscured by fatty degeneration or infiltration of that organ, the leprous involvement may be detected by the changes found in the portal gland. Aside from this gland, the first affection in most of those in the thorax and abdomen occurs in the reticulum cells of the follicles closely connected with blood circulation, and the changes in the lymph sinuses seem to be of little significance.

2. SPLEEN

In the spleen there is no conspicuous contrast between the leprotic nodules and the surrounding tissues, as there is in the liver, but those close under the capsule are often seen through it as white spots of needle-point size. On the cut surface of the organ minute nodules,

often as large as 1 mm. in diameter, and sometimes yellowish-brown in color, are seen along the branches of the splenic artery.

Under the microscope the region of the splenic arteries is found to contain the most numerous leprotic foci, and next the intersinous pulp. Many plasma cells are found in these foci, but they never contain bacilli. The lepra cells are seen among the splenic cells of the pulp and in the perithelium of the arteries. Though elsewhere the arterial perithelium is usually not the part favored by the leprosy bacillus, in the spleen it is the part that is first involved, and nodules are formed there.

A few rows of lepra cells are sometimes seen around the trabeculae, but this is not as favorable a site for the bacillus as the periarterial zone. A few bacilli are sometimes seen in the connective tissue cells of the trabecula but they do not seem to multiply there.

The endothelium of the splenic vein that leads to the trabecula often protrudes into the vein in a polyp-like mass, as a result of lepromatous growth under the endothelium. Usually the endothelial cells of the venous sinuses do not take up bacilli; though in the skin and testicle the endothelium of the vein is a favorable site for the bacillus, that is not the case in the spleen.

That the large monocytes in the venous sinuses contain bacilli was noted by Rickle, and is usually seen in the spleen of lepra nodosa (C type). Whether those cells correspond to the bacillus-containing large monocytes found in the circulating blood in that type of the disease is a question that should not be answered too hastily.

The reticulum cells of the spleen follicles, as those of the lymphatic gland, first turn into lepra cells, and then, having multiplied, finally cause atrophy of the follicles.

Hyalin thickening of arteries of the spleen, and their stainability with Sudan III, are usually seen in lepra nodosa, irrespective of the age of the patient. A fact which deserves special mention is that, though the endothelium of the splenic sinuses does not take up the bacillus, that of the capillaries in the pulp often contains large numbers of bacilli.

3. LIVER

No student of visceral leprosy has ever failed to take note of the pathological changes in the liver. In lepra nodosa minute nodules

are usually seen in the interlobular connective tissue, their shape varying from dot-like to dendritic; with them there is increase of connective tissue. Next in frequency to the interlobular connective tissue, the walls of the central veins present nodules visible to the naked eye. A number of such nodules regularly arranged in and out of the small hepatic lobes is a beautiful sight.

Seen under the microscope, the Kupffer stellate cells of this tissue are swollen with bacilli. If the pathological changes are severe, not only is the number of stellate cells large, but they also show vacuolar degeneration, and often a number of nodules are formed in the lobes. In these nodules, whether in the interlobular connective tissues or around the central veins, lipoid degeneration is always intense, and there is often infiltration of plasma cells. The bacilli present are mostly old, and usually few in number, but in the Kupffer cells there are many comparatively fresh ones. Rods that simulate leprosy bacilli are often found in the liver cells, but they are nothing but fat or bile-pigment crystals; as in the suprarenal glands, bacilli do not seem to penetrate the parenchymal cells.

4. DIGESTIVE TRACT

Discussion of the digestive tract will begin with the esophagus; the pathological changes of the tongue and pharynx will not be considered here.

In the mucous membrane of the esophagus leprotic tissue is sometimes seen around the blood vessels, but the number of bacilli found in it is small.

In the tunica propria of the stomach there are groups of vacuolate cells, with scanty bacilli. Of special interest are collections of such cells in or around the muscularis mucosae, especially near the pyloric valve where sometimes they are as large as 10 x 0.1 mm. For the most part these cell groups remain close to the capillary walls. Infrequently isolated lepra cells occur in the gastric muscle.

