

## CURRENT LITERATURE

*It is intended that the current literature of leprosy shall be dealt with in this department. It is a function of the Contributing Editors to provide abstracts of all articles published in their territories, but when necessary such material from other sources is used when procurable.*

- JORDAN, P. *Lepra in Öffentlichkeit und Presse.* [Leprosy in newspaper and the subject literature.] *Der Hautarzt* 1 (1950) 130-133.

As elsewhere, the public in Germany takes a keen interest in leprosy, although the country has long been free from the disease. This interest is doubtless evoked by the tragic fate of the leprosy patient, which is touching and at the same time incites curiosity. The popular concept of leprosy is dominated by the idea that the danger of infection is extraordinarily great, that the disease is incurable, and that expulsion of the patient from the community—in the sense of being buried alive—is inevitable. The expression “to be treated like a leper” is quite current in Germany. The newspaper reports on leprosy can be classified according to certain aspects. Popular topics for headlines are those concerning the discovery of single cases of leprosy, leprosy colonies with hundreds and thousands of infected people isolated in them, and progress in science, above all new remedies. Instructive popular articles follow, and occasionally there is also a publication on the social history of the disease. Then there is the group of the horror stories on the danger of leprosy, of the dreadful conditions in certain European colonies, and those which are nothing more than fairy tales. Unfortunately, objective reports are very rare. Most of the news has a sensational trait, is exaggerated or distorted, and not infrequently even misrepresented and in bad taste, an excellent source for trashy journalism and cheap entertainment for the reader. [Proper instruction of the general public by the press would lend considerable support to the endeavors to eliminate leprosy.] —E. KEIL

- JORDAN, P. and WULF, K. *Lepra-Uebertragung auf deutschem Boden.* [Transmission of leprosy on German soil.] *Der Hautarzt* 1 (1950) 418-419.

In the past 50 years, apart from the Memel cases (and not counting the occasional foreigners with leprosy who have been there, usually for short periods), the Germans with leprosy who have lived in the country had been infected elsewhere, mostly in South America. The last case of the Memel epidemic, the 94th one, occurred in 1920 in a Lithuanian. This brief report tells of a new case found in Germany in a ship's musician, aged 55, who had lived in Mexico from 1939-1946 as a war internee and who subsequently had shared for one year a cabin with another musician of the ship's band who was suffering from lepromatous leprosy, unrecognized. The contact developed tuberculoid leprosy. It is assumed that the infection was contracted on board. —E. KEIL

- D'IGNAZIO, C. *Lebbra, lebbrosi e lebbrosari in Ethiopia.* [Leprosy, lepers and leprosaria in Ethiopia.] *Arch. italiano Sci. Med. Trop. e Parassit.* 31 (1950) 759-768.

In a somewhat sensational style this paper tells of the widespread and

uncontrolled movement of persons with leprosy which the Italians found when they occupied Ethiopia. There is a harrowing account of the native treatment given by certain "priest- or saint-doctors." The Knights of Malta set up a large leprosy settlement to take 1,000 cases at Sela-Clacá (Tigrai), but this was destroyed in the war-time upheaval. The (American) Sudan Interior Mission had set up a settlement on a fine site a few miles from Addis Ababa, and this was developed by the Italian authorities. There were about 400 inmates in 1938-1939, increased to 535 by 1947. The structural additions have been of impermanent materials and are hardly suitable for the accommodation of patients. For the children of leprosy patients there is a crèche and nursery about 12 miles away which had 32 inmates, aged 5-6 years, by the end of 1947. These children had come from all over the country, after overcoming strong parental opposition. In April 1941 the settlement at Harar was returned to the charge of the French mission which had originally set it up. The disease presents the usual 3 types—cutaneous, neural and mixed. In mixed cases, serological reactions for syphilis are practically always positive; but syphilitic infection is very widespread. Meinicke's flocculation test is said to have been negative in most cases. The blood serum cholesterol was found markedly raised in 80 cases, even when few bacilli could be demonstrated. The sign of LeDantez, which is said to characterize leprosy in white races, is an osteo-periosteal pain elicited on percussion of certain areas over the humerus, clavicle, sternum and frontal bone. This sign was found to be absent in many of these patients but present in about 1,500 other Africans who were observed over many years and remained free from leprosy. These included 750 members of the police force, 85% of whom showed clinical manifestations of syphilitic infection, confirmed by serum tests in 78%. In the Ethiopian cases few of the leprosy patches showed anesthesia. In over 3,000 individuals without any evidence of leprosy, discolored skin patches were found to show little or no pain on pressing with a pin point.—[From abstract in *Trop. Dis. Bull.* 48 (1951) 473.]

8 DAVIES, E. J. Report on Leprosy Survey and Medical Inspection in the New Hebrides. Lepers' Trust Board, New Zealand, Christchurch, June 25, 1951. Mimeographed, 20 pp.

This is a summary report of an extensive survey made by a lady doctor at the request of the Leper Trust Board and the British Government in the New Hebrides. Between April 1948 and April 1951 she spent two full years at the work, and succeeded in visiting every inhabited island except two whose total population is less than 100. In most places, apparently, the people cooperated; in some they were hostile or suspicious and tended to evade examination. In total, 21,516 individuals were seen. [In one reference work available the total population is given as 46,000, in two others as about 60,000.] The survey was concerned not only with leprosy but also malaria (6,983 enlarged spleens were found), frank tuberculosis (363 cases), and elephantiasis (119 cases). Of leprosy, 96 cases were seen, including 1 French woman, and data on all of them are tabulated; 9 of them are listed as suspects. The distribution is very spotty, and on not a few of the islands no cases were encountered. The frequency was lowest in the two districts of the southern half of the archipelago, with only 11 cases among 5,866 people (1.9 per 1,000). In the Southern District itself, comprising five islands, cases were seen only

on Tanna—one of the noncooperative places—and there only 4 among 1,252 people. In the two northernmost districts, 15,650 people yielded 85 cases (5.4 per 1000), but this figure is due largely to the number found on Espiritu Santu, 31 in 1,246 people (24.5 per 1000). On nearby Aoba only 7 were found among 2,076 people (3.4 per 1000), and only 2 of them were Aobans; on Maew, just beyond Aoba, none was seen among 475 people. Again, in the Banks Group farther north, Motalava constituted a "pocket," with 9 cases (24.3 per 1000), whereas none was found among 1,137 people in the five other islands visited. Apparently few of the primitive bush people inhabiting the interiors of certain of the larger islands were seen, but 2 of the leprosy cases were in such people. Relatively few of the affected persons are in any sort of isolation. —H. W. W.

FLOCH, H. Rapport sur le fonctionnement technique de l'Institut Pasteur de la Guyane française et du Territoire de l'Inini pendant l'année 1948. Institut Pasteur publication No. 188, March 1949.

Idem, 1949. Institut Pasteur publication No. 207, April 1950.

Idem, 1950. Institut Pasteur publication No. 229, April 1951.

1. In this report 44 pages are allotted to the subject of leprosy, under several chapters. Among other things the studies made in the Institut are recapitulated, the conclusions of the Havana congress are summarized, and the developments in French Guiana are discussed. During the year 58 new cases were recorded, 15 lepromatous, 28 undifferentiated, and 15 tuberculoid.

2. A report of which 34 pages were devoted to leprosy, covering much the usual ground. During the year 80 new cases had been found, 12 lepromatous, 41 undifferentiated, and 27 tuberculoid.

3. This report includes 53 pages on the subject of leprosy. Besides the usual review of studies made, there is a chapter on the problem of leprosy in Brazil and another on that in Santo Domingo. During the year 73 new patients were discovered, 17 lepromatous, 30 undifferentiated, and 26 tuberculoid. The questions of isolation and of the social aspect of the problem are discussed, and also the seriousness of leprosy in the penal population, the occurrence of Lucio leprosy in Guiana, the neural classification in leprosy. —AUTHOR'S ABSTRACTS

ZANCHELLO, S. A. Comportamento epidemiologico della lepra in Sardegna dal 1896 ai nostri giorni. [Epidemiology of leprosy in Sardinia since 1896.] *Rassegna med. sarda* 53 (1951) 39.

This study deals with 160 cases of leprosy in Sardinia during the last 50 years. In the last 25 years no decrease in the total number of new cases was observed, although active autochthonous and immigration nuclei decreased, possibly because of sanitary regulations. The most frequent age of clinical onset was between 21 and 30 years for both sexes. There was no difference in the frequency in males and females, and no significance with respect to occupation. Individuals with not very bad conditions of life became leprosy with some frequency, although not so often as people living under worse conditions. The most frequent causes of death were pulmonary, pleural and bronchial diseases (30.9%), "senile marasmus" (9.5%), heart diseases (7.9%), and leprosy cachexia (4.8%). Transmission within the family occurred in 44.4% of the cases, outside of the family in 55.6%. Conjugal transmission was ascertained in only 2.1%. Regarding

transmission from parents to children, 5.2% of the 248 children involved became leprous, 65.3% did not fall ill, 29.4% died of non-ascertained diseases.

—M. TERNI

- SAUTET, J. Les traitements actuels doivent-ils abandonner la ségrégation de lépreux et amener une refonte totale de la prophylaxie de la lèpre? [Should the present treatments lead to abandonment of segregation and a complete revision of the prophylaxis of leprosy?] *Presse Méd.* **59** (1951) 428-437.

The improvement in the prognosis of leprosy through the use of sulfones leads the author to envisage a new concept of the prophylaxis of this disease. In the first place, abolition of segregation, which too often leads the patients to hide themselves. The contagious cases, and the invalids and abandoned ones, should be treated in special establishments consisting of (1) a hospital properly speaking, with a laboratory and an operating room; (2) a leprosy clinic-dispensary, with special consultations (eye, ear, nose and throat and dentistry); and (3) an asylum for the incurables and for those whose condition requires years of treatment, an asylum of the "hansenian village" type with provisions for individual life and occupation. The clinic-dispensary should be used both for the inhabitants of the "hansenian village" and for outside patients. The author hopes that the absence of restraint will encourage the patients, treated first at the dispensary, to submit themselves for hospitalization.

—R. CHAUSSINAND

- GRECO, N. V. Conducta que debe observarse con una persona sospechosa de enfermedad de Hansen. [Conduct to be observed with a person suspected of Hansen's disease.] *Semana Méd.* **99** (1951) No. 3018, supplement, pp. 1-6.

After praising the accomplishments of the Patronato de Leprosos of Argentina, the author discusses the known measures of the campaign against leprosy. He concludes with a series of aphorisms, some of which reveal personal opinions: the introduction of the bacilli through the use of utensils, sharp or pointed objects, the bites of insects or rats, or by apparently healthy persons who are carriers of the germ.—G. BASOMBRI

- DUBOIS, A. and RADEMECKER, M. A. Valeur sur la chronaxie comme méthode de diagnostic précoce des formes nerveuses de la lèpre. [Value of chronaxie as a method of early diagnosis of the neural forms of leprosy.] *Rev. belge Path. Med. expér.* **21** (1951) 108-118.

The difficulties of diagnosis and the limitations of the various diagnostic procedures are discussed, with reference to the forms of the disease with few or no bacilli. Even the biopsy findings are not entirely characteristic in neural cases, for the changes may be quite banal (indeterminate cases). Regarding anesthesia and anhydrosis for determining local nerve disturbance, the latter is regarded as the more reliable of the two, but both have their limitations. [The histamine test is not mentioned.] The literature of electrical modifications in leprosy patients is reviewed briefly; very little has been done in this field, although it might be expected not to be devoid of interest. The authors have investigated the chronaxie in the few (5) cases available, to ascertain how useful a study of that electrical procedure might be. There was no difficulty of diagnosis in

these cases, except for the improvement that had occurred in two. The findings in each case are recorded in some detail. In all of them the examination still elicited important signs of abnormality, even in clinically negative regions, evidencing invasion of the nerve branches. On the whole, the authors find the electrical and chronaxie examinations to be of interest. Nerve changes thus observed exceed in spread the cutaneous signs, exist without appreciable muscle atrophy, and seem in fact to extend very early into numerous nerves. The test is more objective than are those for anesthesia. It is suggested that this method of examination may be of real diagnostic, and perhaps also prognostic, value, and its usefulness should be determined in early cases. —AUTHORS' ABSTRACT

- 6 DUBOIS, A. A propos du diagnostic de la lèpre. La chronaxie. (On the diagnosis of leprosy; chronaxie.] *Ann. Soc. belge Méd. trop.* **31** (1951) 525-529.

This article covers much the same ground as the preceding item, it being pointed out that there exists equipment for the procedure which is not cumbersome, although electric power (110 or 220 volts) is required. The five cases previously reported are summarized briefly, and the findings in another one are given. That patient, a European woman, had a very slight eruption of macules which were poorly discernable but were hypo- or anesthetic; paresthesia was present, and anhydrosis. Bacilli were not found (7 scrapings). The electrical examination showed increasing chronaxie in the cubital area and also the external popliteal nerve, undoubtedly indicating polyneuritis. This observation, in the opinion of the author, confirms and justifies the diagnosis of leprosy. —AUTHOR'S ABSTRACT

[Chronaxie, or chronaxy (Blakiston's New Gould): The duration of time that a current twice the rheobasic (galvanic threshold) intensity must flow in order to excite the tissue being tested. Chronaxie is related to irritability and is used for testing for irritability changes in nerve and muscle. Or (supplied by Dubois): "The chronaxie may be briefly defined as the shortest duration of a current necessary for excitation when its strength is twice the rheobase." The rheobase is "the intensity of a current which when allowed to flow for an indefinitely long period is just capable of exciting the tissue (intensity threshold)."]

