

## ABSTRACTS

*Premonitory Symptoms in Leprosy.* S. K. CHAUDURI, S. C. BASU, and D. K. CHAKRABORTY. *Leprosy in India*, **31**, 3; July, 1959, pp. 85-89.

The authors describe as promonitory manifestations of leprosy which are helpful in early diagnosis the following: pain, burning sensation, and weakness in the limbs, progressive loss of weight, anorexia and anaemia, spontaneous sores on the limbs, eczema of long duration, and epistaxis. Some of these are only unrecognized signs of established leprosy, e.g. epistaxis. Some of them may belong to other conditions, but the authors think that early leprosy serves as a cause of some of them.

*Genetic Control of Isoniazid Metabolism in Man.* D. A. PRICE-EVANS, K. A. MANLEY and V. A. MCKUSICK; *Brit. Med. J.*, Aug. 13th, 1960, pp. 485-491.

(The authors deal with a drug of more general use in tuberculosis than in leprosy, but it is used in leprosy, and the principle of genetic control of drug metabolism will be of great interest to all concerned with therapy.—EDITOR.)

In 484 patients the authors ascertained the concentrations of INH in the plasma at six hours from the ingestion of the drug, and found a bimodal curve of frequency distribution. There are rapid and slow inactivators of INH, no influence of sex or age, nor influence of race in the cases treated (American negroes and whites). The slow-inactivating character appears to be recessive. A "dosage" effect of the allele controlling the dominant character is demonstrable in that there is a significant difference between the mean plasma isoniazid concentration of recognizable heterozygotes and the mean value of all other rapid inactivators. The authors make some speculations concerning the factors responsible for the presence and maintenance in populations of the two INH inactivator phenotypes. The metabolism of INH *per se* is unlikely to have been much of a factor in the past, though it could become significant in the future. It is possible that there are naturally occurring compounds which are metabolised in the same way as INH, and that these may possess anti-tuberculous activity. The influence of such a class of compounds might be a mechanism whereby the recessive character might be preserved in populations. Possible advantages of the dominant character are unknown. Harris (1958) found that there is a much higher incidence of rapid inactivators among the Japanese than in European populations. One may presume that the dominant character is more advantageous in the Asiatic environment.

Therapeutic implications of the polymorphism of human INH metabolism are important in three aspects: (1) the development of

polyneuritis with long-term therapy with INH; (2) the response of tuberculous disease to INH therapy; (3) the development of INH-resistant tubercle bacilli. It would seem from the authors' experiments that the trend is for patients with the higher serum INH concentrations to have a quicker reversal to infectiousness than those with lower serum concentrations. The frequency of reversal also tended to be much higher in the slow inactivator group (high serum INH concentration). There seems to be no association between the INH inactivator phenotype and the development of tubercle bacilli resistant to the drug. Further work will go on to try to establish whether the INH inactivator phenotype has an influence on the outcome of the patient's tuberculosis when the disease is treated solely with this drug.

*Associação de Estreptomicina e de DDS no Tratamento da Lepra Murina (Association of Streptomycin and DDS in the Treatment of Murine Leprosy.)* A. C. MAURI. Rev. Inst. Med. Trop., Sao Paulo, 2, 1; pp. 5-7.

The author found clear evidence that the administration of DDS and streptomycin together to rats inoculated with *M. lepraemurium* resulted in a more pronounced and more rapid regression of lesions than when DDS was used alone. The evaluation depended on a comparison of the size of lesions and their histological picture, and the average duration of the life of the animals. There seems to be a synergistic action between these drugs in murine leprosy.

*Tratamento das Amiotrofias Leproticas pela Vitamina E (Treatment of Muscle Wasting in Leprosy with Vitamin E).* Priliminary Note. V. M. SARMENTO. Rev. Brasil. de Leprologia, 27, 2, Apr., Jun., 1959, pp. 103-107.

