Abstracts

The following 4 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 8:

1. **Tissue reactivity to tuberculin and ink in lepromatous leprosy with respect to the 'isopathic phenomenon'**, by P. KANAAR. *Derm. Int.*, 1967, **6**, 11.

The tissue reaction of leprosy patients to injected materials (tuberculin, leishmanin, milk, peptone, BCG or Indian ink) has been stated to resemble the histology of the leprosy lesions of the patient, regardless of his classification (see for example *Trop. Dis. Bull.*, 1955, **52**, 785; 1964, **61**, 795). This "isopathic phenomenon" would imply that the anergy of lepromatous leprosy is non-specific. However, some workers have failed to confirm these observations.

The present author failed to obtain any evidence in support of the isopathic phenomenon. Tuberculin and Indian ink were injected into apparently normal skin areas in 7 volunteer patients with treated lepromatous leprosy. Serial biopsies were made at intervals of 8 hours to 12 weeks, with fixation in Zenker's fluid. There were no more foam cells at the injection sites than at control sites in the same patient, and the irregular fluctuation with time of the number of foamy cells suggested that they were not associated with the response to the injected material. The foam cells were due to small randomly sited pre-existent lepromatous foci. All the other histological features were compatible with a normal reaction to tuberculin or ink. Further studies on 14 additional patients also gave negative results.

D. S. Ridley.

2. **Thalidomide therapy in the lepra reaction**, by J. CONVIT, J. M. SOTO and J. SHESKIN. *Int. J. Lepr.*, 1967, **35**, 446.

In this trial carried out in Venezuela, 24 patients (16 men and 8 women) were selected to test the efficacy of thalidomide in suppressing lepra reaction. Those not previously treated with corticosteroid were given 400 mgm./day, in divided doses orally, and fever settled in 48 hours; all symptoms disappeared within 4-5 days. There was one failure. Those previously treated with corticosteroid were given 500 mgm./day, steroid being suspended at the start of the trial; there was marked aggravation of the reactional state during the first 48 hours, regressing during the next 7 days and disappearing after 12-14 days. In both groups dosage of thalidomide was gradually reduced to a maintenance dose of 50 mgm./day. The authors state that patients previously intolerant of dapsone (DDS) were able to resume therapy while taking thalidomide, but no details are given. The only side-effects were constipation (at higher dosage) and temporary oedema of hands and feet.

[The abstracter wishes to criticize two aspects of this trial. Firstly, it would have been preferable if 12 of the 24 patients had acted as a control group and had been given a tranquillizer such as chlorpromazine (Largactil) 25 mgm. 4 times a day instead of thalidomide. Secondly, he feels compelled to protest most strongly against the inclusion of women. Although the authors say that these women "had been submitted to special control to eliminate all suspicion of pregnancy", mistakes could have been made. Furthermore, this trial will encourage clinicians in other parts of the world to include women in their trials of thalidomide and disastrous results are foreseeable.]

W. H. Jopling.

3. **Tratamento experimental da lepra com Ro-4-4393** (Experimental treatment of leprosy with sulphormethoxine), by S. F. TARLÉ. *Publções Cent. Estud. Leprol.*, 1967, **7**, 2, 12.

The English summary appended to the paper is as follows:—

"In anti-leprosy therapeutic the author uses a new sulfa of prolonged action, Ro-4-4393 (Fanasil—'Roche'), in a group of 6 lepromatous patients, in the doses of 1.5 gr. to 2.0 gr. per week (single dose). The recession of the bacilloscopic indices was noted in practically all the patients, the action of the drug being comparable with that of sulfona, but showing as important facts almost an absence of side effects and acute manifestations, besides the convenience offered to the patient of a single weekly dose. One patient who had shown an aggravation of heart insufficiency owing to the use of sulfona, when submitted to our treatment showed excellent general health with no heart insufficiency.'

4. **La Kelfizina nella terapia della lepra** (Kelfizina in the treatment of leprosy), by A. A. BACCAREDDA-BOY, R. BERTAMINO and G. FARRIS. *Derm. Int.*, 1967, **6**, 109. English summary (5 lines).

Ten patients suffering from the leprotic form of leprosy were treated with Kelfizina (sulphalene) in the dermatology clinic at Genoa, Italy. Two were recent cases and had not had any other specific treatment; 4 other patients could not tolerate any specific treatment because of the violent leprotic reactions they experienced [3 of these had previously been given steroids]; one patient showed a recurrence of the disease 2 years after suspension of treatment by azosulphone and the remaining 3 had shown very little response to combined cycloserine+azosulphone treatment.

