STUDIES ON THE RETICULUM IN THE DIFFERENT TYPES OF LEPROSY [1]

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INTRODUCTION

The modifications or alterations of the reticular structures in the pathological processes of leprosy have not yet awakened the interest of investigators of that disease, and their rôle in those processes is still unknown. Their importance is great, however, because these elements are intimately related to the pathological physiology of the reticulo-endothelial system.

The literature on the significance of the behavior of the reticular tissue in many other fields of pathology has been studied extensively, especially from the histological point of view. Numerous papers have been published regarding the nature of its fibers, its origin and its relationship to the cellular elements of the connective tissues. However, this abundance of publications does not mean that the problems concerned are solved; on the contrary, opinions expressed by different authors are very much in conflict.

Despite the existing uncertainties regarding many features of this matter, there are several facts that have been definitely established. The fibers which constitute this tissue can be differentiated from the collagen fibers, because they are profusely anastomosed. The substance from which they are formed, although very closely related to collagen, is not identical with it. The reticulum fibers do not swell under the action of acetic acid, and they are resistant to potassium hydroxide (10% solution). They are not stained by the acid dyes employed for the demonstration of collagen, and they take up colloidal silver—applied by the methods of Bielchowsky, Achucarro, and Rio Hortega and their modifications—more intensely; they change to dark brown or black, while the collagen becomes yellowish or a pale yellow.

Authors like Mallory and Parker do not believe that reticulum is fundamentally different from collagen, because there is no interruption of continuity between them. Foot thinks that the

[1] Presented at the Fifth International Leprosy Congress, held in Havana, April 3-11, 1948. The basic English translation from the original Spanish was supplied by the authors.

special property of fixing silver shown by reticulum is due to a substance with which its fibers are impregnated, and which can be dissolved by sodium hydroxide. Dublin considers reticulum as a precursor of collagen and very similar to it, though differing in some of its physico-chemical characteristics. Siegfried believes that the substance which forms reticulum has specific characters, and calls it reticulin. Mall is of the same opinion, although at first he thought the substance was related to elastin. Laguesse considers reticulum as a variety of collagen containing elastin. Del Rio-Hortega distinguishes two varieties of these fibers: (*a*) one which forms the network of the hemopoietic organs and the thymus, which according to his opinion would be the reticulin, and (*b*) one found in other organs and glands, which would be precollagen. We ourselves use both terms—reticulum and precollagen—indiscriminately, since a distinction has not yet been sufficiently established.

Another of the matters of discussion is the relationship between these fibers and the cellular elements—the connective-tissue and reticular cells. For some authors the fibers are independent of the cell protoplasm, and are formed by different mechanisms in the intercellular spaces, while others believe they are of intracellular origin. According to Nageotte and Guyon, the reticulum of nerve and muscle contains fibroblasts; but in the adipose tissue those cells are found only in the collagenous connective-tissue zones about the fat lobes, so the question remains what cells are responsible for the formation of reticulum.

Apparently there is no doubt of the intraprotoplasmic situation of these fibers when the stromas of the splenic, tonsillar and lymphoid tissues are considered. The fibers of these stromas are in intimate relationship with the endothelial cells of the vessels, constituting what was formerly known as the reticuloadenoid tissue. Recent data have proved that this is true, at least under some circumstances.

Many authors accept the intracellular origin of the collagen fibers. Tello speaks of "endocellular inofibers" in describing his tissue cultures, and Bloom and Sanderstroom have the same belief. So has Costero as a result of his study of the placenta; both he and Del Rio-Hortega, who differentiated sarcomas, found argyrophil precollagen fibers in the cytoplasm of fibroblasts.

Taking for granted that the reticulum derives from the cellular elements, directly or indirectly, only the endocellular theory is capable of explaining satisfactorily the activities and functions which this substance performs in normal and pathological processes (inflammatory, productive, scarring, etc.), and

also its permanence and growth in determined zones in which other fibers degenerate or die. It must be remembered, however, that the reticulum fibers are absent in tuberculous caseation, where the elastic fibers are not destroyed, a fact which is related to the absence of blood vessels in the tubercle (Costero).