Following O. Sigall, the author in 1956 selected eight cases of wasting of the thenar, hypothenar, and interosseous muscles for treatment by local application of an oily solution of DL alphetocopherol. The results were encouraging but the trial could not be continued at that time. A year later the trial was resumed, using this time also a water-soluble form of acetate of DL alphetocopherol (Ephynal) of which local application of 100 mg. was made weekly for 16 weeks, reaching a total of 1,600 mg. in each region of atrophy. Following Sigall, the needle was introduced into the muscular mass in an oblique direction and obliquely, the needle being drawn back gradually so as to spread the injected substance better. The author reports on one case. The results were very good. After the fourth application the patient began to feel the injections and the thenar and hypothenar eminences began to fill out and flexion and extension improved. This was in the right hand. Treatment was then begun in the left hand, with surprising results, for the hand seemed to return

to normal after the twelfth injection. Photographs are given to demonstrate the improvements.

*Effect of Roentgen Rays on Leprous Nodules of Lepromatous Cases.*

N. MUKERJEE, S. P. BASU, N. R. SEN and S. KUNDU; *Leprosy in India*, 31, 3; July 1959, pp. 81-84.

The authors discuss this question and describe their own experiments. They find little evidence of effect in doses sublethal to tissue cells. When the X-rays are lethal to bacteria they are lethal to tissue cells. They propose to follow up their 12 cases for any possible late improvement. The dose they gave was 68r per area for two days a week for six weeks.

*Treatment of Lepra Reaction with Chloroquine.* C. K. JOB. *Journ of Christian Med. Assoc. of India*, 35, 3; May 1960, pp. 184-190.

In the Leprosy Research Sanatorium, Karagiri, the author selected 96 cases of lepra reaction, 81 acute and 15 chronic, and treated them with chloroquine and found it very effective in dosage of 150 mgm. thrice daily for one week, followed by 150 mgm. twice daily for the second week, and 150 mgm. daily thereafter. No serious toxic symptoms were noted, even in some cases who had continuous treatment for 12 months.

*Some Recent Chemotherapeutic Work in Leprosy.* T. F. DAVEY. *Transact. Royal Soc. of Trop. Med. & Hygiene*, 54, 3; May 1960, pp. 199-206, with discussion pp. 207-211.

The author gives eight illustrations in colour and four black and white of the accompanying histology of cases given Etisul therapy, combined with DDS or DPT (Ciba 1906). He first described the general usefulness of DDS and the sulphones, which have made mass campaigns possible, and there are signs that the sulphones may have a prophylactic value. The need for alternative drugs still remains, to shorten the long periods of treatment and to solve the problems of hypersensitivity to the sulphones, and intolerance to them, and persistent reactive phases, and sometimes failure to respond to sulphone therapy. In the search for such drugs workers owe a great debt to their colleagues in tuberculosis, for new antileprosy drugs seem to come from that field. Controlled therapeutic trials in leprosy face many problems arising out of the lack of knowledge of the bacteriology, immunology, and precise classification in leprosy, and in difficulties about the selection of patients in small groups. In practice the author relies on bacterial indices in smears taken from the skin, takes note also of changes in bacterial morphology under treatment, and uses as a control the curve of bacterial indices worked out over several years for sulphone therapy.

The author described his findings in trials of Ciba 1906 and Etisul. He made trial of Ciba 1906 at the suggestion of Dr. F.

Hawking. He found it as effective as DDS, and more rapid in the first year, non-toxic, so a full dose of 2 g. daily could be given from the start. It did not seem to cause so many reactions, and it combines well with DDS, and he considers it a valuable drug. The work of Davies and Driver led to the choice of Etisul (diethyldithiolisophthalate) as the most powerful of this group against animal tuberculosis. In human leprosy Davey used it by inunction twice weekly in a dose of 6 cc. of the cream. He found it in many cases to have a rapid effect on reducing the bacterial count in six to eight weeks, but an apparent drug resistance is liable to develop in the third or fourth month. He combined it with DDS and Ciba 1906 and found that drug resistance did not occur and the total effect was satisfactory. Etisul seemed to have little action once the bacilli became granular, and erratic results reported by others may be explained by this. He recommends its use in cases with active bacilli, and that its use be preceded and accompanied by DDS and Ciba 1906, or both.

