

ALLERGIC ERYTHEMATOUS ERUPTIONS IN LEPROSY¹

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In 1926 one of us (Ramos Baez) observed a typical Herxheimer reaction in a female patient with latent leprosy, twenty-one days after treatment with a large dose of ethyl esters, without any previous medication (1). This reaction, which was mild and transient, was confirmed later by the other of us (Hoffmann) in El Rincon leprosarium. Four years later we recorded another observation of a Herxheimer reaction occurring after the first injection of chaulmoogra ethyl esters in a patient whom we afterwards had the opportunity to treat for a long time (2). This reaction was both general and local, the localized reaction being in one testicle that had formerly been the site of gonococcic orchitis. This second case and one other are reported here.

REPORTS OF CASES

CASE I.—F. H. S., white, 48 years of age, born in Canarias. Has had measles, mumps, pneumonia, paludism, gonorrhea with complicating orchitis, frequent grippe, and several attacks of pulmonary congestion. No history of leprosy in the family or contacts; parents and four brothers living and healthy. The first symptoms appeared about 14 years ago, when following suffocation from a fire in a bamboo grove he had fever of more than 40°C., with marked profuse sweating, which lasted several days. This left him very weak, with big wheals all over his body that later subsided. After a year he had new febrile attacks of from 20 to 30 days duration, with eruptions of macules of various degrees.

On examination the patient is found to be slender and emaciated. The skin shows no lepromata, but several violaceous-red macules on the lower ex-

¹ We use the term "erythematous eruption" to signify the acute or subacute inflammatory reaction which is without anatomical lesion but which may become the site of specific anatomico-pathological changes after successive repetitions of the eruption in the same place.

tremities. No palpable glands. The nervous system reveals slight anesthesia on both feet, but no atrophy of the muscles; reflexes normal. Slight loss of hair of the eyebrows. The ears are reddish, almost violaceous, a little elongated and thick. No stigma of leprosy in the face. In the nose no ulceration, but a perforation of the septum, without external deformity. In the mouth some teeth are carious and several missing; the tonsils are normal. Thyroid, heart, liver and spleen are normal. In the lungs, fine and medium crepitant râles in the upper lobes. On September 8, 1928, a slight hemoptysis occurred suddenly, without premonitory symptoms. Radiological examination (Dr. Pedro L. Fariñas) revealed extensive fibrocaceous lesions in both upper lobes, fibrous lesions with emphysema in both lower lobes, and pleurisy at the right base.

A differential count showed eosinophiles 3, juveniles 10, polynuclears 36, large mononuclears 27, transitionals 2, and lymphocytes 22 per cent. Lymph contained a few Hansen bacilli (+), all of them isolated and loose, with several granular forms.³ Sputum (macerated) was inoculated intraperitoneally into several guinea-pigs; these survived from 3 to 4 months and on autopsy showed no typical histopathological lesions of tuberculosis, but lesions considered due to the Hansen bacillus.

Following the first series of injections of chaulmoogra ethyl esters an orchitis appeared as a consequence of a congestive allergic reaction, simultaneously with discrete papular eruptions in the lower extremities and other parts of the body. The skin lesions improved considerably with every series of injections, while the pulmonary lesions were manifested by catarrhal processes accompanied with fever, blood-streaked expectoration, and even slight hemoptysis following any heavy work. In March, 1929, a profuse hemoptysis followed a severe effort, and in spite of treatment this recurred frequently for some time, although in milder degree; afterward evening fever continued, from 37.5° to 38°C. Pneumothorax could not be performed because the patient developed cardiac insufficiency, which continued until he died, on April 17, 1929.

CASE II.—G. S., mestizo, 24 years of age, born in Limonar, province of Matanzas. Has had mumps, varicella and frequent colds. There is a suspicion that his disease was contracted by contagion from his grandmother, though she died with a psychosis at 80. His parents died of diseases not related to leprosy; five brothers are all living and well. Patient says that at seven he had recurrent eczematous lesions on the legs, and at thirteen papular eruptions all over the body, principally in the extremities, and a few small nodules in the ears; he can not tell whether or not this eruption was accompanied by fever and sweats.