One of the most interesting points about the reticulum is its capacity of development, not only in the physiological processes (regeneration of the uterine mucous membrane and of the formation of the corpora lutea), but also in certain pathological processes. Its development increases, according to Costero, after a necrotic process. Foot says, "this growth is stimulated by the tubercle," an assertion which, in our opinion, is an error of interpretation because it is known that reticulum is the constituent element which appears with regular characteristics and simultaneously with the cells which form the tubercle. In the scarring processes apparently, reticulum performs a very important function, as has been pointed out by Foot with respect to regression of the tubercles in chronic pulmonary tuberculosis, and by Espin in the regressive phenomenon of the tuberculoid nodule produced by the eggs of *Schistosoma mansoni.*

It seems that not only the fibroblasts and reticulo-endothelial cells are capable of producing reticulin, but that the endothelium of the blood capillaries also possesses this capacity (Corner). That is why the blood capillaries have these fibers as constant elements in their structure. We do not find them in the lymphatic capillaries.

The papers which deal with the intervention of reticulum in the pathology of the skin are few. Bizzocero, using Bielchowsky's procedure, studied the behavior of reticulum in syphilis, tuberculosis and leprosy, the conclusions of his short note being as follows: The chronic inflammatory process of syphilitic nature provokes neoformations of reticulum; in the leproma the reticulum fibers are arranged in such a way that they give lodgment to the specific vacuolate (Virchow) cells; in the tubercle the fibers are profusely branched in the lymphocytic zone but are very scarce in the central, epithelioid zone. Way studied the reticular changes in the dermis in a large series of dermatological affections but makes no reference to the behavior of the reticulum in leprosy, tuberculosis, or Boeck's sarcoid. Dublin, dealing with the reticulum in general, refers to the reticular formations in different specific granulomas, among them tuberculosis of the skin, and arrives at conclusions similar to those of Bizzocero. In syphilis, like Costero, he also found abundant neoformations of reticulum mainly in the gumma; in leprosy, he

states, the histiocyte deposits reticulum freely in different ways, according to whether the lesions are tuberculoid or lepromatous.

METHODS

The material studied by us consists of biopsy specimens which are sent as a matter of routine from the dispensaries and leprosaria to the Laboratory of the Central Leprosy Service in Caracas. All the material had been fixed in 10 per cent formalin. Most of it was imbedded in paraffin and impregnated by Wilder's silver method, but some was cut by the freezing technique and impregnated by Del Rio-Hortega's method. The former method is the more useful one for routine work, but the results obtained with it do not show the fine details revealed by the latter method—which, however, has the disadvantage of being the more laborious and necessitating the use of frozen sections.

A total of 40 specimens has been studied, including both the lepromatous and neural types, the latter in its two forms, tuberculoid and simple macular. This number of specimens is small, but they were selected with much care from a collection of one thousand, choosing only cases which were typical from the clinical and anatomopathological points of view.

RESULTS

A common and fundamental characteristic of all our material studied is that the reticular formations found were located exclusively in the inflammatory zones. That is to say, we have not observed any alterations in the reticulum outside of the granulomas or the zones of inflammation.

Simple macular patches.—In these lesions the inflammatory infiltrations are found in the proximity of capillaries and small blood vessels as well as around the nerves and pilo-sebaceous follicles. The reticular formations observed are very slight, and are represented by very thin threads placed radially, starting from the preexistent reticulum belonging to the structures mentioned.

These fibers are very fine and almost straight; rarely are they branched. It is only occasionally that they anastomose with each other directly or by secondary branches, and they do not form real nets. The fibers grow thinner as they move away from their supposed centers of formation, until their distal extremities finally make contact with the dermal collagenous bundles. (Fig. 1).

Lepromatous type lesions.—Here we must separate the small, incipient lesions from the highly developed lepromatous

granulomas which involve extensive portions of the dermis. In the former case, the normal structures of the skin are undamaged, and only in small zones do we observe the typical lepromatous condition, which generally centers around a small blood vessel or capillary. The reticular threads can be distinguished easily, since they appear clearly and precisely and form a net which joins the collagen with the granuloma. The fibers of this network are of different thicknesses, but in general thin ones predominate. There is much anastomosis among them, by the intervention of other smaller and thinner fibers which form the nets whose meshes adapt themselves to the sizes of the cells forming the granulomas. This type of formation reminds us of the lymphatic nodules scattered about in the intestines, though they differ because their fibers are more delicate and their course more sinuous (Fig. 2).