In the discussion following this paper Dr. R. J. W. Rees pointed out the importance and significance of Dr. Davey's work and that carefully controlled clinical trials are not impossible, and confirmed that granularity of bacilli goes with degeneration, as shown by his recent studies with the electronmicroscope. Dr. G. W. Driver gave an account of the laboratory background to Etisul. Its activity is due to the release of ethyl mercaptan in the body. Oral dosing gives rise to ethyl mercaptan in the gastro-intestinal tract and some of this escapes and gives rise to an unpleasant garlic smell. It is absorbed by inunction but the action is systemic. Dr. W. H. Jopling raised the question of the clinical problem of finding a successful and reliable therapy for nerve pains in leprosy and mentioned his clinical trials for leprosy with Vadrine, which in combination with DDS is giving significant results. Dr. D. S. Ridley said that bacteriological analysis of skin biopsies supports the results of Dr. Davey with the new drugs he has tried. Dr. K. R. Chatterjee discussed the possibility of there being different strains of *M. leprae*: he himself thinks this is possible. The granular form may be a stage in development (Manalang) or there may even be a form which is not acid-fast. He found Ciba 1906 effective, and its advantages are low toxicity and effectiveness in some sulphone refractory cases. He found Etisul active when combined with oral DDS and particularly so in patients with no previous treatment.

*The Action of Electronegative Colloidal Particles on the Inflammatory Reaction Induced by M. leprae and M. lepraemurium in Rats, Guinea Pigs, and Rabbits.* W. A. HADLER, Revista Brasileira de Leprologia, 37, 1, Jan.-Mar., 1959, pp. 9-14.

Rats, guinea pigs and rabbits were studied histologically in the lesions caused by the inoculation of suspensions of *M. leprae* or

*M. lepraemurium* together with colloidal suspensions of Prussian Blue, Trypan Blue, or Charcoal. The injections were given by intraperitoneal or intracutaneous routes. In the rat the late lesions produced by the combined inoculation were stronger and more localized and contained larger numbers of macrophages than the lesions due to purely mycobacterial inoculations in the control animals. In limited areas of the lesion the macrophages phagocytise the bacilli and athrocytise the injected particles, and there is some sign of lysis of bacteria and digestion of the electronegative particles by the macrophages. The macrophages in these areas after lysing the bacilli transform into epithelioid cells and the structure of the lesion itself is modified, so that tuberculoid-similar areas develop within lepromatous lesions, though the total histological picture is not modified. The bacilli and particles acting together seem to give an enhanced stimulus, by activating the lytic enzyme system of the rat macrophage.

*Correlação e Antagonismo Lepra-Tuberculose: Alguns Aspectos Estatísticos Observados no Estado do Rio Grande do Sul (Correlation and Antagonism between Leprosy and Tuberculosis: Some Statistical Features Noted in the State of Rio Grande do Sul)* E. C. DE CAMPOS. Rev. Brasil. de Leprologia, 37, 3, Jul. Sept. 1959, pp. 117–128.

The author quotes the ideas of the various authors for and against the theory of antagonism between leprosy and tuberculosis. He gives data and maps regarding the State of Rio Grande do Sul and compares the coefficients of morbidity for the two diseases which indicate a definite antagonism between them. There is a clear-cut and natural division between the north and south of the State in the matter of the favourable influence of tuberculosis on the leprosy endemic. He thinks there is a practical possibility of stimulating the human body to develop a state of resistance to leprosy, and asks for further investigations in order to reach a definite decision on BCG and other possible agents.

*Influencia da Vacinação pelo BCG sobre a Lepromino-Reação em Pessoas Sadias Comunicantes e não Comunicantes de Casos de Lepra (Influence of BCG Vaccination on the Lepromin Reaction in Healthy Contacts and Non-contacts of Leprosy Cases).* CANDIDO SILVA and A. RABELLO NETO. Rev. Brasil. de Leprologia, 27, 3; Jul.–Sept. 1959, pp. 129–143.