- 7 GOMEZ ORBANEJA, J. and VIVANCOS. Lepra nodular tuberculoide infantil. [Nodular tuberculoid leprosy of childhood.] *Actas Dermo-Sif.* **42** (1951) 415-416.

A case of nodular tuberculoid leprosy in a child 4 years old, a native of Caceres, who two years ago presented the first manifestations on the right forearm. One year later there appeared lesions on the cheeks, the left forearm and the buttocks. The lesions observed were of two types. Some were nodular, elevated, dark red and of firm consistency, not surrounded by inflammatory halos. These resembled tumid lupus in their appearance, but not their consistency, which was more firm. Coexisting with them there were ordinary macular lesions of tuberculoid leprosy. The mucus and skin were bacteriologically negative, the Mitsuda reaction was positive (2+), and histologically the structure was typically tuberculoid. Despite the good prognosis of this variety of leprosy, the patient was given sulfone treatment and the disease quickly underwent regression, which was complete in 5 months leaving only a few areas of depressed

cicatricial atrophy. The difference between this peculiar childhood form of tuberculoid leprosy and those which occur in adults is pointed out.

—FELIX CONTRERAS

- MONTEL, L. R. La lèpre tuberculoïde en Cochinchine. [Tuberculoid leprosy in Cochinchina.] *Bull. Soc. française Derm. et Syph.* **78** (1951) 296-300.

The author gives a detailed description of the various aspects of tuberculoid leprosy from the clinical, bacteriological and histological points of view. He envisages minimal, minor and major tuberculoid lesions, and points out the coexistence of tuberculoid and lepromatous lesions. Finally, on the basis of histology, he considers tuberculoid leprosy to be the first stage of the lepromatous form. (In the discussion, M. Tisseuil refused to view tuberculoid leprosy in that manner.) —R. CHAUSSINAND

- THEVENARD, A., DELARUE, J. and MARQUES, J. M. Deux cas stéréotypés de lèpre tuberculoïde au même foyer, a Tahiti. Polynévrite sensitivo-motrice parcellaire de l'hémiface droite et hypertrophie homolatérale du plexus cervical superficial. [Two stereotyped cases of tuberculoid leprosy in the same focus in Tahiti. Sensory-motor polyneuritis in various areas of the right half of the face and homolateral hypertrophy of the superficial cervical plexus.] *Rev. Neurologique* **82** (1950) 245-259.

A Tahitian, aged 48 years, and his adopted daughter, aged 23, showed the same syndrome consisting of sensory-motor polyneuritis of the right half of the face, and a homolateral hypertrophy of the superficial cervical plexus involving mainly the auricular branch. Despite the insignificance of the skin lesions in the man and their absence in the girl, and the failure to find the Hansen bacillus in either patient, the diagnosis of leprosy was made on the basis of the clinical study. This revealed leprosy paralysis (partial affection, juxtaposition of normal and paralyzed muscles in the territory of a given large branch, predominance of motor disturbance in the upper facial region, marked electropion, discreet fibrillations, uneven distribution of the changes of the electric reactions, absence of contracture), which was quite different from the paralysis called "a frigore" (complete paralysis of the corresponding side of the face, effacement of the wrinkles of the forehead, importance of nonclosure of the eyes, sometimes contracture). The sensory disturbances were equally typical (hypoesthesia rather than anesthesia, involving the different modes of superficial sensitivity and not corresponding to the territory of a nerve but extending beyond it). The Mitsuda reaction was strongly positive in both patients. Finally, biopsies showed involvement of the nerve tissues and lymph nodes, the lesions being of the tuberculoid type.—R. CHAUSSINAND

- HUFNAGEL, L. Un cas de lèpre européenne chez un Espagnol a l'Hôpital St. Jacques d'Agen. [A European case of leprosy in a Spaniard at the St. Jacques d'Agen Hospital.] *Bull. Soc. française Derm. et Syph.* **57** (1950) 431-434.

A Spaniard, 37 years of age, who had emigrated into France in 1939, had for 16 years frequented numerous hospitals in Spain and France because of lesions on the legs of syphiloid character. The Bordet-Wassermann reaction being positive since the beginning, antisyphilitic treatment

had been given. On many occasions the lesions had healed, but then reappeared. In January 1949 the diagnosis of leprosy was finally made, the case an advanced lepromatous one. After treatment by chaulmoogra and then Cimédone the bacilli disappeared from the nasal mucus and the serological reaction became negative. An inquiry in the family in Spain revealed no other case. The author points out that leprosy is among the infections which may give rise to a false serum reaction, and calls attention to the problem of medical control of immigrants and frontiersmen.

—R. CHAUSSINAND

- DEBES, M. (Jena). *Lepra und Auge*. [Leprosy and the eye.] *Deutsche Gesundheitswesen* 6 (1951) 1029.

A 52 year old patient suffering from lepromatous leprosy developed a parenchymatous keratitis and diffuse iritis. The miliary lepromas in the iris collar calcified; later there was leproma formation in the angle of the chamber with adjacent limbus-leproma. Deterioration was continuous despite treatment with gold and PAS. Arrest of the process following local treatment with Greifswalder dye (a mixture of various aniline dyes) and large doses of atropine.

—E. KEIL

- TELKKA, A., PUTKONIN, T., TEIR, H. and HORTLING, H. Leprosy. A case report, with a discussion of diagnostic difficulties and the present incidence of leprosy in Finland. *Ann. Med. Intern. fenniae* 39 (1950) 263-278.

A case of leprosy is reported, a woman of 27 years in whom cutaneous lesions appeared at the age of 8. They grew larger and became annular and anesthetic in the center. Extensive neurotrophic changes appeared in the bones. Bacilli were not found. The Mitsuda reaction was negative twice. Histologic examinations showed cutaneous and nerve lesions characteristic of leprosy. The case does not definitely fall under any of the headings of the new classification (lepromatous, tuberculoid or indeterminate); it is most probably some pretuberculoid form. At the beginning of 1950, there were 7 cases of leprosy in Finland.—[From abstracts.]

- MILLER, J. L. Leprosy. *Arch. Derm. & Syph.* 63 (1951) 783-784. (Case presentation.)

Case of a 22 year old Puerto Rican man who was hospitalized because of acute arthritis, hyperpyrexia and a cutaneous eruption of one week duration. The onset was characterized by painful swelling of the joints of the extremities, shortly followed by fever and a general erythema multiforme-like eruption most evident on the face and extremities. The patient had had a similar episode 5 years previously in Puerto Rico at which time the diagnosis of nephritis and urticaria was made; the illness had subsided in about one month and the patient has remained well until the present episode. Smears from the earlobe showed numerous acid-fast organisms typical of Hansen's bacilli. Biopsy of a macule disclosed "change almost certain due to leprosy which shows minimal reactivity." The discussion brought out three interesting features: (1) there were no lepromatous features of the face in spite of diffuse infiltration of both earlobes; (2) there was a thickened ulnar nerve without sensory disturbances; (3) in the typical erythema-multiforme type of reaction eosinophilia and leucocytosis may or may not be present; in this case both were present. Since

malignant manifestations of the disease was manifest, it was suggested that medication with diaminodiphenyl sulfone be started—F. A. JOHANSEN

- 7 GARRETT, A. S. Mass treatment of leprosy with D.A.D.P.S. (Dapsone). *Lep. Rev.* **22** (1951) 47-53.

This is an account of the treatment of 9,000 patients in 30 different treatment centers in the Onitsha province of Nigeria, where the approximate number of leprosy cases is between 20 and 30 thousand out of a population of 1 million. Only patients able to come to the clinics regularly or to segregate themselves in special villages receive this treatment. At the settlement it is given 6 days a week, starting with 100 mgm. daily for the first 6 weeks and then 200 mgm. daily. In outpatient clinics and villages the drug was given twice a week, 100, 200 and 300 mgm. per dose, 3 weeks for each, to a maximum of 400 mgm. for a strong adult. Complications noted were: Early in the treatment the great majority complained of general weakness and depression which, however, passed off as treatment continued. Dermatitis was noted in 3% of the cases. Lepra reactions were mild in those having twice-weekly treatment, but often severe in those having the drug daily. The same was true of nerve reactions. Psychosis occurred in 24 cases; 1 committed suicide and 2 were violent. Recovery usually occurred within 8 weeks if treatment was stopped. On the whole, twice-weekly treatment has proved less likely to cause complications and to give as good results. —G. O. TEICHMANN

- 7 BARNES, J. and BARNES, E. J. Liver damage during treatment with diaminodiphenyl sulfone. *Lep. Rev.* **22** (1951) 54-56.

A report of an African woman of 30 suffering from mild maculo-anesthetic leprosy who developed subacute necrosis of the liver and died after receiving only 7.8 gm. of DDS. She had been given 100 mgm. for 6 days and then 200 mgm. daily for 6 days a week afterwards.

—G. O. TEICHMANN

- 7 RAMANUJAM, K. and SMITH, M. Haemolytic anaemia during treatment of leprosy with diaminodiphenyl sulphone by mouth. *Lancet* **260** (1951) 21-22.

This is a report of a case of leprosy treated with DDS by mouth in Madras. The patient was a male Indian of good physical condition, aged 36, who had had leprosy for three years. Treatment was started with 100 mgm. of DDS daily for 13 days, followed by 200 mgm. for 10 days and 300 mgm. for 13 days. On the 36th day he complained of nausea, weakness, low fever and constipation. The blood sulfone level was 1.3 mgm. per 100 ml. Next day he was taken to hospital with temperature 101.4°F., the spleen 1 inch below the costal margin, much vomiting and extreme asthenia. Methemoglobinuria, bilirubinemia, reticulocytosis and urobilinuria developed and the case was diagnosed as acute hemolytic anemia. Acute hepatitis was excluded. The patient gradually improved and was discharged after one month, but an attempt to restart treatment resulted in a return of symptoms. Attention is drawn to a possibility of hemolytic jaundice when DDS is given by mouth. —G. O. TEICHMANN

- X 7 CHATTERJEE, S. N. Modern treatment of leprosy. *J. Indian Med. Assoc.* **20** (1950) 19-21.

The author discusses the efficacy of sulfone drugs in leprosy, with



their dosage and modes of administration, the toxic effects which they can produce, and methods of overcoming these effects. He concludes that the results obtained with sulfone treatment are highly satisfactory, the treatment being simple and capable of being taken up by general medical practitioners.

—N. MUKHERJEE

- RAY, A. T. Use of the derivatives of diamino-diphenyl-sulphone in leprosy, a guide. *Indian Med. J.* **44** (1950) 228-229.

The author gives a short description of the sulfone derivatives and their doses and mode of action in leprosy, laying special stress upon their toxic action. He concludes that these derivatives, especially sulphetrone, can almost safely be given to cases of leprosy irrespective of type. Iron and yeast should also be given in adequate doses. Special attention should be given to the hemoglobin percentage and constipation. With good diet, hemoglobin does not deteriorate as rapidly in poorly fed patients. As a symptomatic treatment of leprosy affections of the eyes, throat and nose, these drugs are excellent.

—N. MUKHERJEE

- FLOCH, H. and DESTOMBES, P. Thérapeutique de la lèpre par les voies buccale, intraveineuse et intramusculaire (sulfone-retard) à l'aide des sulfones françaises. [Therapy of leprosy by the oral, intravenous and intramuscular routes (sulfone-retard), with French sulfones.] *Presse Méd.* **58** (1950) 1094-1095.

Conduite du traitement de la lèpre à l'aide des sulfones françaises (1358-F et 1500-F). [Treatment of leprosy by French sulfones (1358F and 1500F).] *Méd. trop.* **10** (1950) 850-857.

A statement on the sulfone treatment of leprosy in French Guiana from the beginning of 1950 with diaminodiphenyl sulfone and succinyl sulfone (1500F). The former can be administered in doses of 200 mgm. daily by mouth and intramuscularly. There is good tolerance of these products when precautions in their administration are taken. The value to the leprologist of having at his command a variety of products and of different ways of administering them is emphasized. —AUTHORS' ABSTRACT

- FLOCH, H. and DESTOMBES, P. Synergie de sulfones dans la lèpre (sulfone-mère et 1500-F). [Synergy of sulfones in leprosy (the parent sulfone and 1500F).] *Bull. Soc. Path. exot.* **44** (1951) 151-156.

Recognizing the difficulty of interpreting such experiments, especially in the clinic in a disease of such prolonged and capricious evolution as leprosy, the authors believe that the combination of DDS and 1500F is less toxic than would be equivalent doses of either drug alone. The combination permits giving the patient a larger dose of sulfones for a similar degree of toxicity. This is important for all patients treated by these products, for it is certain that they should be given the maximum non-toxic dose. There is too often a tendency to diminish the dosage, often to lower the cost of treatment, a problem which is practically non-existent with the low-priced parent sulfone. Attention should be given to the question of the drug resistance of the Hansen bacillus. The proposed combination is also of great interest in the treatment of patients presenting lepra reactions, with whom it is often necessary to remain below the threshold of reaction; this threshold may easily be raised by the

combination, and the patients can thus be submitted to a sulfone therapy with doses which are surely active. —AUTHORS' ABSTRACT

FLOCH, H. and DESTOMBES, P. Réaction léprotiques et traitements sulfonés. [Lepra reactions and sulfone treatments.] Bull. Soc. Path. exot. **43** (1950) 726-732.