Similar leprous tissue is also found above and below the muscularis mucosae at the bottom of Lieberkühn's gland adjoining the duodenal pylorus, and quite a few groups of lepra cells are seen in Brunner's glands. Similar groups occur in the lower part of the duodenum along the muscularis mucosae, more below the muscle than above it. The same is true of the jejunum; also of the ileum, though here the changes are milder than in the other two locations. Lepra cells are found around and in Peyer's patches. In the caecum there

are groups at the lower part of the muscularis mucosae, as also in the mucous membrane of the upper rectum, on and under its muscularis mucosae, especially at the lower part.

The foregoing is merely a rough statement, but it is obvious that in the stomach and intestine the favorable location of the leprosy bacillus is at the upper and lower parts of the muscularis mucosae, invariably along the capillaries. The number of bacilli may be quite small, but it is not difficult to detect some in every lepra-cell group. It has already been said that vacuolar degeneration can be found in the follicles of the corresponding mesenteric glands.

In view of the fact that some of the changes here described are invariably seen in the organs of lepra nodosa, the writer is inclined to call this condition "stomach leprosy" or "intestinal leprosy," as the case may be. Reissner obtained innumerable supposed lepra bacilli from an intestinal ulcer, and named the condition intestinal leprosy, but in the author's opinion the lesion that he dealt with must have been tuberculous. Absence of ulceration is a characteristic of intestinal leprosy, and therefore there seldom if ever is any clinical disturbance. There may be, if anything, some such thing as susceptibility to dysentery, or to other inflammatory conditions of the digestive organs, in patients with intestinal leprosy.

For the reason that, where there are leprous changes in the upper esophagus and air passages, leprosy bacilli are swallowed with saliva, the nasal secretion or sputum, and can usually be detected in the excreta, it is possible that bacilli thus swallowed may be absorbed together with the food during their passage through the alimentary canal. There may be many who believe in this theory, but the writer is inclined to think that, as in the case of other organs, leprosy of the stomach and intestine is caused by bacilli conveyed to those organs by the circulating blood.

Very few bacilli are found in the pancreas or salivary gland; at most a few small groups of lepra cells can be found in them.

5. THE HEART

It is true that no marked pathological change due to leprotic invasion occurs in the heart. Is it possible, however, that this organ alone is free from invasion by the bacillus, which is capable of entering the blood stream?

In cases of nodular leprosy, examination of the heart by means of Sudan III often shows that histiocytes in the intermuscular con-

nective tissue give rise to the lipoid reaction, and they grow to form tubercles similar to the rheumatic nodule. Lepra cells giving rise to this reaction, whether they occur singly or in groups of several, usually contain one or more bacilli. It is to be noted that, although these cells sometimes contain at the same time some needle-like fatty crystals, no error can be made on that account if specimens defatted by ether, alcohol or acetone are studied.

This leprous change can be found in any part of the heart, but more readily near the apex than at the auricles, and also more readily near the endocardium than near the epicardium, though not a few may be found around the Tawar-Hiss bundle. Because of the location of the changes noted, near the terminations of the vessels of nutrition, the writer believes that the entrance of the bacilli into the substance of the heart is by way of these vessels and not by penetration from the blood in the cardiac chambers.

What clinical symptoms are caused by this pathological change in the interstitium? There are no marked symptoms to be observed, but it seems possible that the systolic sounds heard in the complication of leprosy known as erythema nodosum leprosum ("lepra reaction"), and also in pulmonary tuberculosis, are due to it.

6. THE LUNG

Rarely are macroscopically visible nodules found in the lung, but the bacillus is to be seen in the histiocytes in the interstitial tissue, in the endothelial and perithelial cells of the blood vessels, and in the dust cells.

In the first-mentioned location the bacilli not only are numerous, but new ones are introduced from the blood stream. There are also groups of lepra cells that sometimes are from 0.01 to 0.1 mm. in diameter. The dust cells, heavily laden with coal pigment, change into vacuolate cells upon the entry of the bacillus and stain orange by Sudan III.