The dosage of Kelfizina was as follows: a single oral dose of 1 gm. the first week, 1.5 gm. the second week (1.0 gm. on the first day, and 0.5 gm. the second day) increasing by 0.5 gm. to 2.5 gm. till the total dose amounted to 62 gm. Laboratory and clinical examinations on blood and urine were done every 15 days and bacterial examinations of the nasal mucus and of films from the skin of the ear lobes and from 5 other sites were carried out. Three patients showed no reactions; 4 had mild leprotic reactions for 5-14 days which disappeared in 10-25 days while treatment continued; 3 patients showed severe leprotic reactions and in one of these patients treatment had to be suspended. [Before admission to the authors' clinic, this patient had been treated by steroids under the diagnosis of polymorphous bullous erythema.]

With regard to side-effects, although all patients showed some alteration in liver function before treatment started, no effects on the gastrointestinal tract, blood, liver or kidneys were noted and one patient already had a duodenal ulcer. In 5 patients the nodules and infiltration regressed, 3 improved slightly, one was unchanged. In 6 out of 8 the nasal mucus became negative and the Bacterial Index in the skin showed a definite reduction with an increase in the numbers of abnormal bacilli and of those with granules.

The authors conclude that Kelfizina has a definite effect on leprosy and is well tolerated, but it also has a tendency to provoke leprotic reactions which may be either slight or severe. These reactions, however, will disappear if treatment is continued but it is considered that a longer period of observation is advisable.

W. K. Dunscombe.

The following 2 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 9:

5. **Leprosy and genetics. A review of past research with remarks concerning future investigations,** by B. Beiguelman. *Bull. Wld Hlth Org.*, 1967, **37**, 46.

This paper, which should be studied in the original, summarizes critically and very competently recent investigations into various aspects of the possible genetic basis of leprosy.

Attempts have been made, without success, to correlate susceptibility to leprosy with such genetic markers as taste sensitivity to phenylthiourea, ABO and Rh blood groups, glucose-6-phosphate dehydrogenase deficiency, haptoglobins, transferrins, Au(1) antigen. Discrepancies in published results are attributable to such sources as imprecise data, bias, small series, selected populations, and deficiencies in technique. Pedigree analyses of families that include those suffering from leprosy have so far contributed little to knowledge of susceptibility and resistance to leprosy. Studies of the familial distribution of the late lepromin (Mitsuda) reaction are discussed in some detail because of their bearing on the possibility that transmission of the specific dimorphism of macrophages in respect of *Mycobacterium leprae* (presence or absence of ability to lyse) may be hereditary.

Geneticists interested in leprosy have concentrated on the investigation of inherited qualities that may be related to susceptibility to the disease, but the practical usefulness of any such correlations—even if established—is doubtful. The author indicates the vast lacunae in our knowledge of such fundamental matters as the significance of the late lepromin reaction in man, which is the only trait completely associated with leprosy, and suggests a research programme through which geneticists might contribute towards a better understanding of this reaction and its bearing on transmissible susceptibility to leprosy infection. By employing the experimental techniques of blood monocyte culture and observing the transformation of these cells into macrophages possessing or not possessing the ability to lyse living *Myco. leprae*, the author considers that real progress may be achieved.

S. G. Browne.

6. **Syndromes paraplégiques en milieu lépreux. A propos de 12 cas observés en Nouvelle-Calédonie** (Paraplegic syndromes in a leprous environment), by G. Desmoulins and G. Zeldine. *Bull. Soc. Path. Exot.*, 1967, **60**, 482.

Among 721 patients of Melanesian race suffering from leprosy in New Caledonia the authors have found 12 with spastic paraplegia of obscure origin, whose case histories they give; there were also another 4 possible cases. This trouble was not found among 158 non-Melanesian patients with leprosy. Among the general population the disease is rare and when found has obvious causes.

The only common factors were Melanesian race, leprosy of any type, and treatment for some years with sulphones. Investigations showed no evidence of compression of the cord, and no definite evidence of infection. Although some of the patients showed serological changes of treponematosis, these were probably due to yaws rather than syphilis. No evidence could be obtained of viral or rickettsial infection. Spinal fluid showed no notable changes, and the raised serum globulin levels occur in all leprosy patients

The authors speculate on possible plant poisons, and on the relationship to kuru. [They do not mention the similar condition, occurring in Africa though not essentially in persons with leprosy, which may be related to aneurine deficiency.]

A. C. E. Cole.

The following 5 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 10:

7. **Gynécomastie du lépreux et obstacle au flux lymphatique spermatique** (Testicular lymphatic obstruction in gynaecomastia in leprosy), by A. Carayon, J. Languillon and G. Foucher. *Bull. Soc. Méd. Afr. Noire Lang. Fr.*, 1967, **12**, 552.