In patients treated by various sulfones, de Souza Lima observed 50% of lepra reactions, Fernandez and Carboni 61%, and the authors 40%. In some of the cases the first reactions appeared only after the institution of sulfone treatment. Sometimes there exists a veritable threshold above which reactions are precipitated. The authors have observed many more reactions to the same doses of DDS or 1500F when given orally—47% for DDS, 44% for 1500F—than when given intramuscularly—8% for DDS, 7% for 1500F. It is consequently logical to think that the liver plays an important role in the pathogenesis of lepra reactions. To avoid them, the intramuscular route is recommended. When they occur, decrease the dosage and return to it gradually. When the oral route is used and the reactions multiply, one may remain below the reaction threshold (noting that these low doses are often active) and attempt from time to time to go beyond this threshold, or else change the route of administration. For the reactional lesions of the eye the intramuscular route is preferable, and better still the intravenous one (1500F). Interesting results are obtained in tuberculoid reactions with the aid of vitamin D<sub>2</sub> in high doses. These tuberculoid reactions are also susceptible to sulfone treatment.

—AUTHORS' ABSTRACT

SAENZ, B. Lepra reaction; its treatment with dihydrostreptomycin. A.M.A. Arch. Dermat. & Syph. **65** (1952) 59-69.

In this discussion of lepra reaction the author goes into detail regarding the clinical manifestations and other features, the interrelations of the reactional processes observed in the evolution of leprosy, and the treatment of the condition. The use of various drugs and other therapeutic methods are held to be based upon the following theoretic considerations: (1) counteraction of the possible untoward effects of previously administered drugs (e.g., chaulmoogra and the sulfones) as factors in the production of the reaction; (2) alleviation of the allergic status of the patient; (3) improvement of his general condition; (4) control of possible coexisting infections, specific or nonspecific; and (5) reactivation of the reticuloendothelial system. Previous experience in the treatment of leprosy with streptomycin and/or dihydrostreptomycin is reviewed. Since dihydrostreptomycin was found to enhance the therapeutic action of the sulfones, its use is deemed advisable in lepromatous patients not only in the treatment of lepra reaction but also during the rest period of sulfone therapy. Nine cases are reported in detail, and it is concluded that the experience in them indicates that the two most actively efficacious agents in leprosy are the sulfones and streptomycin, or its less toxic compound dihydrostreptomycin. During acute reactions, when sulfones have effected no improvement or have had to be discontinued, dihydrostreptomycin has proved to be an excellent therapeutic agent, the best one for that condition in use at this time. There is an excellent discussion of this paper by four leading dermatologists. —F. A. JOHANSEN

- 6 RIO-LEON, E. Tratamiento de la lepra por las sulfonas en el Dispensario PSLEC de Santa Clara. [Treatment of leprosy with sulfones in PSLEC Dispensary in Santa Clara.] *Rev. Sif. Lep. y Derm.* **7** (1951) 53-68.

The results obtained in 127 cases of leprosy—95 lepromatous, 12 tuberculoid, and 20 indeterminate—treated with promin and diasone are given. In all cases it was possible to reach the full dose of the drug (5 gm. with promin and 1 gm. with diasone) by gradual increase. The treatment periods varied between 6 months and 4 years. The most frequent side-effect was slight and easily controlled anemia (63%). Eruptions of the erythema nodosum type were observed in 29%, and lepra reaction in 20%, mostly in the first months of treatment. Only 6% presented crises of acute neuritis. Almost all of the patients (94%) were greatly ameliorated in their general health (appetite and weight increase), and the cutaneous lesions disappeared in 44% of them. Mucous lesions were favorably affected in 94%, and were completely healed in 29%. In 40% of the cases bacteriologically positive before treatment there was a diminution in the number of germs, but only 4.5% reached complete negativity.

—F. R. TIAN

- 6 O'BYRNE, A. Sulfones and pyridoxine in treatment of leprosy. *Heraldo Méd.* **9** (1951) 155.

In 1948 the author used pyridoxine to control vomiting of pregnancy in a leprosy woman. The treatment not only controlled vomiting but also greatly improved the cutaneous lesions, which had remained unchanged during daily treatment with glucosulfone sodium (promin). Good results with this combined therapy in 17 leprosy patients are reported. At the last examination bacilli could not be demonstrated in 6 of them. Pyridoxine was given intravenously either every morning or every other morning, in an average dose of 50 mgm. Glucosulfone sodium was given intravenously in the afternoon on the same day, beginning with 1 gm. and increasing progressively to 5 gm. per day. Two patients showed, initially, symptoms of gastric intolerance after administration of sulfoxone sodium (diasone). The author suggests that this combined treatment should be given further trial to determine its actual therapeutic value, and to find out whether pyridoxine has definite effects on sulfones as a coadjuvant of these substances or whether it acts as a catalyzer of sulfur, with action similar to that of vitamin D on the metabolism of calcium.—[From *J. American Med. Assoc.* **147** (1951) 1296 (Foreign Letters, Colombia), supplied by F. A. Johansen.]

- 6 WADDINGTON, E. Leprosy under treatment with diaminodiphenyl sulphone (two cases). *Proc. Roy. Soc. Med., Sect. Derm.* **44** (1951) 681-682.

Points of some interest in these two case reports concern type diagnosis and an apparent lack of even inhibitory effect of PAS. The first patient, diagnosed as lepromatous, had noticed anesthesia on the lower third of the left leg four years before, and later developed an indolent ulcer on the anterior aspect of the ankle and a scaly pigmented area on the medial side. Slit smears were negative, but bacilli with little inflammatory reaction were found in a portion of the saphenous nerve. The lepromin reaction was negative. A reaction occurred six months after the

sulfone treatment was begun, the pigmented scaly lesion becoming shiny, erythematous, infiltrated and succulent, "of the lepromatous type," and during the next month the "leproma" spread in a broad band up the lateral side of the calf. Biopsy showed heavy infiltration with large foamy and sometimes necrotic histiocytes and other cells, and a "small number of bacilli." The lesions subsided under continued treatment. In the other case, diagnosed as tuberculoid and reactive to lepromin, new leprids continued to develop during the first three months of treatment, when PAS (18 gm. daily) was used, but slowly subsided after change to the sulfone.

—H. W. W.

LAUGHLIN, E. M. Physical therapy in the National Leprosarium. *Phys. Ther. Rev.* **32** (1952) 3-11.

This article was written primarily for the benefit of physical therapists who might be called upon to treat leprosy in endemic areas since all states do not have segregation laws. It is based on two years' experience at Carville, and deals chiefly with treatment of neurological symptoms as paralysis, anesthesia, neuritis and contractures of the hands and/or feet. Every new patient gets a muscle test of the hands and feet, and when weakness is found an electrical test is given. Electrical stimulation employing galvanic or sinusoidal currents was used to treat 32 patients. Of these, 5 were early cases, 2 of which improved considerably under galvanic treatment. The other 27 patients, who had had neurological symptoms for from 1 to several years, required very high milliamperage. Improvement was obtained in only 2 of them; in 17, no change in muscle power was noted; 11 showed slight improvement, while in 2 the paralysis progressed. The majority of the patients were treated for from 3 to 10 months, the longest 18 months. The various types of hand surgery are described with follow-up of physical and occupational therapy, illustrated by several photographs; there are case histories and follow-up records of 4 cases. The usual treatments given the hands are some form of heat such as infra-red, diathermy, whirlpool, paraffin baths, or galvanic baths. Heat is followed by electrical muscle stimulation and muscle reeducation.

—F. A. JOHANSEN

CONTRERAS, F., GUILLEN, J. and TORRELLA, E. Microinjertos cutáneos en úlceras tórpidas posthansenianas. [Cutaneous micrografts of torpid postleprosy ulcers.] *Actas Dermo-Sif.* **42** (1951) 812-814.

At the beginning of this study, in 1943, 163 of 260 patients at Fontilles had specific ulcers, and in 156 of them bacilli were readily found. None were found in the other 7 patients, they being among those who had tolerated massive doses of chaulmoogra oil, which at that time was employed in treatment. After three years of continuation of the same treatment its activity had been confirmed because, although the number of patients had increased to 266, those with ulcers had dropped to 127 and most of them were in regression. The population of Fontilles continued to increase, to over 300, but with the use of the sulfone drugs all kinds of manifestations had improved, and in 1950 only 92 of the patients had ulcers of the legs. Summarizing these excellent results, the percentages of the patients with such ulcers were: 62.6 in 1943, 43.1 in 1946, and 30.4 in 1950. In some of the patients whose ulcers had decreased notably in size and were of good appearance and negative for bacilli, and whose other specific manifesta-

tions had regressed and disappeared, it was decided to make a detailed study of the associated microbial flora, so as to treat them accordingly. When this did not exist, and the ulcers were considered to be due to ecstasis, they proceeded to perform micrografts. In some cases they obtained cicatrization of torpid ulcers of many years duration.

—AUTHORS' ABSTRACT

2 MOMOSE, T. Pharmaceutical chemistry of sulfone drugs. *La Lepro* 20 (1951) 6-11 (in Japanese); English abstract, p. 6.

After speaking of the molecular configuration of the sulfa drugs with relation to their action, it is stated that the mechanism of 4,4'-diaminodiphenyl sulfone and of promizole has been thought to be the same as that of the ordinary sulfa drugs. Promin, diasone and sulphetrone, which are in actual use, dissociate to 4,4'-diaminodiphenyl sulfone partly inside the body after treatment and act effectively against bacteria; hence it is logical to use that substance, as Lowe has done. The last sentence, verbatim: Here, I introduced newly synthesized sulfones and ether-type compounds which had a growth inhibiting action against antiacidophilic bacteria.—[From abstract.]

6 LEVER, W. F., SCHULTZ, W. L. and HURLEY, N. A. Plasma proteins in various diseases of the skin. *Arch. Derm. & Syph.* 63 (1951) 702-728.

This is a thorough study of the various protein fractions as they occur in a number of diseases of the skin, with a good review of the methods and results obtained by other workers. The study was of protein changes as they occur in inflammatory diseases, pemphigus, allergic diseases, collagen diseases, infectious diseases, metabolic diseases and tumors. Electrophoretic analysis was used in the study. Although the authors made no such analyses in cases of leprosy, they recall that Seibert and Nelson had done so on three patients with advanced leprosy, in which the total proteins averaged 7.93 gm. per ml.; the albumin showed a moderate decrease to 43.2%, while the alpha and gamma globulins were markedly increased to more than twice their normal values. Data obtained by fractionation methods by Frazier and Wu, Cerutti, Midana, and Faget and Ross are given. The abnormalities observed in the electrophoretic patterns of patients with various diseases are held to reflect their reactions to their disease. Since patients affected by the same disease tend to react similarly, there is considerable consistency in the electrophoretic pattern among them, but it cannot be said that that pattern is diagnostic in any cutaneous disease since similar changes occur in unrelated diseases. The various changes in the electrophoretic pattern tend to be proportional to the severity of the disease and therefore may be slight, or even absent, in mild cases of a given disease. In some diseases the pattern varies with the stage or the duration of the disease. It is a basic rule that in acute inflammatory diseases there occur decrease in albumin and increase in the alpha globulins, whereas in chronic granulomatous or fibrotic diseases an increase in the gamma globulin is observed. The authors feel that electrophoretic patterns in cutaneous diseases are of no diagnostic value, but contribute to the understanding of the effect that a given disease has on the patient.

—F. A. JOHANSEN

KHANOLKAR, V. R. Studies in the histology of early lesions in leprosy. Indian Council of Medical Research, Special Report Series No. 19, 1951, 18 pp., 2 text-figs. and 30 figs., 17 in color. Price Rs. 2/8/-.

