MODERN ASPECTS OF THE EPIDEMIOLOGY OF LEPROSY[1]

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The epidemiology of leprosy remains today the same enigma that it was many years ago. True, it seems that the time has passed when there was great controversy as to whether the disease is transmitted by heredity or by mere contact, but in view of new discoveries it seems necessary to take up again this question from a new viewpoint.

In 1910, in the *Memorias do Instituto Oswaldo Cruz,* there appeared a paper of extreme interest by Fontès, one of the collaborators of the Institute. In it the author reported that the tubercle bacillus must be classified as a filtrable virus. This conclusion was so contrary to established views that it met with incredulity and was soon forgotten. However, in 1922 Vaudrémer came quite independently to the same conclusion. Since then the question has been taken up by many workers, and though their findings have often been contradictory the sum total of the results, especially those of studies carried out in the laboratory of Calmette, have compelled acceptance of the view that the tubercle bacillus has a filterable phase. Similar experiments have been carried out with the Hansen bacillus, but for self-evident reasons only to a limited extent. However, by analogy with tuberculosis we must agree that the leprosy bacillus is probably filterable.

Most of us realize what a great revolution has taken place recently in our concept of the heredity of tuberculosis. Only thirty years ago we held, as a dogma, that heredity of tuberculosis was not direct but indirect; that the children inherit a constitution that makes them especially susceptible to the disease. Now we think otherwise. Not denying the constitutional factor, we see that the principal one is the direct transmission of the Koch bacillus from the sick mother

[1] Report read before the All-Russian Epidemiological Conference, Moscow, March 20-25, 1934.

to the fetus through the placenta. Some time ago the pathologists debated whether such transmission could take place through a placenta free from tuberculous lesions, but this controversy now seems more of academic than practical character, for if the tuberculosis virus can pass through the pores of the filter-candle it can certainly traverse the placenta. Thus, by denying the germinative infection, we have recognized only the infection in utero, and we apply the Calmette antituberculosis vaccination only to children born of a tuberculous mother. These facts gained in the study of tuberculosis are significant with respect to leprosy, since on account of the exceptionally close morphological similarity between their bacilli we feel quite justified in assuming a full resemblance in their behavior.

In leprous patients there commonly is a considerable involvement of the testicles, and often of the seminal vesicles, with large numbers of bacilli present. Under these conditions the sperm may contain a large admixture of the organism. This only tends to indicate that a leprous man can transmit the infection to healthy women through sexual intercourse, but it can hardly have any importance in a discussion of the question of hereditary transmission of leprosy; only the mother can be concerned in that. So again we have to face the question of the manner in which the infection is transmitted, whether in the womb of the sick mother or from the outside world.

This question may sound paradoxical at a time when the heredity of leprosy has long since been dismissed as an epidemiological problem, and when it is recognized by all that only the outside medium plays an important part in the epidemiology of the disease. I need only point out that it often happens that what is considered the truth to-day is questioned tomorrow. Therefore I consider it useful to resubmit this question to discussion in the light of recent scientific developments.

Modern clinical medicine and pathology distinguish two forms of tuberculosis, that of children and that of the adult. It is held that in children the lymphatic apparatus is chiefly affected and the process tends towards generalization; that in adults tuberculosis is mostly localized, often attacking the lungs while the bronchial glands are affected secondarily; and that in children tuberculosis has a lymphogenic and haematogenic origin while the primary involvement of the lungs in grown-up patients takes place by aspiration. This classification rests upon strong evidence, but my own view on the subject differs from it considerably.

On the basis of my own experimental observations I am inclined to believe that the tuberculosis virus, passing from the mother to the organism of the child, is detained chiefly by the reticulo-endothelial apparatus of the lymphatic glands and, possibly, by the bone marrow, and that to this is due the frequent involvement of the lymphatic apparatus and bones in children. The disease of these organs may be very severe, or it may be so mild that it will give rise to no external manifestations. In the latter case we speak of a veiled infection, and there is plenty of evidence indicating that such an infection can continue for years, and perhaps for scores of years, constantly threatening to pass into an active form if favorable conditions should arise. Thus I hold the view that an endogenous infection is possible in adults as well as in children. However, this does not mean that I deny the possibility of the exogenous route, but of this I shall speak later.