Lepra cells containing both pigment and bacilli with the consequent vacuoles give rise to increase of the interstital tissue, but nothing like the leprotic pneumonia that has been reported by other workers has been seen in our material. It seems probable that those workers either saw scattered lepra cells in genuine pneumonia (tuberculous caseous pneumonia or catarrhal pneumonia, conditions which occur quite frequently in lepers), or leprosy bacilli which happened accidentally to be in the alveolar epithelium or leucocytes.

Besides the conditions mentioned, the tissues under the bronchial mucosa (i. e., around the mucous glands and the veins in the tunica propria), often show an infiltration of lepra cells coming from the upper air passage.

7. KIDNEY, BLADDER AND PROSTATE

In cases of nodular leprosy the bacillus is unmistakably present in the glomerulus of the kidney, where it causes hyalin degeneration of the glomerulus and interstitial nephritis. In addition, there are a few microscopic groups of lepra cells in the interstitial tissue around Bowman's capsule and the interlobular arteries and veins. The number of bacilli in these parts is smaller than in the glomerulus, where there are no cells with vacuolar degeneration. It is probable that the bacillus lives in the endothelium of the capillary veins.

In the bladder and prostate very few bacilli are found. In the former organ two or three lepra cells are sometimes seen around the submucous blood vessels, and in the latter quite a few isolated cells of this type occur in the smooth muscular tissue.

8. SUPRARENAL GLAND

Being important organs, the kidney and the lung have received much attention from leprologists, and even the conditions in them that are not directly connected with leprosy have been studied extensively. As for the suprarenal gland, only a very few workers have ever mentioned the existence of leprosy bacilli there, and that only as a rare finding. The fact of the matter is that whenever there are leprous nodules in the liver and spleen, some of them are usually to be found in the suprarenal. Indeed, even in cases where such lesions are difficult to see in the liver and spleen, either because of their small size or other changes that obscure them, the suprarenal may show conspicuous nodules.

These nodules occur under the capsule, in the zona fasciculata and the zona reticularis, and around the medullary veins. Those most clearly visible to the naked eye occur in the last two places mentioned; in size they sometimes reach 0.2 to 0.5 mm. in diameter. Since the parenchymal cells in the zona reticularis contain brownish pigment, the yellowish leprotic nodules stand out conspicuously in this area. In the elevated parts of the gland where there is no medulla there are series of nodules, arranged at regular intervals along the wall of the central vein. The author used to describe the loca-

tion of the leproma as at the boundary between the cortex and medulla.

These lesions are often overlooked because the bacilli in them are usually very scanty, but they can be recognized because of their peculiar location, adhering to the wall of the vein. No leprosy bacilli are noted to gain entrance into the parenchymal cells, even when those cells have undergone fatty degeneration and marked vacuolization. However, bacilli are sometimes seen in the endothelium or the perithelium of the blood vessels in the zona fasciculata, and their proximity to the parenchymal cells often misleads the observer. The situation here is to be compared to the relationship between the liver cells and the Kupffer cells. The fact that the vascular cells of the suprarenal may contain comparatively fresh bacillary bundles, due to bacilli coming from the blood stream, is another point of similarity, but this does not happen as frequently here as in the Kupffer cells.

Our so-called macroscopical nodules are the usual changes in the suprarenal gland in lepra nodosa, and because of their favorable appearance in the zona reticularis they may provide good material for the study of internal secretion in that part. It may be remarked that in the so-called black leprosy of olden times in Japan (lepra nodosa, particularly the infiltrated form), the pigmentation of the skin may be the result of chronic inflammation, and since much of that pigmentation fades as a result of treatment of the disease it probably has no relation to the pathological changes of the suprarenal gland.

9. UTERUS AND OVARY

Along the capillary veins of the connective tissues in the muscular layer of the uterine wall, lesions are produced in nodular leprosy that attain a size of 0.5 mm. in diameter. Their vacuolar tissue gives peculiar reactions, and the leprosy bacilli therein are very few in number.

This pathological change is distributed evenly all through the uterus, but the color of the tissue makes it difficult to see with the naked eye. Occasionally lepra cells are also found in the endometrium, and groups of them may be seen along capillaries in the vaginal membrane; a few also occur under the epithelium of the fallopian tubes. If a woman with the above symptoms becomes pregnant, the lepra cells that happen to exist in the decidual membrane may penetrate into the embryo by the medium of leucocytes.