This well-illustrated report is chiefly a histological study of biopsy materials from contacts, "pre-leproma" patients, and early lesions of the neural and lepromatous types. Various fixatives and stains were used, including silver for nerve fibers and the [so-called] Fite-Faraco modification of the Ziehl-Neelsen stain for bacilli. Of 109 contacts, 42 with positive lepromin reactions were found bacteriologically positive. [See Figueredo and Desai, *THE JOURNAL* 18 (1950) 59 and 19 (1951) 165.] Biopsies were made of 17 such cases, and in all which were examined systematically it was possible to demonstrate the presence of stray acid-fast microorganisms, 5 to 10 in number, morphologically characteristic of leprosy bacilli. One or two were occasionally inside fixed macrophages which also contained acid-fast particles. Being found in the vicinity of small blood capillaries, they were assumed to be adventitial cells in the process of digesting phagocytized acid-fast bacilli, and the author calls them "fuchsinophils" and considers this stage as the silent phase of the disease. Thirty biopsies were of early "simple macules," which showed two types of changes in the dermis: (1) Most commonly, there were foci composed mainly of histiocytes, lymphocytes and a few epithelioid cells; stray microorganisms were frequently seen in the remnants of nerve fibers and in the cellular exudate invading and investing the nerves. (2) Less often, whorl-like accumulations of lymphocytes enveloped twigs of small, normal-looking nerves, without any other change; it was almost always possible to demonstrate acid-fast bacilli in the nerve fibers. The former condition is regarded as the early stage of tuberculoid lesions, the latter that of lepromatous lesions. In slightly more advanced simple macular lesions, fragmented nerve fibers were demonstrated in commencing tuberculoid cellular exudate. Seven biopsies were of "pre-lepromatous" macules. Bacilli were demonstrated only in the nerves and often in the finest nerve twigs, none in the perineural tissues or the adjoining subcutaneous tissue. They were seen to lie in the axonal space, following closely the contours of the nerve fibers, thus presenting the appearance of fish migrating up stream. Occasional clusters were seen irregularly grouped in the cytoplasm of Schwann's cells, and it was sometimes possible to demonstrate blisters or saccules in the perineural sheath, with bacilli breaking through. [For an abstractor's comment on these points, see below.] Early lesions of tuberculoid type (minor leprids) presented branching granulomatous cords extending from the finest nerve twigs in the papillary layer to the superficial subcutaneous tissue. In early lepromatous lesions, a hyaline appearance of the endoneural tissue, saccular or fusiform swelling of nerve fibers, as well as an exudate of mononuclear cells around slightly altered or unaltered nerve fibers, were observed. Large numbers of bacilli were seen in the nerve fibers. The clear subepidermal zone which is characteristic of the lepromatous type is ascribed to the occurrence of cellular exudate only in the reticular part of the dermis, as a result of discharge of bacilli from the perineural fusiform or saccular swellings. The author's chief contention is that bacilli may enter through unbroken skin, healthy or slightly altered, and find their way anywhere under the epidermis through the intercommunicating superficial lymphatic network,

after which they seek out the fine nerve twigs in the superficial dermis. In travelling from the initial place of entrance along the superficial plexus it is the nerves and not the lymphatics which form their path, they being attracted especially towards the nerves in that plexus which, because of injury, are constantly degenerating and regenerating, which is probably very marked in children thus explaining their susceptibility to infection. It is in these nerves that the original foci lie, the histiocytes gathering around and forming the epithelioid or Virchow cells according as the patient's resistance is strong or weak. Another outcome of the hypothesis that bacilli live, travel and multiply inside or along nerve fibers is that in therapy "the therapeutic agent or its products must reach the axonal substance so as to be able to exert their influence on the bacilli." [From an abstract supplied by N. Mukherjee, supplemented from one in *Trop. Dis. Bull.* **49** (1952) 56. In the latter the abstractor (E. Muir) comments, at the point indicated above, "The illustrations of these two last statements, though well executed, are not at all persuasive that the bacilli are actually inside the axis-cylinders. The idea of lepra bacilli actually travelling up inside axis-cylinders is a very revolutionary one, more like a small snake swallowing a large frog than fish swimming up a stream, and would need considerably clearer evidence than is given in this paper before it could be accepted."]

7 [KHANOLKAR, V. R.] Method of taking biopsy tissue for histological examination. *Lep. Rev.* **22** (1951) 83-85 (editorial matter).

This method was devised to avoid distorting or otherwise damaging leprosy skin material. After sterilizing and anesthetizing the skin a piece of thread is "passed a little beyond the upper end of the area selected for biopsy." With a very sharp knife the cuts are made down to the subcutaneous tissue so as to include fat. The elliptical piece of skin and subcutaneous tissue, 1.5 by 0.5 cm., is then freed by cutting parallel to the surface of the skin, while one end is raised by pulling on the suture. After cleaning with blotting paper, fixation in Zenker's fluid, and washing in running water the tissue is placed in 40% rectified spirit and may be sent to a pathological laboratory for examination. This description is given with much more detail in order that specimens from Africa and elsewhere may be sent to the medical secretary of the British Empire Leprosy Relief Association who will have the material sectioned and send detailed reports. A description is also given of the [so-called] Fite-Faraco method of staining *M. leprae*, which technique "enables bacilli to be detected even when they are only to be found in the small subcutaneous nerves of the corium."—[From abstract in *Trop. Dis. Bull.* **49** (1952) 155.]

7 KIKKAWA, H. Biochemical genetics of human beings. *La Lepro* **20** (1951) 1-5 (in Japanese); English abstract, p. 1.

In this discussion of the role of genes in various disease conditions certain questions of the day, including leprosy, have been discussed from the viewpoint of biochemical genetics.—[From abstract.]

6 SAIKAWA, K. The histo-pathological studies on the peripheral nerves in the various clinical phases of leprosy. *La Lepro* **20** (1951) 12-15 (in Japanese); English abstract, p. 12.

The following observations were made on three cases of acute relapse which occurred in the course of neural leprosy. Histologically, the erythema corresponded with tuberculoid leprosy. Examination of peripheral nerves revealed the same changes as in the so-called "macula tuberculoides" of tuberculoid leprosy. The clinical symptoms were like those of bulbar palsy. In the course of the acute relapse the Mitsuda reaction became more strongly positive. As the cause of the acute relapse, it is thought that lepra bacilli which have been latent in the peripheral nerves are poured into the circulation and cause the manifestations seen in the skin and nerves.—[From abstract.]

TORRELLA, E. Lepromin visceral procedente de capsula suprarenal. [Visceral lepromin from the adrenal capsule.] *Actas Dermo-Sif.* **42** (1951) 847-851.

Great numbers of bacilli are harbored in the cortical portion of the suprarenal glands of advanced lepromatous cases, due to the special predilection shown by the reticuloendothelial elements. Selecting those which were rich in germs two lepromins are prepared, one integral according to the Mitsuda-Hayashi technique, the other bacillary according to that of Fernandez and Olmos. Clinical observations and histological examinations of the reactions obtained with these lepromins were made after 48 hours and 21 days. It is concluded that visceral lepromin made of the suprarenal capsule behaves similarly to that made of cutaneous lepromas. Although it has a lesser capacity to induce the early or Fernandez reaction, it is identical with respect to the late or Mitsuda reaction. From the practical point of view the larger visceral organs, such as the liver and the spleen, are considered preferable, or the lymph nodes if these can be collected in quantity. —FELIX CONTRERAS

ZUBIRI, A. and MAR, R. <sup>Jedal</sup> Las reacciones con tuberculina (Mantoux) y <sup>monis</sup> lepromina (Fernández y Mitsuda) en sujetos de zona exenta de lepra. [The tuberculin (Mantoux) and the lepromin (Fernández and Mitsuda) reactions in persons in a leprosy-free area.] *Actas Dermo-Sif.* **42** (1951) 872-882.

Zaragoza province is considered not endemic for leprosy, since the 2 known cases there originated elsewhere. For this reason it was deemed a suitable place to follow the recommendation of the Second Pan-American Conference that the indices of lepromin positivity be studied in healthy individuals in nonendemic areas. The lepromin used was prepared at Fontilles by the usual method, and the tuberculin by the IBYS according to the procedure of Koch; also, the usual dilutions and methods were employed. The Fernandez and Mitsuda reactions were frequently positive, 42.6 and 57.3%, respectively. The Fernandez reaction was always observed when that to tuberculin was positive. If only the 1:10,000 tuberculin dilution is considered, the concordance between the two reactions was 72%. This figure reached 100% in cases with active skin tuberculosis. The concordance between the Fernandez and Mitsuda reactions was 78%. That between the tuberculin and the Mitsuda reactions was 70%. It is concluded that there exists a certain relation between the Fernandez and tuberculin reactions which may represent an allergy of the individual to the genus *Mycobacterium*, common to both the leprosy and tuberculosis species.

—FELIX CONTRERAS



DAUDÉN VALLS, F., MORA COMAS, J. and DAUDÉN SALA, C. Influencia de la BCG y otras vacunas en la leprominorreacción. [The influence of BCG and other vaccines on the lepromin reaction.] *Actas Dermosif.* **42** (1951) 505-523.

After reviewing the literature concerning the lepromin reaction in healthy persons, the authors report observations involving 56 children of leprous parents at the Chapineria preventorium, 26 boys and 30 girls, aged from 1½ to 15 years. In all but 3 instances the affected parents were lepromatous; the others were tuberculoid. The children had experienced the contact nearly all of their lives; 91% had used the same bedrooms, and 86% the same beds. On admission they had all been tested with tuberculin and lepromin and examined by x-rays. The dosage of tuberculin (OT) was 1:1,000, and then 1:100 and 1:10 when the previous reactions were negative. The lepromin was of the integral (visceral) kind prepared at Fontilles, and usually two lots were used, made from livers and from lymph nodes; the latter gave the stronger reactions. The negatives were also tested with a bacillary lepromin supplied by Basombrio, the results with which were similar to those obtained with the lymph-node preparation. The 15 children who were negative to tuberculin and on x-ray examination (6 of whom were already lepromin positive), were vaccinated with BCG by the scarification method. Subsequently two of them, and all of the others, were also given other vaccinations against preventable diseases (smallpox, typhoid-paratyphoid fever, diphtheria and tetanus). Comparing the evidences of tuberculous infection in these children and those in school children of nonleprous communities, it was concluded that infection with tuberculosis and consequently tuberculin positivity occurred in the same proportion in both groups. As for the effect of the BCG vaccination on the 15 tuberculin-negative children, all became tuberculin positive. Of the 9 who had been negative to lepromin, only 4 (44%) became positive; the two who received the other vaccines had been and remained negative. (Of the 6 who had been positive, 4 reacted more weakly after the vaccination than before, and none more strongly.) Of the 41 who had received only the other vaccines (3 of whom had been tuberculin negative, 2 remaining so on the final test), 18 had been originally negative and 23 positive to lepromin. Of the 18 negatives, 12 (67%) had become positive, all but 1 of them 1+; of the 23 positives, 4 reacted more strongly, 12 in the same degree, and 7 less strongly than before (one of them changing from 1+ to negative). It is concluded that the various preventive vaccinations used, without BCG, caused a larger proportion of positive results than did BCG (67% vs 44% in original negatives). It is therefore advised that vaccination of such children with all of these vaccines be continued, but without neglecting BCG when it can also be used, for the prevention of the various diseases concerned and at the same time to enhance the condition of resistance against the Hansen bacillus.

—FELIX CONTRERAS

[The conclusion that the other vaccines by themselves induced lepromin positivity is of interest, and the indication that they did so to a greater degree than BCG is of further interest. It would seem to follow that the underlying condition responsible for the tuberculin positivity had a greater effect, in the presence of the multiple vaccinations, in inducing lepromin positivity than did BCG in the absence of the supposed tuber-

culosis infection. Since one individual of the group receiving the other vaccines had been (and, incidentally, remained) tuberculin negative, that one has to be eliminated to evaluate the apparent effect of the original tuberculin positivity, which leaves 11 of 17 individuals, or 65%. The difference between 44% of 9, and 65% of 17, is not statistically significant. Nevertheless, this line of investigation would seem to merit further exploration.—EDITOR]

ARONSON, J. D. and MCGETTIGAN, M. The tuberculin reaction in relation to the local reaction to BCG vaccine in initially vaccinated and in previously vaccinated persons. *J. Immunology* **66** (1951) 715-724.

The local reaction to the simultaneous but separate intracutaneous injection of 0.1 mgm. of OT and 0.1 mgm. of BCG vaccine was studied 48 hours after injection in a total of 3,510 unvaccinated persons, and in 99 persons vaccinated one year previously with BCG vaccine. Among those not previously vaccinated and negative to tuberculin, only a small percentage showed a Koch phenomenon. A high percentage of those previously vaccinated and who gave a doubtful or positive reaction to 0.1 mgm. tuberculin showed a Koch phenomenon. Of the 99 vaccinated persons, who gave slightly positive, doubtful or negative reactions to 0.1 mgm. OT, a higher percentage showed an exaggerated or accelerated reaction to the BCG vaccine after revaccination than was noted among those not previously vaccinated. A higher percentage of previously vaccinated persons reacted to reinoculation of BCG vaccine than to 1.0 mgm. OT. The intracutaneous injection of BCG vaccine is suggested as a test in apparent instances of anergy in suspected tuberculous infection. Such a test could be used to determine the occurrence of hypersensitivity to the bacillary bodies in the absence of appreciable tuberculin hypersensitivity. No untoward reactions have been observed with this procedure.—[From the authors' summary, supplied by J. H. Hanks.]

DELACHAUX, A. and BERGIER, D. Cuti-réactions au B.C.G. [Skin reactions to BCG.] *Schweizerische Zeitschr. Tuberk.* **7** (1950) 54-62.

BCG applied intradermally in a small dose (1/20th of the dose used for vaccination) presents great interest as a skin test in tuberculous allergy. The skin reaction with BCG controls the allergy derived from the bacterial bodies and not from tuberculin. This difference in mode of action makes it possible thus to supplement the results of the tuberculin test. This reaction is often more sensitive than the Mantoux reaction and finds its full value in detecting latent allergies (infra-tuberculin allergy). It does not cause general reactions. —J. H. HANKS

DE SOUZA-ARAÚJO, H. C. and GOMES DE SA, J. Ensaio sobre lepra experimental. Inoculações de três amostras de bacilos ácido-álcool resistentes (amostras "Chaves II," "Emilia" e "Hecke") isoladas de leprosos, em trinta doentes da Colonia Mirueira. [Trials in experimental leprosy. Inoculations of three strains of acid-fast bacilli ("Chaves II," "Emilia" and "Hecke") isolated from leprosy patients into 30 inmates of the Colonia Mirueira.] *Mem. Inst. Oswaldo Cruz* **49** (1951) 659-668.