When the lepromatous granulomas are well developed, we observe that the normal cellular elements of the dermis are missing, and also the collagen bundles. The latter element remains as a thin band in the deeper level and also as thin walls or partitions distributed in the mass of the leproma, limiting the nodules. This remnant of the preexistent collagen is very dense, and its appearance indicates that it is being submitted to much pressure resulting from the growth of the elements of the granulomas. The reticular nets are formed by profusely anastomosed branches, the meshes being arranged by means of the cells in a manner similar to that observed in the incipient lesions. The fibers are generally thicker, however, and—though we cannot say that this is an established rule—the thicker ones tend to arrange themselves perpendicularly to the epidermis. Among these nets there can be distinguished a finer and less branched reticulum which contributes to the formation of tubes belonging to the newly formed blood capillaries; and they also arrange themselves as do the thicker fibers (Fig. 3).

Tuberculoid type lesions.—The development of the reticulum in the tuberculoid granuloma is more irregular than in the lepromatous lesion. This irregularity pertains not only to the thickness of the fibers, but also to the number of the different regions of the granuloma, and in relation to its cellular elements.

The threads may be very broad, and occasionally they appear microscopically as if they were real protoplasmatic bands. Such fibers may coexist with other very fine ones, and between them we observe a wide diversity of thicknesses. The ramifications and anastomoses of these threads are more abundant in the periphery of the granuloma (where the thicker ones are to be found) than

in the inner zones occupied by the giant and epithelioid cells. In fact, the fibers are more scarce in the latter location, and they present fewer branches and grow thinner. In general, we have observed that they do not make contact with the giant cells (Figs. 4 and 5).

When the inflammatory process affects the nerve, the reticular fibers are arranged around it, forming very regular concentric circles, and they settle in the region of the neuritis (Fig. 6). In these cases the fibers are circular, with very little if any branching, and they are not placed in a radial position.

The formations which affect the hair follicles and sebaceous glands are very irregular, consisting of long and thin fibers, with slight branching. In the region of the coil glands the newly formed threads are very thin, at least when the inflammatory process is beginning (Fig. 7). When it is more developed the aspect is similar to the typical tuberculoid granuloma.

In general, the reticular neoformations in the lepromatous and tuberculoid granulomas tend to form a tridimensional network with meshes of different sizes, though always small, which give lodgment to the cells which form the granulomas (Fig. 8).

Occasionally, mainly in the tuberculoid granulomas, we have observed the phenomenon of transformation to collagen, more or less accentuated. We did not observe the intervention of the proper reticulum of the erector pili muscle in any of the described lesion forms. The subbasal reticular layer does not seem to interfere with these formations.

COMMENT

From our observations, and bearing in mind the general knowledge of the reticulum and its behavior in other specific granulomas such as tuberculosis and schistosomiasis, we think that the reticular neoformation which accompanies the different forms of leprosy lesions improves the organic defenses against the activity of the bacillus. These defenses are related to two fundamental processes: first, the providing of a collagen net and its location; and second, the ultimate change to scar tissue. At the same time it is probable that the reticular neoformation cooperates in the nutritive activities.

The movement of the wandering cells (histiocytes) toward the affected zones plays an important role in the defense. Costero demonstrated that the macrophage cells, when passing over precollagen fibers, have about two hundred and thirty times the mobility of which they are capable in a nontissue coagulum.

Moreover, due to the slight expansion capacity of the collagen,

it is natural that other elements are needed which by their characteristics facilitate the building of defensive granulomas such as those observed in leprosy. The reticulin threads are an ideal material for this purpose, because of its self-growth and great flexibility. As an earlier element in the formation of collagen, it facilitates retraction and scarring in the healing process of the lesions.

It would be of great interest to be able to prove the same thing of the regressive phenomenon suffered by the leprosy lesions with the treatments used today (chaulmoogra oil and sulfone drugs). Here it has been observed, in some cases which had a favorable course, that collagen formation and fibrosis are much accentuated in the interior of the lepromatous granulomas (Convit and associates).

SUMMARY AND CONCLUSIONS

We have studied reticulum formation in the two types of leprosy, lepromatous and neural.

Reticulum, according to our observations, is a constant element in the inflammatory reaction zones of the simple macular lesion, and in the lepromatous and tuberculoid granulomas.

These reticulum formations, very simple in the infiltrated zones of the simple macular, grow complex in the lepromatous type, and in the tuberculoid variety adopt the characteristic forms described by other authors in tuberculoid granulomas of other origins.

The normal arrangement of the reticulum is a tridimensional network whose meshes give lodging to the cells which form the granuloma.

Apparently these formations play an active rôle in the defensive process of the organism against the leprosy bacillus.