The patient is slightly overweight. The skin shows small nodules in the ear lobes, on the face, and on the hands and feet (with secondary infection); also violaceous-red macules on the legs. No palpable glands. Nervous system negative. Eyes show marked exophthalmos. Eyebrows normal. On the face are small nodules resembling acne; the ears slightly enlarged, dark reddish, with small nodules in the free borders and especially in the lobes. Mouth and tonsils

³We (Hoffmann) grade smears from one plus to five plus according to the degree of infection and the number of bacilli found.

normal. The nasal mucosa shows ulcers on the lateral walls and septum, rounded or oval, raw or crusted. Before and during the onset of his last congestive eruptions in December, 1933, patient had slight and frequent epistaxis with chronic coryza and disorder of the sense of smell. Thyroid normal notwithstanding the exophthalmos, heart, liver and spleen also normal.

For some three years the lungs were normal, until November, 1933, when patient had high fever with severe chills. This was preceded a few days by parosmia, followed by rhinitis and epistaxis. Little by little there developed a mild maculo-papular eruption which later became frankly macular. It was thought that the fever was due to this congestive reaction in evolution, but because of its persistence the possibility of a congestive pulmonary reaction was finally entertained; and with the appearance of a focus of râles on about the 20th day of fever a radiological examination was made (Dr. Fariñas). This revealed a small congestive focus at the inferior end of the right hilus.

Because he proved refractory at the beginning of treatment to injections and to medication by mouth, one of us (Ramos Baez) submitted him to intensive treatment by intramuscular injections of 6 per cent alepol. After 6 to 8 months the patient developed congestive eruptions (Herxheimer reaction) all over his body with the exception of the face, scalp and neck, with papules approximately the size of a lentil. These began to subside after two years and at present appear wrinkled and fading. A state of generalized fibrosis of the skin took place, rendering intramuscular injections practically impossible.

TABLE 1.—*Differential blood counts of Case II, in percentages.*

Type of cell	Dec. 1930	Nov. 1931	Feb. 1932	May 1932	Mar.* 1933	Nov. 1933
Eosinophiles	10	3	0	0	4	0
Basophiles	0	0	0	0	0	0
Juveniles	18	19	14	15	2	18
Myelocytes	0	0	0	0	0	0
Polynuclears	26	46	59	57	54	56
Large mononuclears	20	9	5	4	20	4
Transitionals	4	2	1	1	10	4
Lymphocytes	22	21	21	23	10	18

* During the preceding 6 or 8 months no treatment given.

During the course of treatment the differential counts shown in Table 1 were made. The original eosinophilia decreased and disappeared, and the large mononuclears also diminished, coinciding with the improvement shown by the patient. At the time of the count made in March, 1933, which was after some 6 or 8 months without treatment, examination of the lymph showed numerous Hansen bacilli (+++), with groups forming globi and degenerated forms. The present condition of the patient is fair, in spite of occasional mild erythematous reactions.

DISCUSSION

Experimental studies by many authors on the biology and morphology of the bacillus of Koch have shown that it has an invisible and filtrable ultramicroscopic form which is responsible for certain well known clinical types of disease. One of these is the so-called inflammatory articular disease of Poncet, which that author in collaboration with Leriche (1909) attributed hypothetically to a modification of the Koch bacillus, and which Vaudremer (1926) succeeded in reproducing by inoculating a filterable form of that bacillus subcutaneously in the guinea-pig, observing "peri-arthritis of the knees which caused complete articular stiffening (Poncet syndrome)." This condition, and many others whose specific characters have not been established because of failure to find the typical histopathological picture or the tubercle bacillus in the lesions, depends on the predeceessory granular or ultravisible form of the bacillus. As a result of the studies of one of us over several years (3, 4) we believe that in leprosy, also, there exists a pre-bacillary period of the disease, during which the bacillary forms—which are possibly in an early phase—will be scarce, or they may only appear later.

Referring again to the Koch bacillus, it is evident that it or its pre-bacillary forms can exist for years in the circulation without producing the symptomatology of classical tuberculosis. But this is not to say that they or their toxins do not affect the different types of susceptible cells, as for instance those of the brain or of the synovial membranes. The toxin may cause serious disturbance but the reaction to it will be like that to any other foreign substance and will not produce typical tuberculosis. In susceptible cases the constant aggression, together with the diminution of the defensive powers of the organism, prepares the ground in certain tissues for the production of the anatomical tubercle by the bacillus.