With the aim of producing the Koch phenomenon, the authors inoculated 30 inmates of the Colonia Mirueira in Recife, of various ages and

clinical types, with live suspensions of three strains of acid-fast bacilli isolated from leprosy patients. Each volunteer received three intradermal inoculations in the thighs, of 0.2 cc. each of strains "Chaves II," "Emilia" and "Hecke," and on the left forearm 0.2 cc. of Souza-Araujo's leprolin (killed antigen). On the 10th day after the inoculations it was found that 24 of the 30 had severe general reactions, and 2 had moderate ones; 16 had lepra reaction, of whom 10 were lepromatous cases and 6 inactive ones. Craters 1 to 2 cm. in diameter, with complete destruction of the skin, had been produced in all 30 by inoculum "C II," and in 29 by "E"; the inoculum "H" did so only in 23, the lesions of minor severity; and the "L" produced craters in 10 patients, evidently due to the concomitant action of the other inocula. Material from 7 patients was cultured on Loewenstein medium, and retrocultures were obtained. From one patient a chromogenic culture, indistinguishable from strain "C II" or "E" was recovered from the leprolin test. On the 18th day after inoculation smears were made from lesions of 13 patients, and 50% of them were positive for one or another of the inocula. The macro- and microscopical morphologies of the recovered cultures coincide with the characteristics of the original cultures from which the inocula were made. In conclusion, the majority of the patients showed partial or complete Koch phenomena, with the classical general, local and focal reactions. Because of lack of laboratory resources at the colony, there are omissions of various kinds in this study.—[From authors' summary.]

- 6 BORZONE, R. A. Método de diferenciación inmunológica y estructural de cicatrices tegumentarias en leprosos blanqueados. [Immunological and structural differentiation of cutaneous cicatrices in recovered patients.] *Semana Méd.* **99** (1951) 1006.

An antigen which the author calls "Dharmendra-Borzone protein," the technique of whose preparation is not described in the report, gives a "positive" reaction in 48 hours in patients with "cicatrices" resulting from clearing up of leprosy lesions under sulfone treatment and "negative" reaction in the case of cicatrices of other origin —G. BASOMBRI

- 6 TRESPALACIOS, F. and GARCIA-OTERO, A. Las reacciones serológicas lueticas en el suero de leprosos. [Serologic reactions for syphilis in the serum of leprosy patients.] *Bol. Soc. cubana Dermat. y Sif.* **8** (1951) 19-29.

The authors have studied the serologic reactions with the Kahn standard, Mazzini, cardiolipin and Meinicke MKR II tests in the sera of 355 cases, 312 lepromatous, 41 tuberculoid and 2 indeterminate. The Kahn, Mazzini and cardiolipin tests were positive in 50% of the patients, the Meinicke only in 15% of them. The percentage of positivity varies widely according to the type of leprosy; it is twice as high in lepromatous leprosy as in the tuberculoid form with the Kahn, Mazzini and cardiolipin tests, but only slightly higher with the Meinicke antigen (15.1% vs. 12.2%). The cardiolipin antigen does not seem to be of any help in the solution of the problem of false positive serologic tests in leprosy.

—F. R. TIAN

- 6 WHEATE, H. A note on the morphological changes in the *Mycobacterium leprae* under sulphone therapy. *Lep. Rev.* **22** (1951) 79-80.

Apart from the changes noted by other workers the writer draws attention to two further changes. After 6-9 months of treatment tightly packed masses of bacilli tend to break down and show irregular staining. Single bacilli showing bipolar staining and granularity are scattered throughout the fields in large numbers, as if they had broken out of the globi. There was also an apparent increase in the number of intracellular bacilli, possibly due to increased ingestion by macrophages.

—G. O. TEICHMANN

MARIE-SUZANNE (SOEUR), SOHIER, R. and NOEL, R. Etude comparative d'un bacille acido-résistant isolé par culture d'un lépreux humain et du bacille de Hansen. [A comparative study of an acid-fast bacillus isolated by culture from a human leproma and of the Hansen bacillus.] Ann. Inst. Pasteur **81** (1951) 238-241.

A leproma rich in bacilli from a little-treated case was ground and placed in saline and kept at room temperature. Six months later, smears of the emulsion revealed acid-fast bacilli. An inoculation in Sauton medium produced a culture with film that could be subcultured. This culture consisted of acid-fast bacilli, almost always grouped in masses. The germ could be recovered from *Galleria mellonella* up to 60 days after inoculation. Inoculations in guinea-pigs produced no lesions, and in the rat it provoked lesions identical with those caused by the inoculation of Hansen's bacilli from human lesions. An antigen was prepared by the Mitsuda method from a culture of this bacillus on Petragnani medium. Its injection provoked strong positive reactions in all leprosy cases, lepromatous or tuberculoid. The nodule provoked by the injection in a lepromatous patient was removed and used to prepare a new antigen. The intradermal reactions with this antigen were negative in 10 lepromatous cases and weakly positive in three tuberculoid ones (duration of the reactions, 4 to 5 days). The authors believe that in some of its characteristics this germ resembles the Hansen bacillus.

—R. CHAUSSINAND

DE ANDRADE, L. Contribuição ao estudo das micobactérias. Fluoromicroscopia e reação citoquímica de Dubos. [Contribution to the study of the mycobacteria. Fluoromicroscopy and the cytochemical reaction of Dubos.] Mem. Inst. Oswaldo Cruz **49** (1951) 7-32.

The author applied the fluorescence and Dubos tests to 123 cultures of mycobacteria. Both were positive in 58 (47.1%), 30 being *M. tuberculosis* and 28 related to leprosy. Of the latter, 6 had been isolated from human leprosy, 2 from rat leprosy, 10 from hematophagi experimentally infected on leprosy patients, 6 from the cesspools of leprosy colonies, and 4 from dust of the domiciles of patients. The results were F+ and D— with 47 cultures, 19 of which had been isolated from leprosy lesions. The remaining 18 cultures were negative to both tests. All of 17 strains of acid-fast bacilli isolated by Souza-Araujo from sputa of leprosy patients at Curupaity gave both reactions as strong (2+) as *M. tuberculosis hominis* (Ratti strain), and the author included these cultures among those classified as of that kind. The leprosy strains "José," "Hecke," "Chaves" and "Emilia" isolated by Souza-Araujo from skin lesions gave F 2+ and Dubos—, but these cultures being highly chromogenic the results are considered as doubtful. Details are given of the many other cultures studied,

they too numerous and the results too varied to be summarized briefly. The Dubos reaction was never positive in cultures negative to fluorescence. Because it was positive in 30% of the cultures not belonging to the group of *M. tuberculosis*, it is concluded that that reaction is not specific for virulent tubercle bacilli. Of the 123 cultures tested, 14% were not fluorescent, and some showed only fluorescent granules (F+) not bacilli.

—H. C. DE SOUZA-ARAÚJO

SATO, S. Animal experiment of leprosy in the fowls. (Progress Report.) Two instances of successful transplantations test. Rep. Res. Inst. Tuberc. & Lep. Tohoku Univ. 3 (1951) 1-11 (in English).

The author has previously reported results obtained in fowls which had been repeatedly inoculated in the chest muscles with leproma emulsions. Besides the changes in the injected parts, many granulomatous lesions, greyish-white or brownish, of various shapes and sizes, appeared on the surfaces of the viscera, especially the peri- and epicardium, and on the liver, spleen, mesentery, and rarely the lungs and kidneys. Some of the fowls died with more massive lesions. In one cock there were even two skin nodules in the cheeks and a macule on the neck. Such positive results occurred in 40-60% of the inoculated fowls. At that time, passage experiments with those lesions were not fully successful. The present report is of two series of successful passage tests, confirmed after 7 years observation. (1) Fowl No. 164: So inoculated 7 times between Dec. 20, 1943 and Nov. 16, 1945, it died on Dec. 16, 1946. Tumor-like leprosy granulomas were found in the capsules of the heart, liver, spleen, kidneys, etc. Some of these lesions, together with granulomatous tissue from the chest muscles were emulsified and injected into the chest muscles of 3 chickens (Nos. 2164-2166). No. 2164 died on Aug. 30, 1949, showing many miliary leprosy nodules on the surface of the heart, liver, spleen and kidneys, but with very slight changes in the chest muscles. Pieces of liver, spleen, kidney and chest muscles were emulsified and injected into the chest muscles of 3 chickens (Nos. 3164-3166). No. 3164 was killed on Oct. 4, 1950. The chest muscles showed almost no changes and no bacilli. The heart showed spotted greyish-white granulomas in the epicardium and the apex. There were brownish-grey lesions in the capsule of the liver, especially marked along the margins inferiorly and laterally, fringing the lobes with slender bands of granulomas. Numerous bacilli with globi were found in smears. Histologically these granulomas consisted of epithelioid cells and histiocytes walled by round cells, with or without central necrosis. (2) Fowl No. 115: Inoculated in the chest muscles with emulsified lepromas 18 times between Feb. 19, 1943 and April 21, 1948, it died on May 16, 1948. More than 10 greyish-white nodules, one-half the size of rice corn grain, were found in the liver capsule; bacilli 3+. Some of these nodules and a bit of the granuloma produced in the chest muscles were emulsified and injected into the chest muscles of 2 chickens (Nos. 2115-2116). No. 2115 died on July 17, 1950. A brownish-grey nodule of rice corn grain size was found in both the pericardium and the apex, a few bacilli were found; many similar miliary nodules also on the surface of the liver, with numerous bacilli and globi; almost no noticeable lesions in the injected parts. In summary, serial subtransplantation of the leprosy lesions produced in the viscera of fowls which were inoculated with leproma emulsions in the

chest muscles seems very likely to have succeeded. The formation of granulomatous neoplasms in the serous capsules of the viscera, especially the peri- and epicardium and the liver capsule, were the characteristics of the lesions produced in every generation. These lesions were all due to the far-reaching effects of the inoculations in the chest muscles, and not to mere mechanical transfer. The histological structure of the lesions, however, were not identical with that of the human leproma, but were chronic granulomas rather suggestive of the tuberculoid state.—[From an author's abstract supplied by K. Kitamura.]

- 6 LEVADITI, C., VAISMAN, A., CHAIGNEAU, H. and BARRAT, L. Virulence du bacille de Stéfansky pour la souris. [Virulence of the Stefansky bacilli for the mouse.] *Compt. rend. Soc. Biol.* **144** (1950) 476-477.

The authors have shown, following Marchoux, Chorine and Koechlin, that the Stefansky bacillus from rat lepromas, after transcranial inoculation in rats and mice, gives rise not only to lesions of the encephalon but also to generalization of the infection in the lungs, spleen and liver. These studies have been carried out using as inoculation material, not the lepromas, but the brain of a rat sacrificed 288 days after having received an intracerebral injection of a leproma suspension. The mortality in mice thus inoculated was 80% in 166 days, whereas it was nil in animals inoculated with a leproma suspension. Moreover, the encephalic lesions are more marked, very rich in bacilli, and the dissemination to the lungs, spleen and liver is more significant. The authors conclude that there is an adaptation of the Stefansky bacillus to the nerve tissue, with the appearance of a certain neurotropic affinity, and also a marked dispersive power in the organism.

—R. CHAUSSINAND

- 6 LEVADITI, C. and CHAIGNEAU-ERHARD. Action anti-microbienne de la streptomycine, de l'acide para-amino-salicylique et de la diamino-diphénylsulfone chez les souris contaminées par le bacille de Stéfansky. [Antibacterial action of streptomycin, PAS and DDS in mice infected with the Stefansky bacillus.] *Compt. rend. Soc. Biol.* **145** (1951) 328-330.

The authors have inoculated mice by the intracerebral route with an emulsion of Stefansky bacilli according to a previously described technique. The mice were divided in 4 groups: (1) control, untreated; (2) treated with streptomycin (1,000 units per day); (3) treated with PAS (20 mgm. per day); and (4) treated with DDS (2 mgm. per day); all drugs given subcutaneously. Within 76 days there was a 16% mortality in the PAS group, and 23% in those receiving DDS, the deaths attributed to the toxicity of the drugs. The surviving animals of the 4 lots were sacrificed on the 77th day. The efficacy of the drugs was judged by the degree of the changes in the meninges and the bacillary findings. It is concluded that DDS is the most active product. Streptomycin follows next, then PAS, which was clearly the least active.

—R. CHAUSSINAND

- 6 YANAI, S. Experimental studies on chemotherapy of leprosy. I. Effects of reducing and oxidizing agents on rat leprosy. *La Lepro* **20** (1951) 16-19 (in Japanese); English abstract, p. 16.

Sodium thiosulfate, a reducing agent, produces a favorable effect upon the lepromas in an inoculated part. With respect to the distribution of

leprosy bacilli in the body, however, there is no great difference between the treated and control animals. Potassium permanganate, an oxidizing agent, makes the leproma markedly worse, and rat leprosy bacilli are found in greater numbers in this case than in the control.—[From abstract.]

- YANAI, S. Experimental studies on chemotherapy of leprosy. II. Effects of several other chemical substances upon rat leprosy. *La Lepro* **20** (1951) 20-23 (in Japanese); English abstract, p. 20.

Sharlach R, thiocol and seraniol make the symptoms of rat leprosy worse. Sephalantin has a tendency to make rat leprosy slightly worse. Citroneral acts somewhat favorably upon rat leprosy.—[From abstract.]

#### ISONICOTINIC ACID HYDRAZINES IN TUBERCULOSIS

- GRUNBERG, E. and SCHNITZER, R. J. Studies on the activity of hydrazine derivatives of isonicotinic acid in experimental tuberculosis of mice. *Quart. Bull. Sea View Hosp.* **13** (1952) Special Issue, pp. 3-11.