Lepromatous leprosy is probably the commonest cause of gynaecomastia, yet the undoubted association of testicular damage in leprosy with gynaecomastia is neither as clearly documented nor as lucidly explained

as it should be. Although some testicular damage is clinically demonstrable in perhaps 30% of (male) patients with established lepromatous leprosy and is histologically apparent in 90%, gynaecomastia was present in only 8% of 250 leprosy patients in the authors' series. [Radiographic examination of the male breast is considered to be a useful procedure for the detection of early subclinical damage.]

In patients with lepromatous leprosy, in whom gynaecomastia was present, histological examination of testicular tissue revealed some hyperplasia and vacuolization of the Leydig cells (which was not due to direct action of *Mycobacterium leprae*), with some significant extracellular oedema. The authors' new and important finding was fibrosis of the testicular lymphatics, with consequent constriction of the lumen of the vessels. Other examinations (*e.g.*, various biochemical determinations, liver function tests, and so forth) and the nutritional state were not considered to be sufficiently abnormal to account for the occurrence of gynaecomastia. By means of lymphography of the testicular and funicular lymphatic vessels, the authors were able to show stasis and back-flow of lymph and blocking either of the spermatic and lymphatic vessels themselves or at the lymphatic node of Horowitz-Zeissl.

The appearance of gynaecomastia would, according to the authors, seem to depend on a concatenation of more than one factor: *viz.*, direct damage of the testes by lepromatous leprosy (as shown by dysfunction of the damaged Leydig cells) and a mechanical lymphatic statis due to fibrosis of the deep lymphatic nodes following leprotic infiltration.

[Further work is required to substaatiate this interesting hypothesis, accompanied by more convincing radiographs.]

S. G. Browne.

8. **Effects of DDS on lysosomal enzymes from leprosy tissues,** by A. G. Palekar and N. G. Magar. *Int. J. Lepr.*, 1967, **35**, 436.

The authors have studied the specific activities of acid phosphatase, cathepsin, ribonuclease and aryl sulphatases from lysosomes of tissues of normal subjects and of leprosy patients:—(i) who had not been treated with dapsone (DDS); (ii) who were being treated with DDS; and (iii) who had undergone DDS treatment for 6-10 years but who were bacteriologically negative for *Mycobacterium leprae*. The examinations were made on 250-300 mgm. of tissue obtained by biopsy from the arms of normal persons and from the lesions on the arms of patients with lepromatous, tuberculoid and maculoanaesthetic types of leprosy.

The results of the examination, the methods of which are given as references, are presented in tabular and graphical form. The lysosomal fraction and the tissues of leprosy patients of all types who had not undergone DDS treatment, showed a significant high activity for all 4 enzymes when compared with the same fraction of normal tissues. In contrast the lysosomal fraction from the tissues of leprosy patients who had undergone DDS treatment for 6-10 years and who were bacteriologically negative, had almost normal activities and the activities of the fractions from tissues of the patients who were undergoing DDS treatment were intermediate. The results therefore indicate that the increased specific activities of lysosomal enzymes from the tissues of leprosy patients of all types decreased significantly with effective DDS treatment.

The authors consider their results suggest that the biochemical evidence could be integrated in an understanding of the general physiology of the cell as an effective device allowing the cell to utilize organic matter incorporated after the DDS treatment. The DDS may be acting principally on the lysosomal component, increasing its hydrolase activity, altering cell metabolism in some way and rendering the cell cytoplasm unsuitable for multiplication and survival of the bacillus.

S. R. M. Bushby.

9. **Acute dapsone poisoning,** by R. S. Rajagopalan and J. Rama Rao. *J. Ind. Med. Ass.*, 1967, **49**, 439.

A woman aged 20 years swallowed 375 mgm. dapsone (provided for her husband, who had leprosy), at 9 p.m. Next morning she was found to be sweating and vomiting profusely and was taken to hospital. She was conscious and complained of severe nausea and giddiness. Respiratory rate was 26/minute; pulse rate 150/minute. The tongue and tips of the fingers were bluish. A sample of blood was greyish black and contained much methaemoglobin on spectroscopic examination. The urine was normal. She was given 1 pint of 5% glucose by intravenous drip, ascorbic acid 500 mgm. 6-hourly and ethylbutamide and propylbutamide 2 cc. intravenously 6-hourly. Cyanosis increased and she became restless. 100 cc. of 12.5% mannitol was given by intravenous drip. Methylene blue (50 mgm. capsule) was given every 6 hours but she vomited. She gradually improved in 48 hours and began to pass urine. On the fourth day, the blood appeared free from methaemoglobin but tachycardia persisted for 2 weeks. The ascorbic acid and methylene blue were given in order to reduce methaemoglobin to haemoglobin.