DESCRIPTION OF PLATES

PLATE 24

FIG. 1. Simple macular lesion. Blood capillary, with slight reticular neoformation. Notice the continuity with the reticulum proper of the capillary. (Wilder's method.)

FIG. 2. Small lepromatous nodule. This shows a capillary and its reticulum fibers anastomosed with the collagen. (Del Rio-Hortega's method.)

FIG. 3. Lepromatous nodule. Almost complete absence of the normal collagen element; abundant reticular fibers, greatly anastomosed, forming a closed net. (Wilder's method.)

FIG. 4. Tuberculoid granuloma, nodular formations. Collagen present; abundant anastomosis of reticular fibers. (Wilder's method.)

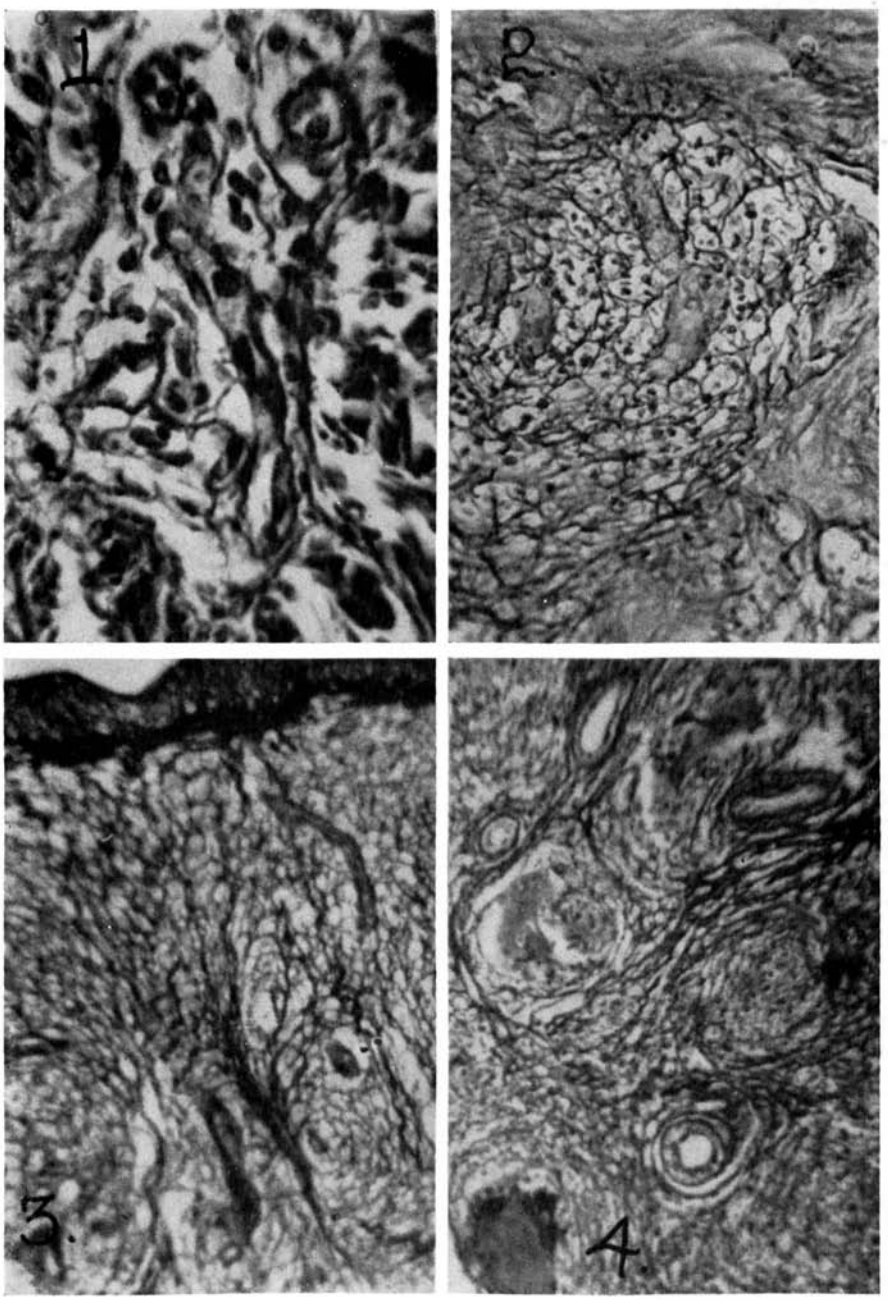

PLATE 24

PLATE 25

FIG. 5. Tuberculoid granuloma. Giant cell and reticulum in the central zone. Notice that the reticular fibers are well separated from the giant cell. (Wilder's method.)

