# ABSTRACTS

*On the Nature of the Kveim Reaction and the Pathogenesis of Sarcoidosis.* R. KOOIJ. Dermatologica, Basle. **117,** 5: 1958: pp. 336-354.

The author describes sarcoidosis, also known as the disease of Besnier-Boeck-Schaumann, and emphasizes that the etiology is still obscure and that its relation to tuberculosis is still unsettled. The diagnosis is made on clinical signs, of multiple infiltrations in the skin, lymph glands, tonsils, lungs, spleen, liver, bone marrow, such lesions being of long duration, and the histo-pathological examination. The latter shows well-defined nests of epithelioid cells with absence of necrosis. This so-called sarcoid structure can however be produced by a number of different agents, such as leprosy, silicates, beryllium and zirconium. The Kveim Reaction is used as a diagnostic test for sarcoidosis: it is useful, but by no means infallible. The Kveim antigen is prepared by extracting in saline from sarcoid tissue. After an intradermal injection of 0.1 to 0.2 ml., a positive reading is recorded if a papule of about 5 mm. develops and persists for one month or more, and for this positive reading some workers also insist on a sarcoid structure as shown by the histological examination of the papule.

The Kveim Reaction has a striking similarity to the Mitsuda reaction of the lepromin test in leprosy, where also the reaction is read at 28 days, but there is the difference that the Mitsuda is not diagnostic but prognostic, and used for the classification of leprosy. Kooij and Gerritsen (1956-58) have shown that the late reaction in the lepromin test can be produced by an antigen consisting of suspensions of non-leprosy skin, and of liver. To a large extent for skin tissues this has later been confirmed by Davey (1958) in *Leprosy Review* **29,** 4, 197-203. The typical feature of the Mitsuda reaction, more than its positivity in the tuberculoid type of leprosy, is its negativity in the lepromatous type. When the preparations of normal skin tissue or liver tissue were used in more concentrated suspensions the results corresponded even more closely to those typical of the regular lepromin antigens. Also, just as in healthy people lepromin gives positive late and very late reactions, so do the suspensions of normal tissue. A few of the reaction papules of the healthy people were examined histologically, and a few of them showed a sarcoid structure. The papules of the positives in tuberculoid leprosy also showed a tuberculoid or sarcoid structure, as occurs with the regular lepromin. Some tuberculoid patients responded to the Kveim antigen by late positive reactions. The author thinks that the active principle in the Kveim antigen, the lepromin antigen, and in normal tissue antigen is probably bound to corpuscular elements. He thinks that the Kveim antigen does not contain a specific substance but there is a sarcoid mode of reaction peculiar to certain people. With

concentrated chloroform-ether extracts of normal tissue he has obtained positive Kveim reactions. It may be the number, the chemical composition, and the size of the particles in the Kveim antigen which determines the activity of the preparation. In any case he thinks the disease sarcoidosis is a syndrome which can be caused by many different agents in certain individuals who are able to respond with a sarcoid reaction, and in support of this hypothesis describes conditions similar to sarcoidosis which were caused by silicates, beryllium, zirconium, spirochaetes, tubercle bacilli, and leprosy bacilli, and 4 clinical photographs and 2 histological are given and 2 illustrative cases are described. He draws attention to variation in clinical symptoms according to the agent, e.g., lung changes in leprosy are rare, bone lesions in beryllium intoxication are rare, and recommends the diagnosis of sarcoidosis being stated in all cases where it is found, even if a specific agent is also found, e.g., sarcoidosis--leprosy, sarcoidosis-tuberculosis, sarcoidosis-silicosis. Because of the major importance of leprosy and tuberculosis, *every* case of sarcoidosis should be studied carefully from the point of view of the possibility of these diseases, and the other causes of sarcoidosis not forgotten.

*El Sindrome Neural Leprosa* (The Neural Leprosy Syndrome): F. BRESANI SILVA. Revista Peruana de Salud Pública, Lima, **5,** 2, 3 and 4: 1956, **6,** 1: 1957 pp. 447.

The author made a systematic study of neural symptoms in 400 leprosy patients resident in San Pablo leprosarium, Loreto, Peru. He found that 95% of patients showed skin and nerve disorders, 3.5% showed exclusively neural primary or secondary lesions, and 1.5% were purely cutaneous in the type of their lesions. He found that the disease began with neural symptoms in 54.7% of the cases, in 36% with cutaneous, and in 9.3% with varied symptoms. Within the neural syndrome, disorders of sensation are the commonest and earliest manifestations. Thermal sensation is first affected, next pain, next tactile sensation. The author differentiates *four stages in the evolution of disorders of sensation in leprosy. The first* is the stage of alteration of thermal sensation. *The second* is the stage of "syringomyelic dissociation", wherein there are alterations in thermal and pain sensation alongside normal tactile sensation. *The third stage* is that of "peripheral dissociation", wherein normal deep sensation is preserved alongside loss in thermal, pain, and tactile sensation. *The fourth stage* is "pseudospinal dissociation" when the three superficial sensations are lost and deep sensation is also impaired. (This loss of deep sensation is denied by most authors.)