There is no doubt that the quantity of toxin produced by a small number of bacilli or pre-bacillary forms is sufficient to cause the cells to react and form antibodies, creating a state of sensitivity. This becomes manifest with the injection of tuberculin. It is also evidenced if there occurs a rapid increase in the number of bacilli or in the production of toxin—as is commonly observed when the bacilli settle in the intima of the blood vessels where the toxins can easily enter the circulation—in which manner are produced fever and other, little-known reactions. This same syndrome may also be

initiated by specific therapy when a large number of bacilli are destroyed and their toxins liberated. It is this last reaction which we have found in leprosy, a reaction which, naturally, also presents all the characteristics of allergy.

Better to explain our view on leprous allergy, based on the resemblance between the bacilli of Koch and of Hansen, we must refer to the experiences of Loewenstein. From more than 10,000 patients showing no signs of tuberculosis examined over several years he succeeded in cultivating, by special methods, the Koch bacillus from the blood and from local lesions in 75 per cent of the cases of certain diseases not previously known to have any relation with tuberculosis. These conditions comprised mental affections such as dementia precox, the acute rheumatic syndrome, and certain diseases of the skin and other organs. In none of these cases were the typical histopathological lesions of tuberculosis ever demonstrated, but their specific nature was made manifest by his bacteriological findings.

The allergic reaction of the tissues in general has an aspect very similar to the reaction of the body organism against any other toxic or irritating foreign substance which, though diluted, incites the tissues and the cells to defend themselves. It is only later, when the allergic reaction has become insufficient, that the bacillus can enter the tissues and produce the typical histopathological lesions. In leprosy ten or twenty years of bacillary invasion are generally necessary before the first characteristic manifestations appear, this referring to the cutaneous lesions that develop when the resistance of the organism has diminished. However, it is possible to diagnose this latent period by serological methods. Further, the latent affection can produce, from time to time, symptoms which show nothing characteristic or suspicious but which nevertheless depend on the bacilli in the organism. This larval form seems to be an allergic reaction to an increasing quantity of toxin resulting from either an increase of the bacilli or the simultaneous destruction of a large number of them. The atypical symptomatology that was presented for some time by our case of precocious leprous choroiditis may have corresponded to such a larval form, which could not be diagnosed for a long time. It is probable that with minute study of suspicious persons, or apparently healthy persons coming from leprous families, many other symptoms of importance can be discovered.

The majority of people living with lepers have in the blood specific antibodies which can be demonstrated by various methods, yet it is rare that even persons who have prolonged contact with large numbers of lepers, as happens in leprosaria, contract a manifest infection. Though the period of infancy is especially dangerous as regards contagion, it is probable that many children infected by the Hansen bacillus will never show evidence of the disease if they live in good hygienic and social surroundings and are adequately nourished. These conditions favor the development of antibodies which succeed in overcoming a latent infection. When the disease does develop in such cases the primary manifestation may not appear until much later, in adolescence. Accepting as a fact that latent leprosy is an infection carried on for years by a small number of virulent bacilli, we have tried to detect this form of the disease by Loewenstein's method, but circumstances have not as yet permitted us to complete the necessary experiments.

It is well to remember that in almost all autopsies it is possible to find evidence of infection with tuberculosis, but that in the great majority the disease is not produced—though it is quite otherwise with primitive non-civilized people. Clearly, tuberculous infection in most people produces an immunity. It is logical to suppose that in such persons the latent infection will produce more or less serious disorders that are clinically abnormal, transitory, and so ill-defined that their diagnosis may not be possible, though such a latent infection may, with the lapse of time, produce a serious condition because of the potential danger of virulence of the bacilli. However, we are confident that in the future there will be discovered serological and cultural methods that will give us the diagnostic key to suspicious cases, and will permit better interpretation of certain conditions now considered as "constitutional" but which may depend upon disorders of function of the sensitive glands of internal secretion due to latent or subnormal infections. This broader view of the infection by the Koch bacillus is very different from the present clinical and anatomical concepts of tuberculosis, which are based on histological lesions and so comprise only one single phase of the infection.

Leprosy, in turn, is an affection which after prolonged periods of latency is frequently initiated with precursory attacks of high fever, profuse sweating, great general debility and other prodromic

phenomena, and with the appearance of eruptions. The macules and papules may disappear partially or completely after several days or months, or may persist indefinitely. If the disease progresses the eruptions may come and go repeatedly, and their sites may undergo specific anatomo-pathological changes. We believe that there is a certain similarity between the macular eruptions of leprosy and the erythematous eruptions of the joints in tuberculosis (Poncet), at least in the congestive or inflammatory character of these reactions.