F. Hawking.

10. **A kinetic method for the study of activity of drugs against** *Mycobacterium leprae* **in mice,** by C. C. Shepard. *Int. J. Lepr.*, 1967, **35**, 429.

Most studies of the activity of drugs against *Mycobacterium leprae* in mice have followed the procedure in which administration of the drugs starts on the day of infection and is continued till termination of the experiments. Thus, only inhibition of multiplication was usually observed and the killing of *Myco. leprae* by the drug was not measured. In an earlier paper [*Trop. Dis. Bull.*, 1967, **64**, 1212), the author reported attempts to measure the bactericidal activity of dapsone (DDS) by allowing the *Myco. leprae* to multiply

to above 10^6 organisms per mouse before starting the drug, and then at intervals counting the bacilli. This procedure was very laborious and in the present paper he describes a kinetic method that takes advantage of the accuracy available in the logarithmic phase of the growth curve of *Myco. leprae*. The drug is given for only a limited period early in the growth curve and its effect is measured by the subsequent delay in appearance of the logarithmic phase of growth.

The growth curve in control mice was monitored from pools of 4 mice, killed at monthly intervals, starting 3 months after inoculation. Soon after the bacterial population had increased to the normal plateau levels above 10^6, counts were made on similar pools of 4 mice from each of the treated and control groups, and the counts were repeated after intervals of 3 months. The drugs examined in the diet were DDS, ranging from 0.1% to 0.00001%, isoniazid 0.01%, 4,4′-diacetyldiaminodiphenylsulphone (DADDS), thiambutosine (diphenylthiourea, DPT) and *p*-aminosalicylic acid (PAS); streptomycin, 2 mgm. thrice weekly, was injected. Some of the drugs were given in combination. In interpreting the results, 2 simplifying assumptions were made: (i) that after the beginning of administration of an effective drug the cessation of bacillary growth is rapid enough to prevent significant increase in numbers of bacilli, and (ii) that as soon as the inhibitory drug disappears from the tissues, bacillary growth begins at the rate observed in the control.

The results are given in tabular and in graphical form and they show that none of the treatments eradicated the infection. Streptomycin 2 mgm. thrice weekly and 0.1% DPT in the diet were each bacteriostatic. Isoniazid 0.01% and PAS 0.6% in the diet were each inactive. DDS 0.01% in the diet was bacteriostatic and probably partially bactericidal, the killing rate being estimated not to exceed 77-84%; 0.1% in the diet was no more effective. The combination of 0.01% DDS with either streptomycin or DPT was no more effective than DDS alone and isoniazid appeared to antagonize the antibacterial effect of DDS.

S. R. M. Bushby.

11. **Improved method for observing elongation of** *Mycobacterium lepraemurium in vitro*, by M. Nakamura. *Int. J. Lepr.*, 1967, **35**, 505.

Elongation *in vitro* of *Mycobacterium lepraemurium* was described by Hart (*Int. J. Lepr.*, 1965, **33**, 504) and by Hart and Valentine [*Trop. Dis. Bull.*, 1964, **61**, 51) and it is a possible guide to the complete cultivation of this organism, but the method used by Hart and Valentine involved the risk of damage through centrifugation and washing for removal of the high concentrations of sucrose in the medium used for culture. The slide culture method is used in the present experiments.

Smears are prepared from lepromas which have been homogenized in sterile water and suspended in 0.1% bovine albumin V fraction. After being dried at room temperature the slide is immediately placed in the medium described by Hart and Valentine, but with slight modification, and incubated at 37°C for periods up to 30 days. A slide is fixed immediately after drying to serve as a sample of the initial inoculum. For fixation, the slide is transferred to 10% formalin water; it is then well washed and stained by Ziehl-Neelsen's method. For assay of elongation, photographs are made of the slides to give a final magnification of 1,000.

In this method, elongation was observed at *p*H 6.0, but not at *p*H 8.0. Infectivity activity of the bacilli was parallel to grades of elongation for 15 days after incubation, as judged by the ability of a 10% lepromatous suspension to produce lepromas in mice after incubation under the same conditions as the slide. However, after incubation for 30 days at *p*H 8.0, but not at *p*H 6.0, infectivity was still maintained, even though no elongation occurred at this *p*H value. Hart and Valentine observed that elongation gradually continued for about 2 months after incubation, but in view of the loss in infectivity it is doubtful whether elongation after incubation for this period represents a vital process.

Further studies on factors affecting the elongation phenomenon observed by this method are now in progress.

S. R. M. Bushby.