Can we reason in the same way with regard to leprosy? The epidemiology of that disease, at least as regards the clinical, bacteriological and pathological features, is so undeveloped that it is impossible to give an exhaustive answer to the question. At present it is only possible to suggest the way of its solution.

In recent years there has been much interest in the puncture of the lymphatic glands as a diagnostic measure, especially in the early stages of the disease. There are reported cases in which the cutaneous lesions, of mild degree, have given negative findings with respect to the Hansen bacillus while material from the lymph glands has been positive. We have such a case in our leprosarium. The clinical and histopathological findings were so indefinite that we were about to conclude that the case was not leprosy, but gland-puncture was positive. In 1914 Leboëf reported obtaining the bacilli from glands of perfectly healthy people who had lived among lepers, though none could be discovered in their nasal mucosa.

Comparing these results with the observations of certain authors (Rabinovitch, Sugai, Manobe, and lately Montero) who found leprosy bacilli in the blood of the diseased mothers, and at the same time in the placenta and in the blood of the immature fetus or new-born babies, we must conclude that the bacilli may pass through the placenta into the blood of the fetus, from where they can be removed by the blood-purifying system, i.e., the reticulo-endothelial cells of the lymphatic glands and, perhaps, of the bone marrow and spleen. How

long they can retain their vitality in these organs we do not know; we can only utilize analogous facts, remembering however that analogy is not proof. For instance, the spirochaete of syphilis can remain for a long time in the organism in a latent state, retaining fully its vitality (syphilis hereditaria tarda, progressive paralysis, etc.). Nearer to leprosy stands tuberculosis, the bacillus of which can remain in the tissues for many years in an inactive state, to resume activity when conditions become favorable.

On the basis of these facts, some of them firmly established and others assumed by analogy, we might perhaps return to the old views concerning the possibility of a hereditary transmission of leprosy, except that the conception of "heredity" as it was understood by Danielssen and Boeck, and others, would be narrowed to that of "congenital infection"—infection in utero. However, such a conclusion would be more than premature. It would stand in flat contradiction to the well known fact, first established by Hansen, that children separated early from their diseased parents rarely develop leprosy. Hasseltine, in Hawaii, observed that when children are separated immediately after birth the incidence of the disease among them is minimal; of 121 children only one became affected. The practical experience of certain leprosaria in India is to the same effect. From this it becomes quite clear that the view of the hereditary transmission of leprosy is untenable.

Passing now to the other factor to which we attach such great importance in the spread of leprosy, namely, infection from the outside medium, we meet with a surprising paradox. There seems to be no correlation of exposure to the microorganism and acquisition of the infection. We may recall the observation of Schäffer that leprous patients with throat involvement discharge enormous numbers of bacilli when talking—he calculated numbers up to nearly 30,000 per minute—and project them to distances up to 1.5 meters. There is no doubt that these germs are inhaled in large numbers by people who are near; this has been confirmed by numerous observations. Nevertheless, experience shows, for instance, that in spite of this constant aspiration of the microbe cases of infection in the medical staff of a leprosarium are so rare as to be negligible.

What is the explanation of this? Some hold that most people must possess an immunity to the infection, but what kind of an immunity that is they do not say. Others think that most of the

bacilli in the diseased organism are dead, and try to prove this quite arbitrarily by the fact that when a double stain is used some of the bacilli take up one dye while the others take another. Both of these theories are dogmatic and perfectly groundless. The incompleteness of our knowledge of the biologic nature of the leprosy microbe is made still more evident when we recall the experiments made by Danielssen, and later by Profeta, who repeatedly tried to inoculate leprosy into healthy people, including themselves, with negative results. These experiments remain unexplained today, and force the modern conception of the contagiosity of leprosy into a corner from which we seem to find no way out.