Lesions of the terminal branches of the nerve fibres are the cause of the most important of the disorders of sensation in leprosy, which is loss of superficial sensation. It starts distally on the limbs and progresses centrally. The author insists that loss of superficial sensation is slowly and gradually succeeded by loss of deep sensation

in a third of all cases, in muscles, tendons, and bones. Of the cases of impairment of deep sensation, most are affected in vibratory sensitivity, and only a few in that to pressure and weight.

*Motor disorders* occur in about 76% of patients and are almost exclusive to the hands and feet, though the facial nerve is sometimes involved. Muscle wasting is common as a later result, and tendon retractions.

*Reflexes* are diminished or absent, either superficial or deep, due to impairment of superficial or deep sensibility. Accentuated reflexes can occur in stages of great activity of the disease or in lepromatous reaction.

*Peripheral neuritis* results from an invasion of the nerves by the bacilli. This leads to changes in thickness, form, and consistency which are very typical and almost exclusive of leprosy. In order of frequency, the nerves affected are the ulnar, lateral popliteal, supraorbital, radial, and superficial cervical. In lepromatous leprosy the nerve increases in thickness and becomes hard and fibrous and uneven of surface. In tuberculoid leprosy the increase in thickness takes the form of a spindle or string of beads, and there may be caseation and calcification. There is no relation between the grade of thickening and the grade of impairment of nerve function. The nerve undergoes a specific infiltration of the perineurium, the endoneurium, and the interstitial tissue, followed by fibrosis and constriction and destruction of the nerve fibres. The original invasion of the nerve trunks may be by way of metastasis through the blood or lymph, or by way of the terminal branches at the point of the peripheral cutaneous vascular plexuses.

*Vasomotor disorders* were found in 27% of the patients under study, mainly on the distal parts of the limbs. Cyanosis and oedema and elephantiasis are associated. The basic lesion is of the nerve branches of the autonomic system, which leads to vasomotor paralysis.

*Disorders of sweating* in the form of segmental anhydrosis occurred in 92% of cases. The limbs are most often affected, sometimes the chest, and in rare cases almost the whole of the body. A compensating phenomenon of excessive sweating occurs in intermediate zones. There is also a local anhydrosis connected with local changes directly due to the mechanical action of pressure by local infiltration of lesions in the skin.

*Trophic lesions* include perforating ulcers, changes in the skin itself, alopecia, and changes in the bones. Perforating ulcer is a very frequent lesion, occurring almost exclusively in the feet (47.5% of all cases), whereas only 0.5% had palmar perforating ulcer. In the feet it is usually at the heads of the metatarsals or in the toes, rarely in the heel. It is caused and maintained by a combination of factors, the nerve factor causing loss of sensation and destruction of autonomic and trophic fibres, the mechanical factor due to standing and

walking, and the traumatic factor plus the secondary factor of infection. Trophic disorders of the skin include glossy skin, colour changes, desquamation, scleroderma, and ichthyosis. These are symmetrical, commonest in the lower limbs, and more frequent and serious in the lepromatous type. Alopecia was found in 64% of the patients, commonest in the eyebrows, also occurring in eyelids, forearms, legs, thighs, axillae, pubes, but very rare in the scalp. There are three factors in this alopecia, pressure of the specific granuloma on the hair follicle, endocrine disorder, trophic damage to the skin. Trophic disorders in bones occurred in 43% of patients, mostly in hands and feet. Osteoporosis and absorption of bone occur, owing to the neurotrophic factor, the direct action of the bacilli on bone tissue, and secondary pyogenic infection.

**Evolution of the Neural Disorders**

In almost all cases the disorders of sensation appear before the motor and trophic. Muscle wasting and tendon retractions come a little after the motor disorders. Thickening of the peripheral nerves appears as early as the disorders of sensation, and the degree of thickening is not related to the time. Anhydrosis is an early disorder. The impairment of superficial sensation is noted first in the lower limbs, then upper limbs, next the head, and finally the chest and abdomen. Impairment of deep sensation follows that of superficial sensation. Among vasomotor troubles, cyanosis is common at the beginning of the illness but as time goes on it occurs less. Oedema is almost more frequent as the years elapse, and elephantiasis is the last to appear. Trophic bone changes occur very late, but appear first in the phalanges and metatarsals of the feet.