Until we have more precise knowledge of the ultra-organism we shall not be able to explain satisfactorily the phenomena of allergy with which, in our opinion, these reactions have so much to do. Besredka has shown the existence of a local immunity in anaphylaxis, and others believe in local immunity. This suggests the existence of a local allergy, but the clinical findings allow us to adduce against this presumptive local immunity, which requires that the histological or histopathological conditions of the field have an influence on the localization of the reaction as well as of the specific organism. However, in our opinion, the eruptive manifestation would have a character which, though seemingly inflammatory, might be due to receptors of the virus and the sensitizers of the field for the future specific localization. Thus, in the supposition that these inflammatory reactions depend on an allergic phenomenon, with premonitory vaso-dilatation of anaphylactic nature and with tissue reaction following the possible introduction of the filtrable pre-bacillary form in these foci, we would hold that the local immunity to which the authors refer would constitute an argument corroborating our presumption about the existence of histological conditions of the tissue that are either unfavorable or favorable to the congestive localization. In other words, the local immunity would reside in the histologically abnormal portions of the tissue.

In leprosy the histological skin lesions would be liable to premonitory allergic eruptions, occurring either naturally through unrecognized reinoculations or provoked by treatment. As stated, we consider that early in a case there will be a congestive or anaphylactic eruption as a phenomenon preceding the localization of the virus, and that later it will become erythematous or inflammatory, with all the characteristics of a true allergy. Repetition, chronicity, or the special condition of the field makes a locality favorable for the definite morphological forms of the germ, whatever it may be; in

tuberculosis, for example, the lungs would be the most sensitive tissue, and in syphilis the skin.

The Herxheimer reaction which we often meet in leprosy would be an attenuated erythematous form. In one of our patients, as a consequence of a congestive reaction in the lower extremities possibly produced by the action of a first injection of ethyl esters of chaulmoogra, there occurred a pronounced glandular infarct which was not related to any perceptible secondary or infective lesion of the extremities. Under the conditions pointed out it would be interesting to study minutely the crises of asthma that develop as epiphenomena of the syphilitic or tuberculous affection—for example, the congestive localization in the articulation of tuberculous rheumatism (Poncet), the pleurisy and the tuberculous peritonitis, and the granula of Empis, which under this view would signify types of allergy.

Our case of choroiditis in latent leprosy may be cited as an attenuated manifestation of allergy. The orchitis in Case I we recognize as a Herxheimer reaction to a localization in sensitized tissue. We consider that the repeated congestive eruptions which apparently had a predilection for the pulmonary apices of this patient—manifested by frequent pulmonary congestions and slight hemoptysis, with fibrocaseous changes evidenced in the skiagram—were of similar nature, and that the small focus of congestive reaction at the inferior horn of the right pulmonary hilus in Case II corresponded to the congestive eruption of the skin.

Repeated congestive reactions of the nasal mucosa with coryza, especially if accompanied by epistaxis, are very significant because they may be symptomatic of a larval, prodromal period of the latent affection, though they also occur in the course of confirmed leprosy. In latent leprosy these lesions are merely congested patches, more or less rounded or oval, most frequently located on the septum and external wall of the nasal cavities. Sometimes they produce slight epistaxis, but on healing no trace is left. In confirmed leprosy the lesions are deeper and may become ulcerative, epistaxis is more abundant, and loss of tissue produces rounded or oval ulcerations which are very characteristic. These lesions may produce perversions or loss of the sense of smell, depending upon their localization.

Another interesting aspect is the reaction of the connective tissue. In many cases of leprosy which we have treated we observed an

abnormal, fibrous consistence of the tissue. A process of fibrosis of the adipose tissue in some patients with benign leprosy produces a condition that, when a needle is introduced to give a subcutaneous injection, gives the operator the sensation of piercing a stiff substance that creaks to the puncture. Ethyl esters injected into these patients are, after a time, discharged through benign fistulous processes that develop in the line of puncture. In other cases the fibrous reaction makes the skin so hard that it is difficult to introduce a large caliber needle. The allergic or congestive reaction of the skin in Case II produced macular eruptions which lasted two years, and now when these macules are subsiding the fibrous reaction which they provoked is of such a nature that it is practically impossible to continue intramuscular or subcutaneous treatment, though before the reaction this patient had been receiving frequent intramuscular injections.