However, these experiments are important inasmuch as they negative attempts that have been made to find the transmitter of the disease in one or another insect, as the mosquito, the bed-bug, or the fly. So far as I know none of these authors have investigated the development of the germ in the insect; it was merely assumed that mechanical transmission of it from the sick to the healthy person takes place. It seems that in the intestines of flies that have fed for some time on the discharge of a leprous ulcer there can be found "great" quantities of the bacilli, which could be deposited upon the skin of people contacted by such flies, and on the basis of this certain authors (Leboëf, Marchoux) draw conclusions as to the possible role of flies in spreading the disease. Muir and Rogers point to mosquitoes as the possible transmitters of leprosy in tropical countries, basing their view on the fact that leprosy usually develops on parts of the body most exposed to mosquito bites. It is obvious that all such opinions are very unconvincing, and they become still more so when contrasted with the experiments in which whole leprous tubercles, containing innumerable quantities of the microbes, were inoculated into and under the skin without causing infection.

The imperfection of our knowledge of the epidemiology of leprosy is further evidenced by the fact that we are quite ignorant concerning the route by which the infection enters the organism. Why does leprosy attack the skin primarily, while in contrast to tuberculosis it never causes any lesion of the lungs or intestines? Why does it affect the male sex-organs very early, while in tuberculosis these are rather rarely involved? The skin being the seat of persistent lesions, many authors have looked for the primary affection there. What I know of the literature of leprosy obliges me to conclude that if the skin serves at all as the place of entry this is

not common. Experiments on human beings, often made by chance, serve to show that a primary leprous granuloma never appears at the place of inoculation of the leprous material. There develops only a small purulent ulcer, with leprosy bacilli in the discharge, but these disappear and the ulcer heals in the usual way. Such was the fact, at least, in Arning's experiment. It becomes quite clear that the portal of entry must be looked for elsewhere.

At the first International Leprosy Congress (Berlin, 1897), Sticker stated that in his opinion the nasal mucosa is the most common point of invasion, because in 83 per cent of 153 cases of all types he found a more or less pronounced nasal lesion, which he considered primary. The Congress accepted Sticker's view in concluding that "the place at which the leprous infection penetrates into the organism must, evidently, be the oral and nasal mucosa." However, disillusion came later, for it was found that lesions of the nasal mucosa were not as common as Sticker believed. These lesions, then, came to be considered as of secondary nature rather than as the primary manifestation. However, I myself am quite ready to accept Sticker's view, suggesting only the following essential addition: that the lepra bacilli can penetrate into the organism through the mucous tissues without causing any pathological change or developing any primary lesion there. Knowledge that has been gained with regard to tuberculosis during recent years justifies that addition.

Now I have reached the question that to me is of the utmost importance at the present moment: In what form does the leprous infection enter the organism? The simplest and most obvious answer is that it is in the form that we observe ordinarily, i.e., the acid-fast rod. However, the observations of Shäffer which have been mentioned, and the rare infection of casual contacts, force me to accept such a seemingly natural answer with some reserve. To come nearer to the solution of the question we must make an excursion into a field that as yet has been given very little study with regard to tuberculosis and especially leprosy. I refer to the behavior of their bacilli outside of the body, in nature.

After Koch discovered the tubercle bacillus many studies were made concerning the spread of tubercle bacilli in the outside world. The microbe was looked for in dwellings, hospital wards, places of public meeting, etc. In all this the notion prevailed that the germ itself does not change, that it retains the morphologic and biologic characteristics ascribed to it by Koch. This work now has only a

relative interest, for in recent years it has been established that the tubercle bacillus can change its morphologic and biologic properties to a great extent outside of the tissues. Of special value in that connection are the studies that prove the mycotic nature of the tuberculosis virus (Reenstierna, Karwacki, Kedrowsky, Feigin, Mollgaard, Weisfeiler). Similar studies were carried out much earlier concerning the leprosy bacillus (Barannikov, Kedrowsky, Reenstierna, Williams, Rost). However, no importance has been accorded them on the epidemiologic side; in fact, no attention has been paid to them except, perhaps, by a few isolated authors of whom besides myself I can only mention Walker.[3]

The importance of this question as a general epidemiological problem justifies fuller consideration of it. When we recall most of the well-known diseases we can see certain phenomena of a systematic character. The common animal parasites secure safety from the influences of the outside world by undergoing certain cycles of development. They become "renovated" in the organism of one or another insect—the parasite of malaria in the anophelines, that of the Pendine ulcer in the phlebotomus, the spirochaetes of African and Persian recurrent typhus in the mite, that of European recurrent typhus and the hypothetical virus of spotted typhus in the louse. The bacteria behave in a different way. The one that causes the Siberian ulcer preserves itself by forming spores as soon as it finds itself in the outside world; the same is true for the tetanus bacillus and for the large group of bacteria causing malignant edema. The staphylococcus is preserved by producing stable forms that can withstand long desiccation and heating up to 80° to 90°C., and the streptothrices and actinomyces produce forms that are surprisingly resistant to desiccation.