**Notation of Neural Disorders**

It is possible to describe 4 grades in all types, which though arbitrary do express the clinical findings fairly closely.

*Tuberculostatiques et Sels de Métaux Lourds: Complexes Métalliques de la D-cyclosérine* (Tuberculostatics and Salts of Heavy Metals: Metallic Complexes of D-Cycloserine); E. NEUZIL and J. C. BRETON; Bulletin Medical de l'A.O.F. **3**, 9: Apr.-June, 1958, pp. 149-172.

After explanation of the nature of metallic complexes and chelates, the authors review the connection between tuberculostatic activity and salts of heavy metals. Most of the chemical compounds active in the treatment of tuberculosis have an affinity for the salts of heavy metals which results in the formation of chelates. The copper chelates seem to be particularly stable. Like other tuberculostatics of high activity, D-cycloserine gives metallic chelates, especially with copper, as proved by spectrophotometric and potentiometric methods. The existence of these metallic complexes poses numerous problems regarding the mode of action of tuberculostatics and the appearance of microbial resistance. This new line of research may lead to a more

efficient chemotherapy of tuberculosis (and also of leprosy).

*Activisima y Acelerada Reproduccion del Bacilo de Hansen Inoculado a Ratas en Severas Condiciones de Prooxidacion* (Very Active and Accelerated Multiplication of M. Leprae Inoculated into Rats Subjected to Severe Conditions of Pro-oxidation) M. BERGEL La Semána Médica, **113,** 25: Dec. 1958, pp. 1119-1124.

The author's severe conditions of pro-oxidation for the experimental rats comprised his special pro-oxidant diet for them (casein 23.8, brewers' yeast 8.9, mineral salts 3.0, maize starch 48.9, and codliver oil 15.5), plus the ingestion of silver nitrate 0.5 per 1000 in the drinking water, and the injection subcutaneously of 1 ml. of a haemolysate (obtained by taking 3 ml. of rat blood from veins which was washed with 3 to 4 ml. of twice distilled water, and filtered). The experimental rats were inoculated in both testicles with 0.1 ml. of a fresh suspension of *M. leprae* derived from the trituration of human lepromatous tissue. The control group of rats were placed on standard diet. At 5 months of the inoculation of *M. leprae* into the pro-oxidant group the testes showed an active and rapid reproduction of the germs, even reaching the point of the formation of globi in the lungs, spleen, and liver. The control animals showed only a scanty occurrence of bacilli in the testes. The author thinks that the conditions of pro-oxidation notably favour the growth of *M. leprae* in inoculated rats. In this experiment the pro-oxidant conditions were made purposely severe and caused the death of the animals and produced a series of lesions attributable to the argyria, the hypovitaminosis E, and the large amounts of polysaturated fats ingested. It would be possible to scale down these features by lessening the concentrations in the diet and arrive at a diet very suitable for the transmission of *M. leprae* to rats. (For further information of the lines of thought of M. Bergel see the abstract in *Leprosy Review*, **30,** 2: April, 1959, p. 126 "Consideraciones sobre Quimioterapia de la Lepra")

*Contribution to the Study of the Lepromin Reaction.* M. FUKUDA. The Reports of the Research Institute for Tuberculosis and Leprosy, Tohoku University, Sendai, Japan. **8,** 2: June, 1958, pp. 137-160.

The author has studied the significance of a brownish red spot which accompanies the papule at the site of the late or Mitsuda reaction of the lepromin test and adduces strong evidence for taking the measurement of this spot as an accurate index of the reaction. He indicates the 8th and 15th day as the best times to measure this spot.

Experimental Transmission of Human Leprosy Infection to a Selected, Laboratory-Bred Hybrid Black Mouse: K. R. CHATTERJEE, Internat. J. of Lep., **26,** 3; July-Sept. 1958, pp. 195-202.