With regard to the ovary, Glück and Wodinsky reported what they called "ovarian leprosy," stating that they had found nodule formation in that organ, and numbers of globi. It would seem that they compare the pathological change of the ovary with that of the testicle. But is it not rather exaggerated?

The ovule and follicle cells of the cortex are almost free from leprosy bacilli. This is quite different from the case of spermatogenic cells of the testicle, which the bacillus enters freely and where it thrives. A large number of swollen, lipoid-containing connective-tissue cells are seen around the corpus alba and in the corpus luteum. After staining by the Ziehl method they are not easily decolorized by sulphuric or hydrochloric acid, and being strongly acid-fast they look almost like globi. Perhaps these are the bodies observed by the workers mentioned.

Is it then the fact that the ovary is absolutely free from infection by the leprosy bacillus? Study of thoroughly defatted specimens shows that the cells around the corpus alba (i. e., the lutein cells) contain a very few bacilli, together with the lipoid substance. It would appear, then, that, while in other organs the lipoid substance in the lepra cell is produced after the entrance of the bacillus, in the ovary the bacillus enters cells in which the lipoid substance has already existed. Although things may be seen that appear like nodules or globi, they are not due to the growth of the leprosy bacillus, as in the case of the skin and testicle, but are probably caused by the cells that exist normally around the corpus alba and the corpus luteum. The author believes that the fact that the ovary is seldom and only slightly affected explains the comparatively few cases of sterility among leprous women.

DISCUSSION

It appears from the above that, although there are certain variations according to the organ affected, the leprosy bacillus invariably penetrates and lives in the so-called histiocytes, or histiocyte-like cells, such as the connective-tissue, endothelial, perithelial, and reticulum cells, and, giving stimulus to those cells, causes them to multiply and form vacuolar nodules. However, in the organs that have been discussed it does not develop into tumor-like masses, destroy ing or deforming the cells of the organs affected, as is the case in the skin, upper air passage, the mucous membrane and the testicle. In the liver and the kidney the affection causes interstitial inflam-

mation in addition to nodules, and the spleen and lymphatic glands become swollen because of the growth of nodules.

The position of the lepromatous foci, which are regularly and evenly scattered, is quite different from that of the granulomata of tuberculosis or syphilis, which are irregularly distributed and form tubercles of various sizes, causing destruction of tissues and the formation of ulcers. It is, of course, quite imaginable for the germs of syphilis and other diseases, acute or chronic, to affect all of the organs of the body at certain stages of those diseases, judging from the distribution of various efflorescences and spirochaetes in syphilis of the foetus. However, there seems to be a tendency among the workers of to-day to attach too much importance to, or to be misled by, the macroscopic findings, with the result that they are likely to overlook the disease if no ulcers or nodules make their appearance.

Referring to leprosy, even the few advocates of intestinal leprosy have depended upon the microscopic examination of ulcers or smears, and have demonstrated the existence of the leprosy bacillus in a case or two. It is no wonder that many scholars deny the existence of intestinal leprosy. They are evidently not aware of the fact that in the upper and lower parts of the muscularis mucosae of the stomach and the intestine there usually develop numbers of lepra cells, and ultimately so extensive a pathological change as to be beyond comparison with that in any other of the viscera, while no change whatever is to be observed in the mucous membrane.

This is also true with regard to pulmonary leprosy. Bonome and Papes saw the lepra bacillus in foci of pneumonia and concluded that the condition was pulmonary leprosy. But it is quite usual in lepra nodosa to find more or less numerous bacilli in the interalveolar connective tissues and the bronchial mucous membrane of the lung, with no pathological change whatever.

Hansen and others who deny the existence of either pulmonary or intestinal leprosy base their argument on their inability to find in the mesenteric or bronchial lymph glands any changes comparable to those in the portal glands in hepatic leprosy. But it is not at all difficult to demonstrate lipoid degeneration and bacilli by staining sections of these glands with Sudan III.

Notwithstanding the fact that the suprarenal gland is an organ favorable to the production of nodules, it has been said that leprotic changes in it are rare. This must be due to inaccuracy of observa-

tion, and the scantiness of the bacilli present. The same may be said of leprosy of the uterus and the heart.