I cannot maintain that this phenomenon is a general rule, for we know little concerning the behavior in the outside world of the streptococcus, pneumococcus, the bacilli of glanders and diphtheria,

[3] Unfortunately, I have been unable to acquaint myself with Walker's original work [Some new aspects of the etiology and endomiology of leprosy. *Journal of Preventive Medicine,* 3 (1929) No. 3], but judging from a short summary in the *Tropical Diseases Bulletin* [26, (1929) 1040], this author, who also considers the Hansen bacillus to be only a development phase of an actinomyces of the soil, regards the epidemiology of leprosy from the same viewpoint as that presented by me.

the spirochaete of syphilis, and other organisms. But in time these gaps will be filled; it is only very recently that it was learned that the organisms of the typhoid group assume resistant filtrable forms (Sanarelli, Hauduroi). Of what importance for epidemiology are the studies, mentioned above, that prove the actinomycetic nature of the tuberculosis and leprosy viruses? There is no doubt in my mind that should these findings be confirmed they will contribute greatly to knowledge of how leprosy spreads and is transmitted.

Here I would like to say a few words concerning the possible developments which, in my opinion, await future studies on the behavior of the bacillus with respect to the transmission and dissemination of leprosy. The course of events seems to be as follows: Lepers discharge myriads of acid-fast bacilli, and these in part are inhaled by people in contact with the patients and in part are deposited upon surrounding objects. Most of the microbes that are detained by the oral and nasal mucosa undergo no further development and perish. By living in the human organism they have become so much individualized on account of their close relation with the cells and fluids of a particular individual that in another one, with his different biochemical and immunological peculiarities, they cannot become adapted. When adaptation does occur it is exceptional and occurs very gradually.

The microbes that are deposited upon the surrounding objects also perish for the most part. However, some—perhaps those that possess the highest vitality—adapt themselves to the new surroundings by making an abrupt and unexpected mutation, thus producing a new form with considerable resistance against harmful outside influences. The filaments of the actinomycoid species and the streptothrices, as well as the mycoids obtained from acid-fast cultures from leprosy and tuberculosis, are distinguished by a great capacity for growth and a striking resistance to desiccation. At a certain stage these actinomyces produce the so-called spores, or conidia, with which the branching filaments end. Any disturbance disseminates these spores in the air, and when they are inhaled by people they are detained by the mucosa of the upper respiratory tract.

Why does the microbe need such a cyclic course in its development? First, in order to renovate its vital capacities, since by passing into another form it must considerably change its vital aims. Second, in order to lose the too-individualized qualities acquired by life in

a diseased person, which interfere with its adaptation to a new one. It may be recalled that I infected the rabbit, not with the acid-fast microbe taken from the leprous nodule, but with acid-negative strains that had lost their former biologic qualities, i.e., their former individuality.

Having penetrated the mucosa, the modified microbe is taken by the blood or lymph stream to the lymphatic glands and in general to the organs rich in reticulocytes and endothelium, by which they are phagocytized. This phagocytosis usually leads either to their destruction or to their further development within the phagocytes. Those organisms that are not destroyed, having reached a certain stage of dissemination and perhaps maturity, finally get to the skin, for which they have a certain affinity just as the organism of typhoid fever has for the lymphatic system or the toxin of tetanus for the nervous system.

It is obvious that the foregoing is only a working hypothesis, for the scientific proof of which a number of links are still missing. These missing links must be supplied by further research on leprosy and tuberculosis. For the present I can only emphasize that I do not stand alone in my views on the epidemiology of leprosy.