Since 1952 the National Leprosy Service has been carrying out a trial of BCG in contacts of leprosy cases in the area of the Nova Iguaçu Dispensary in the State of Rio, Brazil, an area where there is close control. All the lepromin-negative contacts were divided into two groups by lot, one group to be vaccinated and the other kept as a

control. The first was given six fortnightly consecutive oral doses of 200 mgm. of BCG. The other group took a placebo of similar appearance. The BCG was in every case used within six days of its manufacture. A second lepromin test was done six to eight months after the BCG administration. A comparative study of the two groups showed practically the same degree of conversion of the lepromin reaction to positive. Subsequent lepromin tests were carried out at variable periods. The authors noted with surprise that some subjects showed reactional instability, turning back to a negative after having reacted very well.

Another investigation was carried out in contacts and non-contacts of leprosy, and did not show any difference between the percentage of lepromin-negatives in these two groups. It was also noted that there was a persistence of lepromin-negatives among contacts of tuberculosis, even in adults.

The authors describe a serious case of a female adolescent who was persistently lepromin-negative, though between 1953 and 1955 she took 2,000 mgm. by mouth. In 1958 she became lepromatous.

The persistence of lepromin-negatives among the vaccinated and non-vaccinated alike, in about the same proportion, severely restricts the preventive value of BCG in the leprosy endemic, for the common opinion is that BCG is only useful in the group which does not react to lepromin.

*Metabolism of Compounds Related to Ethyl Mercaptan.* J. S. LOWE, Biochem. Pharmac. 3, 1960, pp. 163-172.

Of the striking *in vivo* antitubercular action of ethyl mercaptan and related compounds, also the antileprosy action of an ethyl mercaptan derivative (Etisul or diethyldithiolisophthalate) there are interesting aspects (a) the activity is confined to the ethyl mercaptan series and is not shown by homologous thiols; (b) the antitubercular action *in vitro* is small and no greater than that of other homologous thiols, which suggests that this action is not due to ethyl mercaptan *per se* but to some metabolite.

Snow (Biochem. Pharmac. 65, 1957, pp. 77-82) studied ethyl mercaptan derivatives labelled with S-<sup>35</sup> and found that about a half of the S-<sup>35</sup> appeared in the urine as sulphate and he detected two organic metabolites, one of which was ethyl methyl sulphone and the other not identified. However, neither showed any antitubercular activity when tested *in vivo*. The present author has studied the fate of the carbon of ethyl mercaptan and describes his experiments, which had results in close agreement with those of Snow. There is no evidence of any direct metabolite from the carbon moiety differing from those in which the C=S link is intact, A possible metabolic path for ethyl mercaptan is removal of hydrogen sulphide by desulphydrase action leaving a two-carbon residue. Subsequent

oxidation of the hydrogen sulphide and metabolism of the two-carbon unit would account for the equivalent production of  $\text{CO}_2$  and  $\text{SO}_4^{2-}$ . Desulphydrases seem to occur generally among higher animals.

*Comentarios e Sugestões de uma Campanha Antileprotica Baseados em Nossa Experiencia de 21 Anos no Dispensario de Uruguaiana (Comments and Suggestions for an Antileprosy Campaign Based on 21 Years Experience of the Uruguayan Dispensary)* D. DE MENEZES, Rev. Brasil. de Leprologia, **27**, 3, Jul.-Sept. 1959, pp. 144-153.

He studied 101 cases recorded 1939-1959, and found that 56 came of their own accord, seven were sent for clearing up a dermatological diagnosis, six were notified by the Porto Alegre Leprosy Dispensary, nine were on general notifications, and 26 were discovered during examination of contacts. Thus in over 67% of the patients the origin of their infection could not be decided. The author thinks that BCG should be given to the general population, both contacts and non-contacts. Hardly three per thousand of those given BCG developed leprosy in the region.