K. R. Chatterjee, working in Calcutta School of Tropical Medicine, began an investigation in 1956 to transmit *M. leprae.*

He reports the successful transmission of tissue-free *M. leprae* to a new type of selected hybrid black mouse bred in the laboratory. He used 100 animals and also 48 hamsters, in which also a certain degree of success was obtained. Hybrid mice were derived from crossing male Indian house-mice with female Swiss white-mice. The black mice from this cross were selected to form a special colony. Inoculations were given only to those between the ages of 10 to 15 days. The inoculum was derived from untreated cases of active lepromatous leprosy. Successful transmission was demonstrated so far up to the third serial passage, and the animals had a progressively heavier infection. The onset of the infection in the animals occurred from the end of the sixth or seventh month after inoculation, and the heaviest infections were observed a year or more after inoculation. Intracellular and extracellular acid-fast bacilli were demonstrated in the spleen, lymph glands, liver, kidney, omentum, testis, ovum, skin and peripheral nerves. The possibility of contamination with the tubercle bacillus or other acid-fast bacilli was excluded by test cultures. When an antigen was made from the infected mouse tissues and compared with Dharmendra's antigen in the lepromin test, typical reactions were obtained.

The inoculum used throughout was practically tissue-free after differential centrifugalisation and dilution in normal saline to contain a known number of bacilli per c/c. of suspension. The dose of the first inoculum was adjusted to contain a thousand million bacilli. For passage from animal to animal, this dose was reduced to lie between one and twenty million bacilli. Each animal was inoculated only once.

The author thinks that the success of this transmission probably depends on the tissue-free nature of the inoculum and perhaps on the hybridity of the mice. He refers to Bergel's work from which he reports transmission to white rats who are kept on a special pro-oxidant diet.

*Communicable Diseases in Africa: Leprosy*. WHO Chronicle, **13,** 2: February, 1959, p. 81.

Very interesting information is given about leprosy in Africa and the campaigns against it. Some 2,300,000 cases of leprosy—or about a quarter of the world-wide total—are to be found in Africa south of the Sahara. Half of these cases are already being treated with sulphones, and it is expected that treatment will be extended to all leprosy cases in the region within the next few years. The percentage of "neutralized" patients, i.e., those who have been rendered non-contagious—is already very high and, although the treatment takes some time, the risks of reinfection are relatively low. It is therefore reasonable to hope that the present generation of Africans will be the last to suffer from the disease to any large extent.

Mass antileprosy campaigns in French Equatorial Africa started in 1953, and have been assisted by WHO and UNICEF since January, 1956. The weekly or fortnightly administration of sulphones,

either orally or by injections, is carried out by mobile units. Those who cannot be reached by the units are treated in fixed centres or leprosy villages. Of the 145,000 cases recorded in the area up to July, 1958, 91,700 are receiving regular treatment; more than 20,300 cases are now considered as neutralized. As the lepromatous form of the disease—the most malignant—is rare in French Equatorial Africa, where it affects only 7% of patients, the outlook for the eradication of leprosy from the area is most promising.

The campaign in French Equatorial Africa has served as a pattern for activities in French West Africa, where some 290 mobile units have been formed for the detection and treatment of leprosy. About 300,000 cases, out of a probable total of 400,000, had been recorded by September, 1957. Early in 1958 UNICEF donated 46 million sulphone tablets and supplied 90 motor vehicles and 200 bicycles for use in the campaign.

Case-finding surveys in the French Cameroons have revealed some 26,600 cases of leprosy, of which 18,000 have been or are being treated, 13,700 of them regularly. The total number of cases is estimated at 50,000. Of the 36 motorized treatment units which have been set up, 19 are equipped by UNICEF.

The leprosy control campaign in Gambia started in August, 1957. The total number of cases is estimated at 10,000, of which a quarter were under treatment in June, 1958. The small area of the territory permits treatment to be carried out in existing fixed health centres.

In Ghana, 36,000 cases of leprosy were treated and 300 neutralized between March and December, 1957. Fixed treatment centres are supplemented by 12 mobile teams, 9 of which have been equipped with Land Rovers by UNICEF.

Nigeria was the first African country to use sulphones in the treatment of leprosy. When the antileprosy campaign began in 1951, the number of leprosy cases in the country was estimated at 500,000, but recent surveys indicate that 700,000 would be nearer the mark. WHO and UNICEF assistance to the campaign started in 1954, and about 219,000 cases had been treated by the end of 1957. Treatment is given mostly in fixed centres, to some of which mobile teams are attached, and in leprosy villages.

Sulphones have also been widely used in the treatment of leprosy in the Belgian Congo, Spanish Guinea, and the Union of South Africa, for several years. In Uganda, a campaign to set up leprosy villages near dispensaries or hospitals began in 1957, while an antileprosy campaign is to be started in Sierra Leone this year.

UNICEF has already promised more than $2½ million in material assistance to antileprosy campaigns in Africa for the period 1958-1960. WHO will continue to give technical advice and supply consultants for these campaigns, as well as granting fellowships to antileprosy workers from the African Region.