Are there present in these organs, in any other disease, any newly-produced tissues that contain a lipoid substance similar to that produced in leprosy? To the best of the author's knowledge there are not. Such peculiarities with regard to the parts affected, and the peculiarities of the vacuoles described, are not to be seen in any other disease. Furthermore, it is a fact that a few lepra bacilli are always found in the vacuolated cells.

Only in the ovary does the bacillus seem to penetrate into cells in which any lipoid substance has already existed. The lipoid-containing lepra cells found in organs other than the ovary seem to have resulted from degeneration caused by the presence of leprosy bacilli in them.

A question that presents itself is whether in these organs the production of the lipoid substance discussed is caused, like the globi in the skin or testicle, by the degeneration of leprosy bacilli. The author believes that it is not. Conditions do not seem to be favorable for the growth of the bacillus in the inner organs. Even in the liver and the spleen, where a few bacilli are always seen and where their growth is comparatively good, we see no colonies or globi. In other organs the growth of the bacillus is very insignificant.

Since these always are our findings at autopsy, the conditions are probably the same in the organs of a living leper. If so, the remarkable production of the lipoid substance in the lepra cells in the internal organs cannot be attributed exclusively to the transformation of leprosy bacilli. On the contrary, it may be necessary to consider the biological reaction that may be produced in the cell as a result of the invasion of the bacillus.

It may be argued that, inasmuch as the pathological changes of the inner organs always follow those of the skin, mucous membrane, nerves and the testicle, and inasmuch as this order is also seen in the transition of the lepra bacillus, it may be surmised that the lipoid substance produced from bacilli existing in abundance at such principal foci as the skin will accumulate in cells of the organs under consideration, just as the various inner organs of animals that are fed a special fat will show accumulation of that fat. The point of this argument is clear and rather convincing, but there are other points that cause the writer to hesitate to support this theory. For

example, leprous infiltration and notable lipoid degeneration are sometimes observed in the organs of a patient whose skin changes are not extensive.

It is true that even in the inner organs the leprosy bacillus does grow or degenerate and give rise to the lipoid substance. But in such cases the amount of lipoid substance must be quite negligible, in proportion to the unfavorable growth of the bacillus. The author would rather surmise that, in the majority of cases, the lipoid substance is produced in the cell, as opposed to its origin from bacilli that have entered there. How much of the lipoid is due to transformation of bacilli and how much is the product of the cells is a question the solution of which must await the cultivation of the bacillus and the determination of the chemical formula of the lipoid substance.

At any rate, a very complex relationship seems to exist between the leprosy bacillus and the lipoid substance. Sakurane has published his views to the effect that the lipoid production is due to the growth of the bacillus. However, the author has observed that in the inner organs the existence of lipoid does not go parallel with bacillary growth, and as for other parts of the body he has reason to believe that at the stage where the production of lipoid is active the growth of the bacilli in the lepra cells has already passed the peak, and there appears degeneration which shows that their decay is at hand.

Sugai's experiment, in which he demonstrated that lepra bacilli left standing in a lecithin solution will perish, seems to indicate the natural course of progress. If we examine an ulcerated nodule that has healed or been absorbed as the result of the administration of chaulmoogra oil, either by injection or by mouth, we see that there remains a remarkable vacuolar degeneration of tissues while through granular degeneration the leprosy bacilli have disappeared. Probably the injection or oral administration of this valuable agent for the remedy of leprosy accelerates the production of lipoid substances in the lepra cells and, in turn, causes the natural degeneration of bacilli therein.

Next of interest is the fact that in the serum of leprosy patients there is a substance that reacts in the Wassermann test, the Borge-Meyer lecithin test, and Teruuchi's kaolin test. As the antigen for the above Wassermann test, not only the leproma and leprous viscera

but also extracts of guinea pig heart or dried bonito, lecithin, kaolin, etc. (substances that have no connection whatever with leprosy) serve the purpose, as with the serum of syphilis. The facts that more negative reactions are seen in anesthetic than in cutaneous leprosy, and that in the nodular type the degree of the positive reactions is proportionate to the intensity of infiltration of the nodules, suggest possible relationships between the leprosy bacillus and its degeneration products on one hand and the lipoid substance in the lepra cells on the other.