FIG. 6. Tuberculoid granuloma, transverse section of a nerve. The reticulum fibers are concentric, situated exclusively in the infiltrated zone. (Wilder's method.)

FIG. 7. Tuberculoid leprosy. Very slight reticular formation in the coil-gland zone, more accentuated in the apical zone. (Wilder's method.)

FIG. 8. Lepromatous granuloma. Details showing three types of thicknesses of the fibers and their relations with the collagen. (Del Rio-Hortega method.)

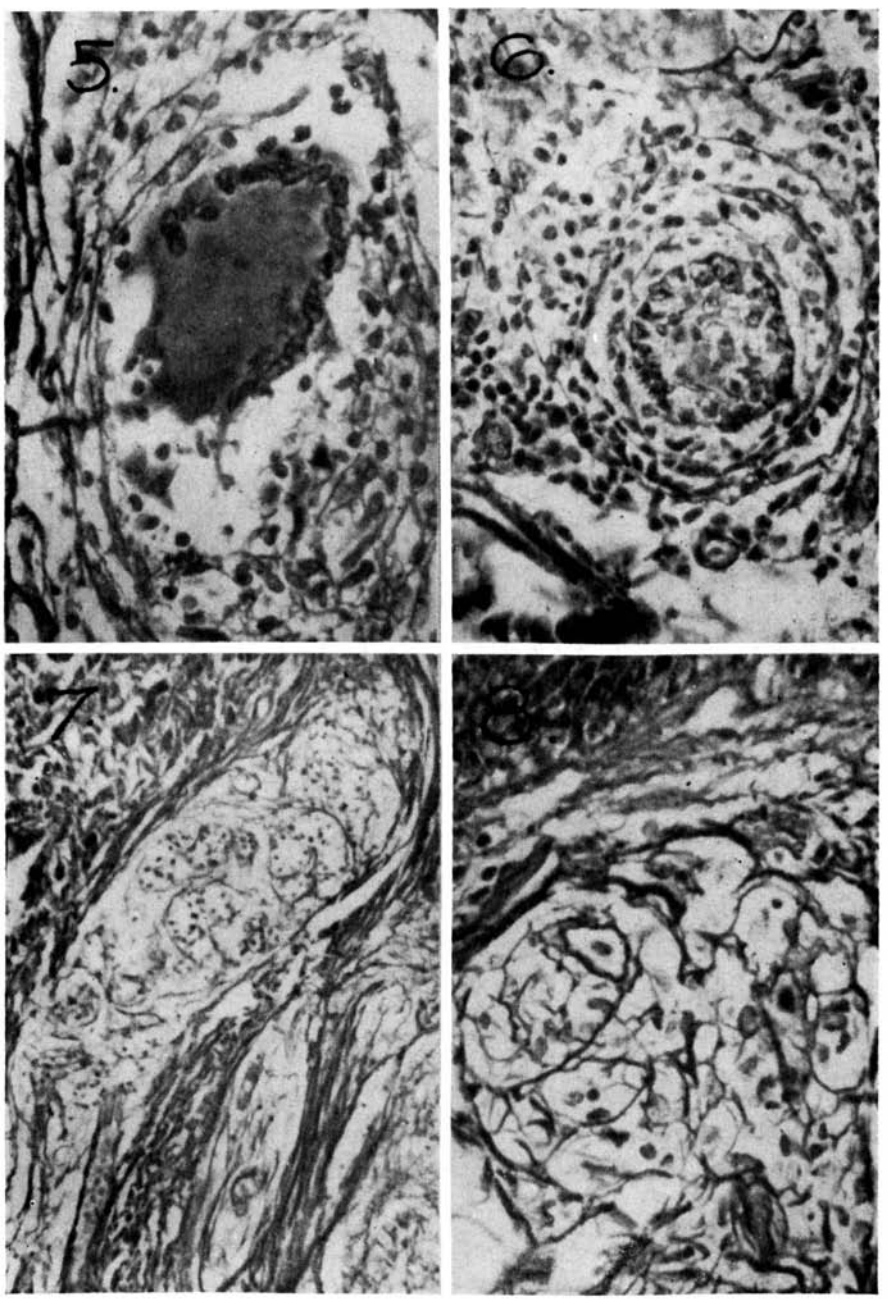

PLATE 25