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DESCRIPTION OF PLATE

FIG. 1. Skiagram of chest of Case I, taken on September 15, 1928, seven months before death. Extensive fibrocaseous lesions in both upper lobes, which with frequent pulmonary congestions and slight hemoptysis are considered of the nature of a Herxheimer reaction in sensitized tissue.

FIG. 2. Skiagram of chest of Case II, taken December 28, 1933, the twentieth day of a febrile period, revealing in the lower end of the right hilus a small congestive focus which is believed to correspond to the congestive eruption in the skin in leprosy.

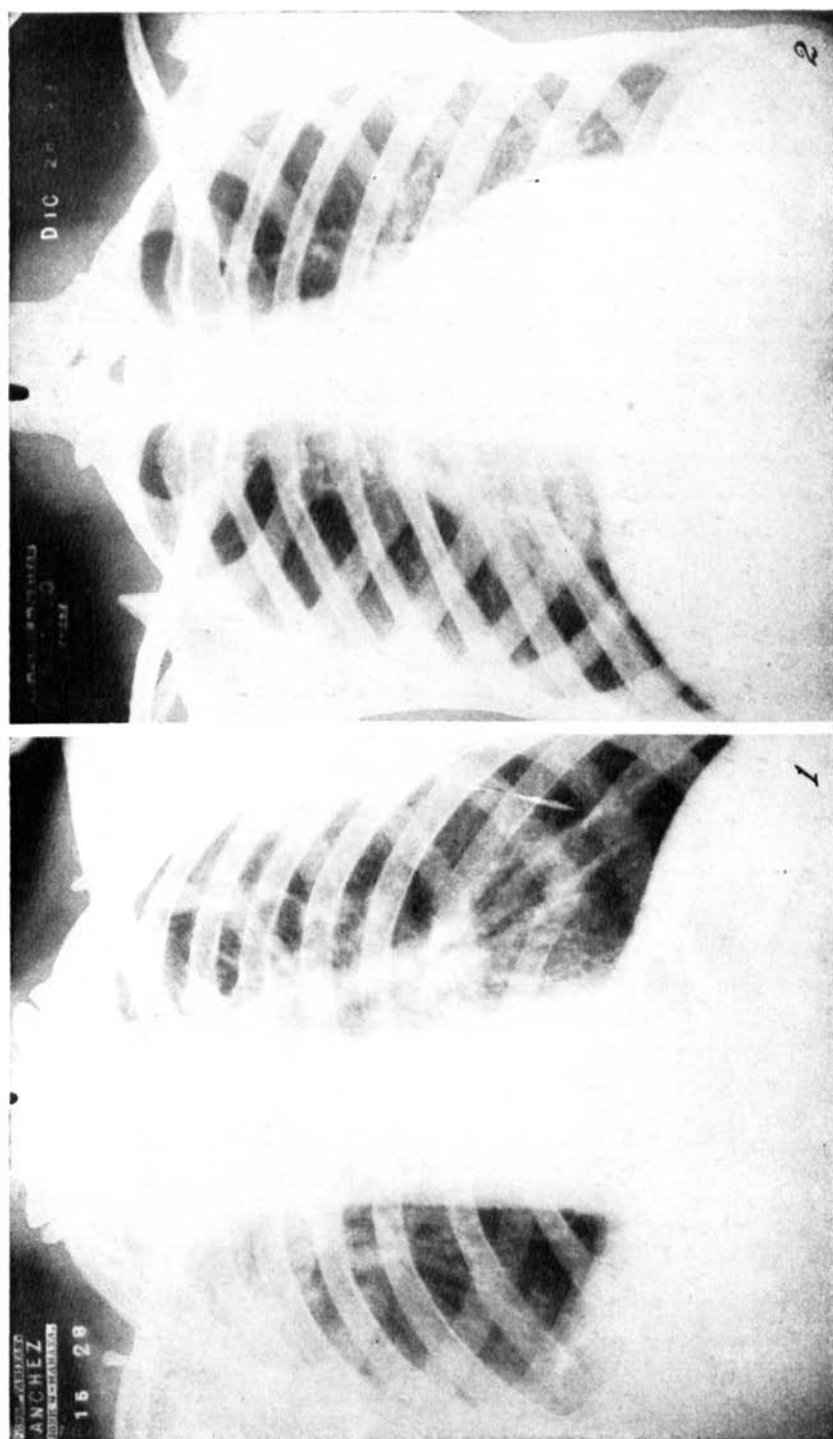


PLATE 1.