The above shows that the lipoid substance has a very important bearing on the pathology of leprosy, and the author believes there are still many points open for further investigation.

The author wishes to express his thanks for the assistance given by Dr. Masayo Segawa in the matter of microscopical classification of lipoid substances.

DESCRIPTION OF PLATES

PLATE 44

FIG. 1. Liver. Glisson's capsule is thickened and the lobulation made conspicuous. Lepromata are clearly visible in the sheath and the central veins. ½ ×.

FIG. 2. Liver. Small, pale lepromata are clearly visible in the lobe of liver and the thickened sheath. 3 ×.

FIG. 3. Spleen. The trabeculae are conspicuous. The pulp is slightly anemic, and lepromata are seen clearly and abundantly, appearing as pale spots. 3 ×.

FIG. 4. Spleen. Many lepromata are present. Trabeculae conspicuous. 6 ×.

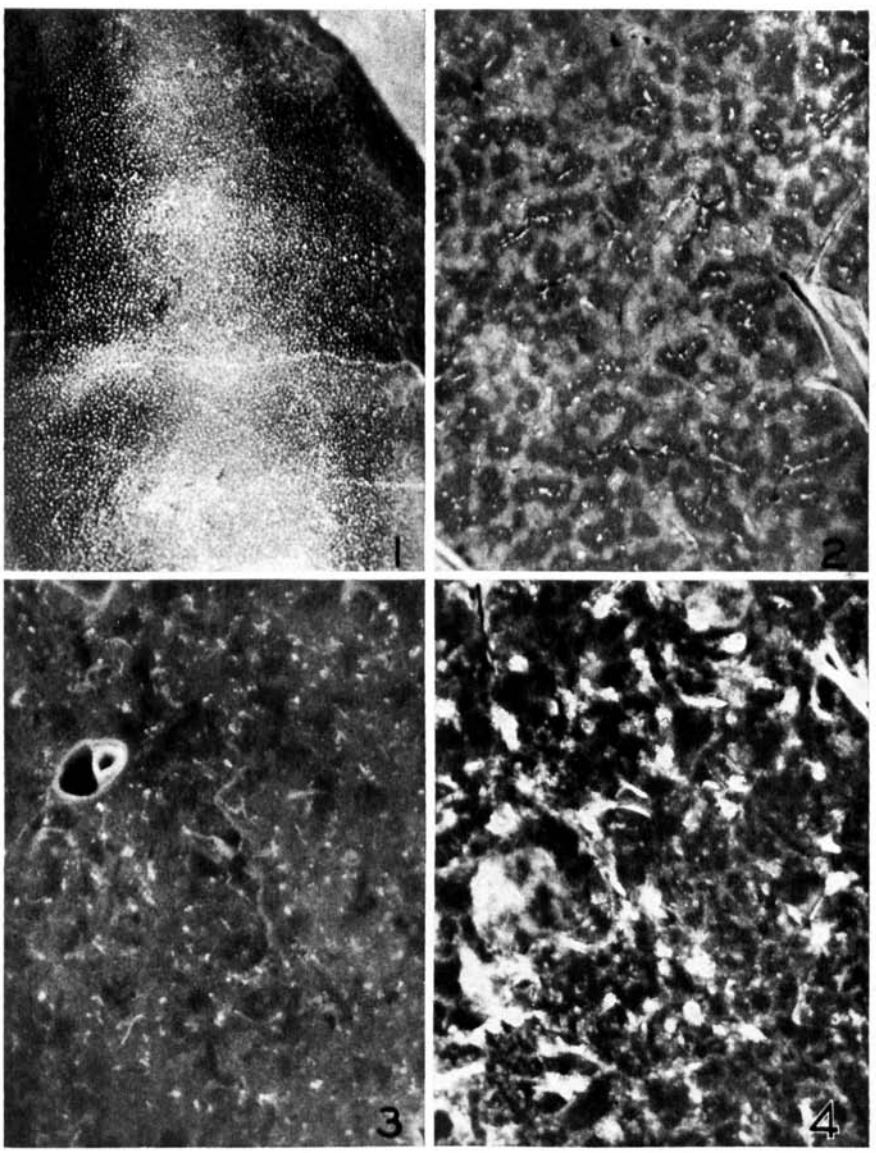

PLATE 44

PLATE 45

FIG. 5. Suprarenal. Atrophy of medulla. Lepromata at the boundary between the cortex and medulla. 3.5×.