The authors (of the Hoffmann-La Roche Chemotherapy Laboratories) describe the antituberculosis activity of two hydrazine derivatives of isonicotinic acid, the hydrazide (known as Rimifon) and the isopropyl derivative (Marsilid). These compounds, with the desired property of lasting damage to the tubercle bacilli, have been found in close connection with earlier studies on the thiosemicarbazone of isonicotinic acid hydrazide synthesized in the Roche Chemical Research Laboratories. The work here reported was with experimental tuberculosis in mice infected, either intravenously or intranasally, with the H37Rv strain of the tubercle bacillus. The new drugs appeared quantitatively to be considerably more effective than streptomycin or Tibione and related substances, and particularly PAS and niacinamide. The 50% protective dose ( $PD_{50}$ ) was found to be 4.6 mgm/kgm for Rimifon and 7.5 mgm/kgm for Marsilid in the intravenous infection, 6.2 and 10.7 mgm/kgm in the intranasal infection. After dosages of 10 and 25 mgm/kgm, respectively, no viable tubercle bacilli were recovered from the majority of animals immediately after a 21-day treatment period by the cultural method employed, an effect which cannot be expected from merely tuberculostatic agents. The bactericidal effects seem to be specific, since these compounds were not effective against other bacterial infections tested *in vivo*. The same effects were observed whether the treatment consisted of continuous medication in the diet, or single daily gavage, or single daily subcutaneous injection. The hydrazide appeared to be the more potent; the isopropyl derivative was much less toxic for mice. The chemical formulas of the two compounds are given [see editorial in this issue]. There are four tables giving details of the effects of these drugs on the pathology and cultures, and the influence of the route of infection and the treatment given. The authors believe that these compounds appear to be the first antituberculosis chemotherapeutic agents which produce demonstrable damage to the viable tubercle bacilli in mouse experiments. This observation encouraged the clinical investigation of the two compounds.

—F. A. JOHANSEN

- ZIEPER, I. and LEWIS, R. A. Tuberculosis in a *Macacus rhesus* treated with isonicotinyldiazine. *Quart. Bull. Sea View Hosp.* **13** (1952), Special Issue, pp. 12-16.

In the course of a study of the effects of the isonicotinyldiazines in normal monkeys the authors (of the Aeromedical Research Unit, Yale University School of Medicine, and the Department of Clinical Research of Hoffmann-La Roche, respectively), had an opportunity to treat one, the subject of a delicate and prolonged experiment, which had developed tuberculosis spontaneously, and thus to bridge the gap between studies in small animals and clinical applications. After employing isonicotinyldiazine for 3 weeks at 10 mgm. daily and the glucosyldiazine for a further 8 weeks, 100 mgm. daily, the disease appeared clinically to be arrested and the animal recovered appetite and gained weight, and experiment was completed. The animal was then sacrificed, and the gross and microscopic findings of the postmortem examination confirmed the clinical diagnosis of tuberculosis, but cultures from the lesions showed no growth of tubercle bacilli after 4½ months. Clinical arrest of the tuberculous process in the monkey is extraordinary, in view of its lack of immunity and the usually rapid course of the infection. This result suggests that, as in smaller laboratory animals, the action of isonicotinyldiazine is long-lasting.

—F. A. JOHANSEN

- SELIKOFF, I. J., ROBITZEK, E. H. and ORNSTEIN, G. G. Toxicity of diazine derivatives of isonicotinic acid in the chemotherapy of human tuberculosis. *Quart. Bull. Sea View Hosp.* **13** (1952), Special Issue, pp. 17-26.

(1) The initial series consisted of 5 "hopeless" patients who had bilateral, cavitating, caseous-pneumonic tuberculosis and were no longer responsive to or suitable for other chemotherapy, antibiotic treatment, or medical or surgical collapse methods. The drugs used were isonicotinic acid hydrazide (Rimifon) and 1-isonicotinyl-2-glycosyldiazine, 1 mgm/kgm per day subcutaneously for 3 weeks and 2 mgm/kgm for another 3 weeks. During this period these patients were singularly free of toxicity. (2) The isopropyl derivative (Marsilid) was administered by mouth to 29 patients in doses of 2 mgm/kgm for 4 to 6 weeks, and then 4 mgm/kgm for 9 additional weeks. Vertigo and constipation were the most frequent side-effects, most common in the 1st week and subsiding in the 4th week. (3) In a group of 44 patients, the dosage beginning with 4 mgm/kgm and continued for 9 weeks, there was a higher incidence of side reactions. Many of the patients complained of urinary retention, most commonly in the 2nd to 4th weeks. Hyper-reflexia and leg twitching were the most commonly encountered symptoms, more frequent than vertigo and constipation. However, all symptoms tended to subside in the 7th and 8th weeks. (4) A group of 10 patients was given 10 mgm/kgm for 7 weeks. Vertigo appeared promptly, but symptoms in general—constipation, twitching of lower extremities, hyper-reflexia, headache, tinnitus, etc.—were maximal in the 3rd and 4th weeks. Laboratory findings in all cases under Marsilid therapy were essentially within the normal range. (5) Rimifon was administered to 10 patients in dosages of 2 mgm/kgm for 1 week, and 4 mgm/kgm for 3 additional weeks. The symptoms noted were the same as with the two aforementioned compounds. In general, the toxic side



reactions to date had been solely of the "acute" variety, and no effects on the parenchymatous organs or bone marrow had been observed. They had been largely related to the autonomic nervous systems, apparently consisting of sympathetic stimulation as evidenced by the constipation, bladder spincter disturbance, and dryness of the mouth. Vertigo appears to be vasomotor in origin, since moderate, transitory declines in blood pressure and increases in pulse rate had been observed; but this, too, is possibly of sympathetic origin. Blood pressures are generally unchanged; there has been no evidence of pressor activity. Central nervous system stimulation is indicated by hyperactive deep reflexes, involuntary twitching, insomnia and drowsiness. These speculations are empirical evaluations, and detailed pharmacological reports and evidence regarding "chronic" toxicity are awaited. The absence of serious toxic effects on liver, kidney and bone marrow is in agreement with primate experiments conducted by Lewis and Zieper [see above]. —F. A. JOHANSEN

- ROBITZEK, E. H., SELIKOFF, I. J. and ORNSTEIN, G. G. Chemotherapy of human tuberculosis with hydrazine derivatives of isonicotinic acid. *Quart. Bull. Sea View Hosp.* **13** (1952), Special Issue, pp. 27-51.

This is a report of the treatment of 92 cases of human tuberculosis at the Sea View Hospital, Staten Island, New York, selected because there was little hope for improvement under antibiotic therapy, chemotherapy or any surgical procedure, with isonicotinic acid hydrazide and its isopropyl and glucosyl derivatives. Definite and important chemotherapeutic effects were observed. The systemic ravages of the tuberculous process were rapidly halted, with subsidence of evidence of toxicity, return of temperature to normal, recovery of appetite and remarkable gain in weight. Even patients who had been bedridden for as long as 2 years got up and about. These changes had occurred with a rapidity, a certainty, and to a degree which the authors had never observed with other chemotherapeutic or antibiotic agents. The authors had also observed a marked effect on anatomical pulmonary lesions, evidenced by marked reduction in cough and expectoration in about one-third of the cases, an apparent—at least temporary—conversion of the sputum to bacteriological negativity in several, and radiological improvement in some. Important effects had also been observed on extrapulmonary tuberculosis, including meningeal, oropharyngeal, laryngeal, etc. These effects, too, were superior to those previously obtained with other therapeutic agents. In the absence of significant toxicity, the isonicotinic acid hydrazide and its derivatives are an important group of chemotherapeutic agents for human tuberculosis and require extensive investigation. —F. A. JOHANSEN

- BOSWORTH, D. M., WRIGHT, H. A. and FIELDING, W. J. Marsilid in the treatment of tuberculous orthopedic lesions. A preliminary report. *Quart. Bull. Sea View Hosp.* **13** (1952), Special Issue, pp. 52-73.

This is a well and convincingly documented report of 6 patients with orthopedic lesions who had been treated with Marsilid. The effects, as stated in the summary, were, (a) decrease of temperature in all cases; (b) restoration of a feeling of general well-being, rapid recession of pain, improvement of appetite and nutritional status, and the possibility of uninterrupted sleep; (c) change to negative in four weeks of sinus washings which had been positive, except for one sinus arising from a denuded

ilium which may yet sequester, in a patient who has already sequestered (though not extruded) a vertebral body. Of 15 sinuses, 5 had healed, 4 of them in one patient. Reaction around all sinuses and drainage therefrom had been markedly reduced. The ostia of sinuses had as a rule considerably filled in. Laboratory and clinical findings seem to show that the drug has no effect on organisms other than the tubercle bacillus. No surgery was carried out on any of these cases during the period of trial of this drug, and no other factor was changed from the preceding period except for the cessation of streptomycin or other antibiotic therapy. No final conclusions are drawn from these observations as to permanency of the beneficial action or late toxicity of the drug. —F. A. JOHANSEN

GRUNBERG, E., LEIWANT, B., D'ASCENSIO, I. L. and SCHNITZER, R. J. On the lasting protective effect of hydrazine derivatives of isonicotinic acid in the experimental tuberculosis infection of mice. *Dis. of Chest* **21** (1952) 369-377.

This is an extension of the study with mice previously reported by Grunberg and Schnitzer [see above], but in this case after infection and treatment for 21 days the animals were allowed to go without any further medication for another 21 days to allow the development of infections that might have been merely suppressed. Among the drugs used for comparison were the thiosemicarbazones of nicotinaldehyde and isonicotinaldehyde, the activity of which Grunberg and Leiwant had recently described [*Proc. Soc. Exper. Biol. & Med.* **77** (1951) 47], confirming results published by Levaditi *et al.* [*C. r. Acad. Sci.* **231** (1950) 1174]. Neither these nor the other control drugs—streptomycin, PAS and tibione—given in sufficient dosage to protect the mice for the duration of the treatment prevented the development of extensive lung involvement after discontinuance of therapy. On the other hand the new drugs, Rimifon and Marsilid, in comparatively low dosage ranges, prevented the development of tuberculous lesions in a substantial number of the animals. The indications, therefore, are that they had a direct effect on the viability of the causative organisms, although no claim can be made at the present time that a permanent sterilization of the infected host has been achieved. —H. W. W.

LEWIS, R. A. and ZIEPER, I. Tolerance of *Macacus rhesus* for isonicotinylhydrazines. A preliminary report. *Dis. of Chest* **21** (1952) 378-384.

The isonicotinylhydrazines have been proved effective in experimental tuberculosis, not only in mice [see above], but also in rabbits and guinea-pigs [Steenken and Wolinsky, see below]. The compounds used in the present investigation were isonicotinylhydrazine (Rimifon), 1-isonicotinyl-2-isopropylhydrazine (Marsilid), and 1-isonicotinyl-2-glucosylhydrazine, all of which in certain dosages have caused some damage to the liver, kidneys or hematopoietic organs of one or another of the species mentioned, and also have considerable toxicity for rats and dogs [Benson, Stefko and Roe, see below]. Three monkeys were used, each of which were given all three drugs during consecutive periods over a total of 10 months, in doses sufficiently high for a possible antituberculosis activity to be expected (the glucosyl intraperitoneally in 10, 25 and 33 mgm/kgm doses successively for a total of 93 days; then Rimifon by mouth, 5 mgm/kgm for 44

days; finally Marsilid in 7, 14 and 18 mgm/kgm doses successively for a total of 142 days). Lack of toxicity in these animals was manifested by their general behavior, weight gain, maintenance of hemoglobin level, and in other laboratory studies recorded. The results of the treatment of another monkey, with spontaneous tuberculosis, have already been reported [see above]. —H. W. W.

SELIKOFF, I. J. and ROBITZEK, E. H. Tuberculosis chemotherapy with hydrazine derivatives of isonicotinic acid. *Dis. of Chest* **21** (1952) 385-439.

To what extent this extensive report differs from the previous one by Robitzek *et al.* [see above] cannot be said but evidently it is very similar, and the points noted here are designed to supplement the other abstract. The experience with the drugs used, mostly Rimifon and Marsilid, which was begun on October 2, 1951, was now of somewhat more than 7 months duration. In total, there had been treated 150 cases of pulmonary tuberculosis, some of which had extrapulmonary lesions as well, and some others had only such lesions, but—as in the first report—only 92 of the former group, treated for from 4 to 15 weeks, are dealt with. All of these had active, progressive, extensive bilateral involvement and were regarded as of poor or hopeless prognosis, none having shown improvement under any other form of treatment during their previous observation in the wards for periods averaging 9 months; all had positive sputums, and 44 of them were febrile. The drugs were given by mouth, three times a day after meals; no other treatment of any kind was given, and no change in their regimen was made with respect to nursing care or otherwise. Although dosages of the drugs varied with different consecutive groups, the over-all dosage levels ranged from 2 to 4 mgm/kgm of the body weight at the outset; this range was not exceeded with the hydrazide (Rimifon, supplied in 25 mgm. scored tablets), but some of the sub-groups on the isopropyl derivative (Marsilid, in 50 mgm. scored tablets) received up to 10 mgm/kgm. The treatment was continuous, and without individualization. None of the patients had failed to show some degree of therapeutic response, with both drugs and all dosage ranges. The most dramatic effects were the rapid elimination of fever and toxic effects, with increase of appetite and of weight, there being an abrupt cessation and rapid reversal of the progressive downward course. In every patient cough and expectoration had been improved or eliminated. The changes in the x-ray picture were less notable, but closure of cavities had occurred in 2 cases and marked reduction in 33. In 25% the sputum had become negative, and in another 28% concentrated smears were only intermittently positive. The extrapulmonary lesions existing in these patients—larynx, ear, intestinal tract, etc.—had improved, sometimes remarkably; these and certain other things are to be reported on by other observers. The toxicological effects—observed mostly during the first 8 weeks—are discussed and tabulated, the principal ones with regard to frequency being leg twitching, hyper-reflexia, vertigo, constipation, urinary bladder retention (in males), and alterations of mood, a “subtle general stimulation” seen with the higher doses and especially with Marsilid. No evidence of antigenicity (sensitization) had been seen, and laboratory findings had been principally negative. —H. W. W.

- RUBIN, S. H., DREKTER, L., SCHEINER, J. and DE RITTER, E. Determination of blood plasma levels of hydrazine derivatives of isonicotinic acid. *Dis. of Chest* **21** (1952) 439-449.

Since this article (by workers of the Hoffmann-La Roche Laboratories) must be examined for details by anyone proposing to make such determinations, little but the summary is given here. A point of some interest is that the factor for converting the weight of the test substance to the weight of isonicotinic acid is 0.898 for Rimifon and 0.688 for Marsilid. The summary follows: A colorimetric method is presented for the determination of blood plasma levels of isonicotinic acid and its derivatives, the hydrazide (Rimifon) and the isopropyl hydrazide (Marsilid). The method is based on the reaction of isonicotinic acid with cyanogen bromide and ammonia. The hydrazide derivatives, which yield relatively slight color per se, are converted to isonicotinic acid by treatment of the protein-free plasma with permanganate. Plasma levels over a 24-hour period after a single oral dose are presented for dogs given 3.5, 7 or 14 mg. per kilogram of Rimifon or Marsilid and for humans receiving up to 3.4 mg. of Rimifon or 3.2 mg. of Marsilid per kilogram. In these limited trials maximum plasma levels are usually found within one-half to two hours after dose and decline rapidly. No significant amount of either compound was found in the plasma after 24 hours. —H. W. W.

- BERNSTEIN, J., LOTT, W. A., STEINBERG, B. A. and YALE, H. L. Chemotherapy of experimental tuberculosis. V. Isonicotinic acid hydrazide, (Nydrazid) and related compounds. *American Rev. Tuberc.* **65** (1952) 357-364.

In these experiments (carried out at the Squibb Institute for Medical Research, New Brunswick, New Jersey) mice were infected intravenously with the bovine tubercle bacillus and the survival times in those treated with isonicotinic acid derivatives and PAS and in untreated controls were compared. The minimum effective daily dose of isonicotinic acid hydrazide (Nydrazid) administered in the diet was less than 2 mgm/kgm. On this dosage, all animals survived for the test period of 35 days. The maximal acceptable level of the drug in the food corresponds to an intake of 65 mgm/kgm per day. The maximal tolerated dose when administered subcutaneously was 125 mgm/kgm daily for 7 days. The close correlation between these figures suggests that the material was well absorbed from the alimentary tract. The minimal effective dose of isonicotinic acid hydrazide is 1/700th that of PAS. Because of the high degree of activity demonstrated in these results, delayed therapy tests were made using a known effective dose of the hydrazide, 1/4th of the maximum accepted level. All mice survived even when the drug was administered orally or subcutaneously 7 days after infection, although neither PAS nor streptomycin showed protection. When treatment was delayed 14 days after infection most of the mice were moribund, but subcutaneous administration of the hydrazide resulted in a high percentage of complete recoveries. —[From abstract in *Synopses of the First Reports, January-April 1952, on Isonicotinic Acid Derivatives, the Newest Anti-tuberculosis Drugs*. Pfizer Overseas, Inc., New York, 1952.]

STEENKEN, W., JR. and WOLINSKY, E. Antituberculous properties of hydrazines of isonicotinic acid (Rimifon, Marsilid). *American Rev. Tuberc.* **65** (1952) 365-375.

The authors (in the Trudeau Laboratory of the Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York) have investigated the antituberculous activity of isonicotinic acid hydrazide and its isopropyl derivative in the test-tube and in experimental infections of guinea-pigs and rabbits. This preliminary report indicates that these drugs have tuberculostatic and tuberculocidal action *in vitro* and produce a dramatic beneficial effect in the experimental animal. With the H37Rv strain of *M. tuberculosis* in media without serum, the dihydrochloride of the isopropyl derivative produced complete inhibition of growth for 14 days in concentrations of 1.6 to 3.1 gamma per ml., while isonicotinic acid hydrazide required only 0.025 to 0.05 gamma per ml. The first of these compounds, in a concentration of 10 gamma per ml., displayed an apparent tuberculocidal action. In the *in vivo* studies, intramuscular injection of the isopropyl dihydrochloride in guinea-pigs caused local necrosis and induration, but use of the drug in the form of the free base minimized these effects. Dosage of 35 mgm/kgm per day was well tolerated for 60 days when administered in two divided doses, but produced steady loss of weight and occasional death when administered in a single daily dose. The hydrazide was well tolerated in dosages up to 35 mgm/kgm per day for 6 weeks. With oral administration, guinea-pigs tolerated 40 mgm/kgm per day for two weeks, using either drug. Rabbits injected intramuscularly were able to tolerate 20 mgm/kgm per day of the isopropyl derivative, and 9 mgm/kgm of the hydrazide, both given in two daily doses. Of 20 guinea-pigs infected subcutaneously with the H37Rv strain of human tubercle bacilli, 10 were treated with the isopropyl compound. Six of them did not survive until the end of the experiment, but died apparently of drug toxicity. [Dosage and duration of treatment not stated in the abstract.] All surviving animals were killed 73 days after infection. Macroscopically, the controls exhibited the usual widespread progressive lesions, but in most of the treated animals slight enlargement of the local and iliac lymph nodes was the only remaining indication of tuberculous infection. Microscopically, the lung sections of 6 treated animals showed no tuberculous lesions, but acid-fast bacilli were found in the hepatic lymph nodes. Of 10 guinea-pigs infected intracerebrally, 5 were treated with the isopropyl compound. The untreated controls died on an average of 21 days after infection, but the treated animals were all living after 60 days of treatment. Twenty-two days after therapy was discontinued, 4 of them were negative to tuberculin skin tests and 1 showed a doubtful reaction. Of 8 rabbits infected intravenously with a virulent bovine strain, 3 were treated with the isopropyl compound for 72 days. The 5 controls died within 22-30 days after infection, but all 3 treated animals survived the treatment. No miliary pulmonary lesions were visible in the roentgenograms of these animals, but they showed relapse of tuberculosis within 10 weeks after treatment was discontinued. —[From abstract in the Pfizer pamphlet.]

- 6 BENSON, W. M., STEFKO, P. L. and ROE, M. D. Pharmacologic and toxicologic observations on hydrazine derivatives of isonicotinic acid (Rimifon, Marsilid). *American Rev. Tuberc.* **65** (1952) 376-391.

To elicit the pharmacodynamic effects and the inherent toxicity of isonicotinic acid hydrazide and its isopropyl derivative, the authors (working at The Hoffmann-La Roche Inc. laboratories at Nutley, New Jersey) performed acute tests with numerous animals, and the responses of anesthetized and unanesthetized animals as well as that of isolated tissue were observed. To determine the limitation of the drug, these compounds were also administered to 2 animal species for 13 weeks, with special attention to hematological and morphological changes. In the evaluation of these agents for parasympathetic blocking activity on isolated intestine, the isonicotinic acid hydrazide showed less than 1/100th and the isopropyl form less than 1/200th the activity of atropine in counteracting the hypertonic state induced by acetylcholine. Extremely high concentrations were necessary to inhibit peristalsis. Tests for antihistamine activity indicated an activity less than 1/1000th of that of benadryl for both agents. In a study of autonomic activity big doses, up to 50 mgm/kgm of isopropyl hydrazine and 25 mgm/kgm of isonicotinic acid hydrazide, did not suppress salivation, nor was the lacrimation induced in rats by methacholine diminished. Observations for effects on pupillary size and local anesthesia were also negative. In testing the hydrazide for bronchiolytic activity, it was found to be about 1/20th as active as atropine, whereas the isopropyl compound has about 50 times the activity of atropine. Neither compound showed activity in the antihistamine aerosol test, or in relaxing isolated tracheal rings. The drugs also proved incapable of reducing temperature. No effect on blood pressure or on normal response to vagus stimulation, carotid occlusion or injection of acetylcholine and epinephrine was observed. The degree of absorption varied in different species, so that in mice the isopropyl was found to be 4.5 to 7 times less toxic than the hydrazide, while in rats and rabbits the hydrazide was the less toxic. Little difference in toxicity was noted by the various routes of administration. In acute toxicity tests, death was due to respiratory failure. In dogs, doses of 70-140 mgm/kgm of the isopropyl derivative were required to produce signs of toxicity, while the hydrazide produced similar results with only 50-100 mgm/kgm. Intrathecal administration of the isopropyl compound produced no respiratory, cardiac or neurological changes in rabbits, speaking against a direct effect upon the central nervous system. However, in one dog adhesions between the dura and the cortex were noted. A significant reduction in the hemoglobin in animals receiving repeated large doses of either drug was noted. Hyperchromic anemia was induced by the isopropyl compound in 2 dogs. Accompanying these changes were a corresponding reduction of the red cell count and an elevation in the reticulocyte count, white cell count and urinary urobilinogen. Oral chronic toxicity studies in rats have indicated that the hydrazide is the less toxic. It produced no significant changes in growth, red cell counts, hemoglobin or hematocrit values. Only in the group with the highest dosage level was the average white count somewhat depressed after 12 weeks of administration. Dogs on the two higher levels of 5 and 20 mgm/kgm showed gross evidence of liver pathology. In the case of the isopropyl compound, a group of 20 rats on oral doses of 0.005-0.080% of

the dihydrochloride in the diet showed a decrease in red and white blood cell counts and hemoglobin values, of moderate degree, only with the two higher dosage levels. Dogs on the lower dose level showed no reduction in average red blood cell counts, hemoglobin or hematocrit value, but significant reductions were observed on the high dose level (14 mgm/kgm). All animals which had received the isopropyl derivative presented gross pathology, most manifest in the spleen, bone marrow, liver and kidney of animals on the highest doses.—[From abstract in the Pfizer pamphlet.]

- 6 RUBIN, B., HASSERT, G. L., JR., THOMAS, B. G. H. and BURKE, J. C. Pharmacology of isonicotinic acid hydrazide (Nydrazid). *American Rev. Tuberc* 65 (1952) 392-401.

Isonicotinic acid hydrazide is rapidly and completely absorbed from the gastrointestinal tract in mice and dogs. Early plasma drug peaks obtained in the dog by oral or intravenous administration are essentially the same. A decline of not more than 66% in 5 hours and an almost complete disappearance in 16 hours is noted. A twice-daily dose schedule of 17.5 mgm/kgm per day or less in dogs showed no cumulative concentrations in plasma. Excitement and convulsions, which are delayed in onset even after intravenous administration, are characteristic of acute toxicity in mice and dogs. A delay in the passage of the drug across the blood-brain barrier, or conversion to a toxic metabolic intermediate, or both, may explain the lag between attainment of peak plasma concentrations and onset of convulsive seizures. Subacute toxicity in dogs was evidenced by anorexia, loss in body weight, tonic and clonic convulsions, ataxia, fatty degeneration of the liver and jaundice. These effects may be reversible upon prompt cessation of drug therapy. In chronic studies with dogs, plasma concentrations of 9-35 micrograms per ml. were associated with anorexia, central nervous system stimulation, liver damage, and death within one month; concentrations of 6-8 micrograms per ml. were not lethal in 15 weeks but caused only anorexia and transient CNS stimulation; lower concentrations caused little or no anorexia and no CNS disturbances. Jaundice is produced at the higher drug levels as a result of fatty liver degeneration. Slight renal tubular damage may be secondary to hepatic insufficiency. Hepatic parenchyma regeneration and areas of fatty degeneration are noted. In one jaundiced dog, bilirubin tolerance returned to normal and signs of CNS disturbance disappeared upon discontinuance of the drug, indicating reversibility. The experimental maximum tolerated subacute or chronic oral doses in mice, rats and dogs agreed with those calculated on the basis of relative body surface area. These doses are approximately 64, 40 and 10 mgm/kgm per day. Conversion of these calculated doses to man suggests a maximum tolerated daily dose of 4 to 5 mgm/kgm. This work was done at the Squibb Institute.—[From abstract in the Pfizer pamphlet.]

- 6 ROBITZEK, E. H. and SELIKOFF, I. J. Hydrazine derivatives of isonicotinic acid (Rimifon, Marsilid) in the treatment of active progressive caseous-pneumonic tuberculosis. A preliminary report. *American Rev. Tuberc.* 65 (1952) 402-428.