FIG. 6. Suprarenal. Lepromata at the boundary of the cortex and medulla. 7×.

FIG. 7. Lymphatic gland, inguinal. Comparatively large lepromata of yellowish-white color. 3×.

FIG. 8. Lymphatic gland, inguinal, showing large lepromata. 7×.

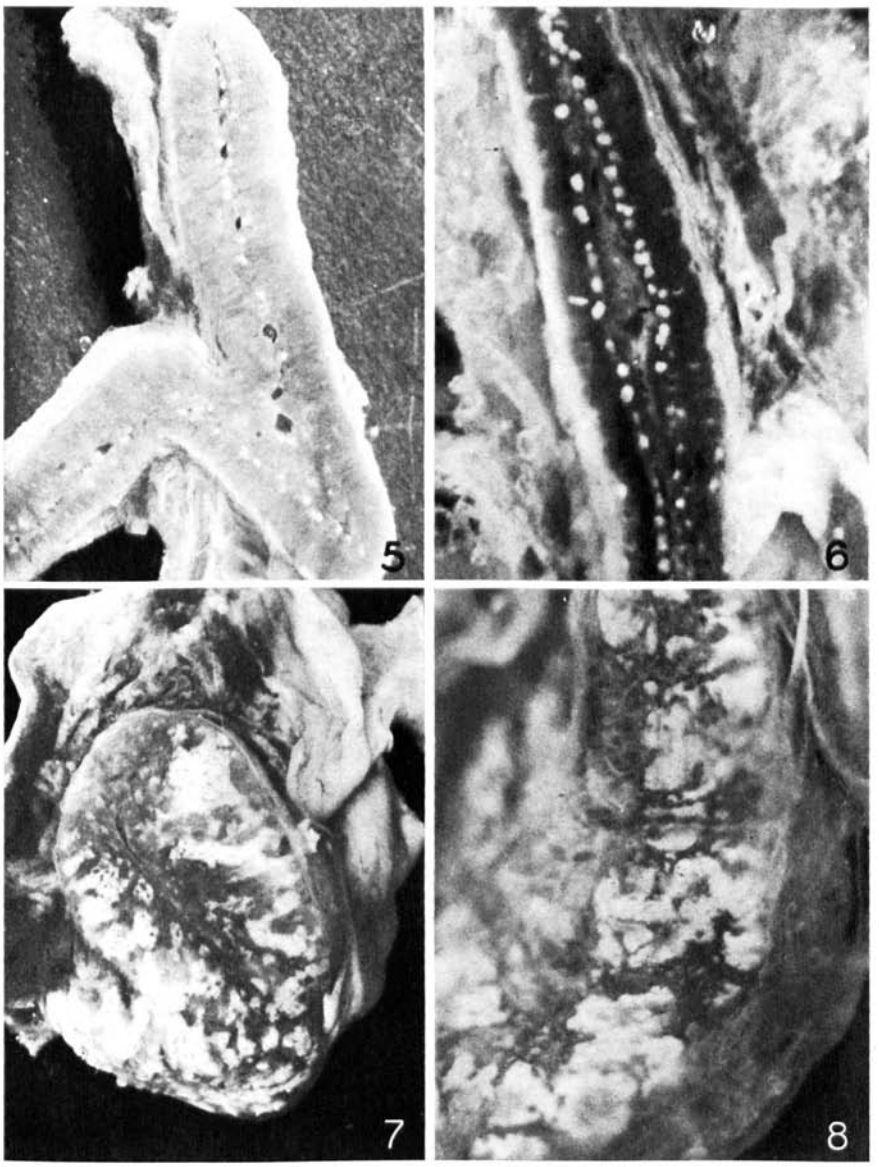

PLATE 45