This study, still in progress, is of the chemotherapeutic effects of three isonicotinic acid derivatives on 44 "hopeless" cases of acute active progressive bilateral caseous-pneumonic tuberculosis at the Sea View

Hospital. The initial trials with the glucosyl derivative demonstrated that humans readily tolerate 1 mgm/kgm per day. Since animal studies with isonicotinic acid hydrazide and its isopropyl derivative have indicated that greater therapeutic benefit could be derived from these more stable compounds, 2 mgm/kgm per day was used, later increased to 4 mgm/kgm, and finally, with the isopropyl compound, to 10 mgm/kgm. These dosages were based on initial weight and were not adjusted for weight gains during therapy. All patients had been febrile for varying periods before the outset of therapy. In 42 of the 44, the temperatures subsided promptly and almost all of them returned to and were sustained at normal after the 10th day of therapy. The weight gains were most spectacular, averaging 19.7 lb. in 8 weeks. Almost every patient treated for more than 8 weeks returned to normal weight. This gain cannot be ascribed to abnormal accumulations of body fluids. Food consumption on the wards increased by at least 50%, with appetites described as "ravenous." All patients claimed to feel better.—[From abstract in the Pfizer pamphlet.]

ELMENDORF, DU M. F., JR., CAWTHON, W. U., MUSCHENHEIM, C., McDERMOTT, W. and DU BOIS, R. The absorption, distribution, excretion, and short-term toxicity of isonicotinic hydrazide (Nydrazid) in man. *American Rev. Tuberc.* **65** (1952) 429-442.

An investigation in man of the pharmacodynamics and antituberculosis activity of isonicotinic acid hydrazide was commenced in November 1951 in the N. Y. Hospital-Cornell Medical Service. The patients chosen for the experiment had far advanced or moderately advanced pulmonary tuberculosis, and most of them had had long courses of streptomycin and PAS and were discharging tubercle bacilli which were insusceptible to streptomycin *in vitro*. For continued administration of 4-6 weeks, isonicotinic acid hydrazide (a highly purified crystalline powder in capsules) was given orally in a total daily dose of 3 mgm/kgm in 2 doses at 12 hour intervals. The 24-hour urine output was collected, and specimens of blood plasma, pleural fluid, cerebrospinal fluid, sputum, saliva, and feces were obtained. Determination of the drug concentrations in the various body fluids was made by the technique of Kelly and Poet. The antituberculosis activity of plasma after ingestion of the drug was tested against *M. tuberculosis* (H37Rv) in a liquid medium. The urea clearance was calculated, the plasma proteins were measured, and the hepatic function was evaluated by appropriate techniques. The subjects remained in bed throughout the period of the investigation, and were observed daily for any evidence of drug toxicity, particularly excitation of the nervous system. The range of the individual dosage was 140 to 200 mgm. The drug was absorbed promptly, with concentrations of 1.3 to 3.4 micrograms per ml. attained in the plasma after from 1 to 6 hours. No evidence of accumulation of the drug in the plasma was observed. Patients who received a single dose of 3 mgm/kgm excreted 47.8-70.7% of the dose in the urine within 24 hours, little being excreted in the 24th hour. The similarity in the curves for plasma concentration and urinary excretion indicates the presence of the drug in the plasma at that time, although it was chemically undetectable. Excretion in the saliva (one patient) and in the feces (others) was also observed. Appreciable concentrations were found in the cerebrospinal fluid of all patients; in those with tuberculous meningitis the concentrations were much higher than is necessary to inhibit *M.*



*tuberculosis* H37Rv *in vitro*. The pleural exudate of one patient with tuberculous empyema also showed drug concentration. No evidence of potentially serious toxicity had been encountered. Any excitation of the nervous system was also significantly absent. However, it is emphasized that the exceptionally good tolerance may be deceptive, and that larger doses for a longer period of time might produce different results.—[From abstract in the Pfizer pamphlet.]

KELLY, J. M. and POET, R. B. The estimation of isonicotinic acid hydrazide (Nydrazid) in biologic fluids. *American Rev. Tuberc.* **65** (1952) 484-485.

Isonicotinic acid hydrazide (Nydrazid) can be extracted from alkalized plasma or urine into an isoamyl alcohol-ether-ammonium sulfate system and subsequently estimated either spectrophotometrically or colorimetrically. The spectrophotometric method using the absorption peak at  $266 m\mu$  is reliable for concentrations of  $5 \gamma$  per ml. in plasma and  $20 \gamma$  per ml. in urine. The colorimetric method using *p*-dimethylamino-benzaldehyde as the reagent has a lower limit in plasma of  $1 \gamma$  per ml.  $\pm 5$  per cent, and  $5 \gamma$  per ml. in urine. [For details of the reagents and procedures of this determination, developed in the laboratories of the Squibb Institute for Medical Research, the original of this brief note must be consulted.] —[Authors' summary.]

OFFE, H. A., SIEFKEN, W. and DOMAGK, G. Neoteben, ein neues, hochwirksames Tuberculostaticum und die Beziehungen zwischen Konstitution und tuberculostatischer Wirksamkeit von Hydrazinderivaten. [Neoteben, a new, highly effective tuberculostatic remedy, and the relations between the constitution and tuberculostatic efficacy of hydrazine derivatives.] *Naturwiss.* (1952) No. 5.

In 1946, Behnisch, Mietzsch, Schmidt and Domagk [*Naturwiss.* **33** (1946) 315] first reported on the high tuberculostatic efficacy of hydrazine derivatives, particularly thiosemicarbazones of aromatic and heterocyclic aldehydes. Subsequent work on the hydrazine derivatives of further aldehydes, particularly those of a heterocyclic nature, stimulated the authors to investigate more closely the relations thus discovered between chemical structure and tuberculostatic effect. Some hundreds of hydrazine derivatives were synthesized, Offe and Siefken studying them systematically at Leverkusen and Domagk, at Elberfeld, investigating their tuberculostatic effects. *In vivo* a number of these compounds showed good efficacy in the guinea-pig and rabbit. There were developed tuberculostatics whose efficacy exceeded those of any hitherto known preparations. A class of compounds was discovered in the hydrazones derived from isonicotinic acid hydrazide (named Neoteben) which proved highly effective *in vitro* in a dilution of  $10^{-7}$  to  $10^{-8}$ . A strain of tubercle bacilli simultaneously resistant against streptomycin, PAS, and thiosemicarbazone was completely inhibited *in vitro* by Neoteben in a dilution of  $10^{-8}$ . This product is undergoing wide-scale clinical testing. —ERNST KEIL

[In a footnote it is stated that after this manuscript had been prepared it was learned from the London *Times* of February 23rd that Hoffmann-La Roche, Inc. and E. R. Squibb and Sons had tested isonicotinic acid hydrazide and a derivative. For further information regarding the report here abstracted, see editorial note in this issue.]

DOMAGK, G., OFFE, H. A. and SIEFKEN, W. Ein weiterer Beitrag zur experimentellen Chemotherapie der Tuberculose (Neoteben). [A further contribution to the experimental chemotherapy of tuberculosis (Neoteben).] Deutsche Med. Wchnschr. **77** (1952) 573-578 (May 2).

The first section of this article deals with effects of conteben, streptomycin and PAS in tuberculosis. The second section deals with experiments with isonicotinic acid hydrazide (Neoteben), the most effective tuberculostatic of over 500 compounds of the hydrazide class produced and studied systematically by Offe and Siefken and tested biologically by Domagk. In one *in vitro* experiment illustrated (photographs), PAS did not inhibit the growth of the tubercle bacillus in the lowest dilution used, 1:35,000; streptomycin was not inhibitory in 1:500,000 or higher; and Conteben, effective in 1:1 million, did not inhibit in 1:10 million; whereas Neoteben was effective in the latter dilution, the highest one used. In most cases, it is stated, it is 10 times more effective than the best thiosemicarbazones. Unlike PAS, it retains its full inhibiting action against all strains of tubercle bacilli tested in the presence of *p*-aminobenzoic acid. In guinea-pigs infected with the human bacillus, doses of 10, 25 and 50 mgm/kgm of Neoteben proved more effective than PAS in doses of 100 and 250 mgm/kgm. Colored drawings show the lesions of the lung, spleen and liver in a control guinea-pig, the much less marked lesions in the lungs and spleen of one treated with streptomycin (100 mgm. dosage), and complete normality of these organs in four treated with Neoteben in doses ranging from 10 to 100 mgm. This drug was effective against all strains of bacilli resistant to PAS and streptomycin (reference to two reports by Domagk in 1951). In the rabbit infected with bovine bacillus Neoteben was again clearly superior to PAS, streptomycin or Conteben. It is effective when given orally or parenterally, and has the additional advantage that a neutral aqueous solution can be used. The use of Neoteben in human tuberculosis is justified, not only as an alternative drug but on its own account. The dosage should be increased gradually from 1 mgm/kgm per day up to the desired daily amount; the maximum in special circumstances would be 15 mgm/kgm for a short period. In tests with the sera of patients given Neoteben, it was found that if the blood was taken 3 hours after the administration of 0.50 or 0.75 gm., as low as 10% concentration of the serum in Hohn's egg medium inhibited the growth of the tubercle bacillus. This inhibiting value of the serum is regarded as higher than should be necessary in most cases in actual practice. Neoteben is eliminated in the urine; it is not yet known whether elimination also takes place by other routes, or whether accumulation occurs in certain organs in the course of prolonged administration. Neoteben and its hydrazones are at least 100 times more effective than streptomycin, and at least 10 times as effective as the most powerful thiosemicarbazones hitherto known. Furthermore, it possesses this action against strains which are resistant to PAS, streptomycin and Conteben.—[Largely from an abstract supplied by Ernst Keil.]

6 KLEE, P. Die Behandlung der Tuberkulose mit Neoteben (Isonikotinsaurehydrazid). [The treatment of tuberculosis with Neoteben (isonicotinic acid hydrazide).] *Deutsche Med. Wchnschr.* **77** (1952) 578-581 (May 2).

This is a report presented before a tuberculosis congress on February 19, 1952, of observations made during the first few months of treatment with Neoteben. The results are those seen in 61 cases (out of 126 given the drug) treated for not less than 6 weeks and up to 5 months, not including cases receiving combination treatment. Gradual increase of dosage proved unnecessary, tolerance being good [no data on this point are given]; the optimal daily dosage is 10-15 mgm/kgm body weight, given in four doses after meals. Because evidence of accumulation has been seen in animal experiments, treatment for 10-day periods with intervals of 3 or 4 days is recommended for the present, the intervals bridged with PAS, but the drug has been administered for 3 months and longer without interruption. In 2% solution it can be given parenterally; with certain precautions it can be given intrapleurally (5 cc., 100 mgm.); intrathecal ("intralumbar") injections of 1-2.5 cc. diluted with 10 cc. of spinal fluid for tuberculous meningitis have been given with no side effects; it can also be introduced into cavities and fistulas without causing irritation. No method of determining the concentration of the drug in the blood having been devised, the biological method has been resorted to [Domagk; see preceding item]. Observations in one case with miliary tuberculosis and tuberculous meningitis indicate that the substance passes from the blood to the spinal fluid in bacteriostatic concentrations. The drug is not entirely free from side-effects, but they are relatively slight—slight migraine-like and vasomotor sensations are mentioned—but they are generally avoided if it is given after meals. Occasionally an indication of drug exanthema was observed, most pronounced in allergic dispositions, and sometimes irritation, and fever in a patient following sensitization, as with PAS. There were no red blood cell changes; eosinophilia occurred, reaching 8-9%, accompanied by improvement in the syndrome. Certain nervous symptoms demand closer attention. Many patients, especially women, complain of false sensations—a furry feeling, itching and formication—in the hands and feet. A few reported slight vertigo, suggesting hypersensitivity of the vestibular system, but that was purely subjective and temporary. Most patients took the average dose for months without any side effects. The first evident clinical effects were, with few exceptions, increase in appetite and weight—in some instances remarkable, up to 7 kgm in 14 days—and improvement in the subjective well-being. In none of the patients was there progression of the disease. More than two-thirds showed remarkably rapid improvement, and the remainder maintained their condition. The blood sedimentation rates ran parallel with the clinical improvement. In 32 of the 45 patients who were febrile at the outset, the fever was overcome in a relatively short time; the other 13 were still subfebrile. There were bacilli in the sputum at the outset in 58 cases; of these 15 had become and remained negative. Two-thirds of them (40 patients) had cavities; in 4 these had vanished without collapse therapy, and in 18 others there was clear reduction. In 14 of the 61 patients, x-ray examination showed good retrogression of the foci, no change in 17; in none was there any evidence of deterioration. Some of the cases had

continually deteriorated during previous prolonged treatment with streptomycin, PAS and thiosemicarbazones; Neoteben led to a surprising improvement within a few months. The same applies for patients whose sputum bacilli had become completely resistant to streptomycin. Laryngeal tuberculosis reacted very well, all cases healing in a short period under oral medication and inhalation. In one of these cases there had been considerable and progressive extension of the process under thiosemicarbazone, whereas with Neoteben the mouth lesions were cured in 3 weeks and the larynx completely in 8 weeks. Tuberculous anal fistulas also healed rapidly. The important question of whether Neoteben can evoke resistance in the bacilli cannot be answered after so short a period of observation. Primary resistance is considered possible, however, because in one case the bacilli were sensitive to streptomycin and PAS but insensitive to Conteben and Neoteben. In one case fever persisted after Neoteben but was overcome with streptomycin and PAS, and in another the fever responded more rapidly to PAS than to Neoteben. On the whole, Neoteben constitutes a very important advance for the permanent treatment of tuberculosis.—[Condensation of an abstract supplied by Ernst Keil.]