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.

COLE, H. N. Antiquity of syphilis with some observations on its treatment

through the ages. A.M.A. Arch. Derm. & Syph. 64 (1951) 12-22. This article is a scholarly review of the literature, with numerous citations drawn from Proksche (1895-1900) and other sources, bearing on the problem of the origin of syphilis. That question is one which, the author concedes, will probably never be solved to the satisfaction of all, but he believes that syphilis under various names was well recognized and treated with mercury long before the discovery of America, although there is a possibility that it was also prevalent in the Americas before the coming of Columbus, brought via the Bering Strait. The feature of present interest is the allusions to leprosy, which may well explain the idea which still persists in some quarters of a relationship of that disease and venereal history, and also bears on the supposed prevalence of leprosy in medieval Europe. Proksche said that many medical men have felt that the leprosy of the ancients was not always lepra vera, but often lepra spuria, i.e., syphilis. A book on surgery by Feodorico Borgognoni of Bologna, finished in 1266, contained the first descriptions of methodical inunction with mercury salve and recommended this treatment for-among other thingsleprosy, in which it was beneficial only in the beginning stages. Theodorich of Cervia, also in the thirteenth century, recommended the rubbing in of a mercury ointment for the beginning stage of lepra as an "experimentum infallibile." A priest, Michael Scotus, wrote in 1477 that a man who slept with a woman having a discharge contracted lepra, and that if conception took place diseased creatures would be born. "Was leprosy or syphilis meant?" Proksche himself, holding that syphilis was well recognized by the laity centuries before the discovery of America, said that up to about 1495 leprosy had been one of the worst scourges of the human race, and that certain other conditions including elephantiasis and formica had also been severe afflictions; yet after this time leprosy almost died out and the other conditions referred to also disappeared. "How can this occurrence be explained," the author asks, "except on the basis that syphilis was the disease the patients had?" Haberling (1935) points out that, along with the term "lepra vera," physicians of the Middle Ages repeatedly used the expression "lepra spuria," applied to a disease which, in contradistinction to lepra vera, did not require isolation and was curable-doubtless, the author holds, syphilis brought in to Europe by returning Crusaders. To clarify the confusion between syphilis and leprosy, Holcomb [U.S. Nav. Med. Bull. 32 (1934) 401-430; Bull. Hist. Med. 10 (1941) 148-177] says that ancient leprosy, so-called, was always regarded as a readily contagious disease spread through contact with a menstruous woman (Bartholemeus Anglicus, Peter Abano, Peter Angelata). The "leper houses" of Europe, he says, were abolished by Papal Bulls of 1490 and 1505, and the Order of St. Lazarus was no more; on the other hand,

syphilis increased in the same proportion. The author believes that the evidence goes far in showing that long before the end of the fifteenth century there was a venereal disease found throughout the Far East, the Egyptian, Grecian and Roman Empires, and in Europe generally, which was variously called leprosy, lepra spuria and many other names.—H.W.W.

[BELGIAN CONGO] Direction Generale des Services Medicaux; Rapport Annuel 1950. (Mimeographed.)

The statistics of this report reveal the very extensive medical work done in this colony, with increased personnel and with facilities that are being improved materially under a three-year plan. Much of the matter is reported by provinces, without statistics on population from which an idea of prevalence of the various diseases might be derived. With respect to leprosy, it is said that so far as can be told the endemic remains stationary, although with improvement in the organization of leprosaria and agricultural villages the number of cases in segregation have increased by 20% over past years. In total, 71,850 cases received treatment in 1950, and there were 4 European patients. The government hospitals and dispensaries accounted for 1,762 cases, rural dispensaries for 4,495, and itinerant services for 47,344; the balance were under the care of numerous other organizations and enterprises, including Catholic and Protestant missions (5,000 and 6,792, resp.). A total of 22,037 patients were in the leprosaria and villages, 5,685 of them new ones. Tables by provinces show a total of 91 institutions: 50 government, with a total of 6,614 cases in 48 of them (range from 12 in the smallest to 484 in the largest); 11 Catholic missions, with 2,620 cases (range 43 to 1,096); 27 Protestant missions, with 7,561 cases (range 22 to 1,107); 2 National missions, with 1,742 cases (289 and 1,453); and 1 Red Cross, at Pawa (3,771 cases). Only 7 institutions had more than 500 patients; the average for all the others is but 154. Besides the advantages of moral and social nature offered by the centers of segregation, it is stated, they permit the proper control of treatment with the newer drugs. Very encouraging results have been obtained with the mother-sulfone (DDS), and with TB-1 plus streptomycin.

-H. W. W.

O DINIZ, O. Endemia e profilaxia de lepra em Minas Gerais. [Leprosy and its control in Minas Gerais.] Folha Med. 31 (1950) 132-134.

The index of infection of the whole state is said to be 2.09 per mille. It is lowest, 1.48, in the north central area; 1.53 in the east; 2.92 in the west; and 2.95 in the south. At the end of June 1950, there were 17,719 known cases; some were in leprosaria, some living at home, but there remained 4,710 needing the attention of the health authorities. Lepromatous cases largely predominated, forming 68.8% of the whole; tuberculoid cases were 18.1%, and indeterminate cases the remaining 13.1%. Control measures suggested are on the usual lines; including the systematic examination of contacts, of whom there are said to be 50,950, and dispensaries for treatment of suitable cases.—[From abstract in *Trop. Dis. Bull.* 48 (1950) 166.]

SIMONS, R. D. G. Ph. De leprabestrijding in Suriname en de noodzakelijkheid harer reorganisatie. [The fight against leprosy in Surinam and the necessity of its reorganization.] In Holkema's Boekh. en Uitg. N. V. Amsterdam, 1950, 33 pp. Also, Report to the Surinam Government, 1950.

There is much leprosy in Surinam, but almost no cases are known among the Indian tribes living far inland and consequently it is believed that the disease was introduced by Negro slaves. About 700 cases are accommodated in the 3 out-of-date leprosaria from which desertions are common. A thorough reorganization of the antileprosy campaign is urgently needed. The author's views of the modern conceptions concerning compulsory segregation [see THE JOURNAL 17 (1949) 158] are used as the basis of suggestions for this reorganization. Classification is made particularly on the religion of the patients, and the author recommends classification on medical lines. Tuberculoid (kokobe) cases should be allowed free, and only the lepromatous (boassi) cases should be isolated, and for this 2 leprosaria would be sufficient. Occupational therapy and home work should be encouraged, and other welfare measures to promote the aftercare of the patients are discussed. There should be no objection to the sale of special articles, e.g., gold souvenirs, made in leprosaria. According to local superstition (the so-called "treef," arising from African fetishism and Jewish food laws) leprosy is caused by eating of a "forbidden fruit," i.e., food which someone has dreamed should not be eaten. This idea may lead to excesses causing malnutrition and avitaminoses and thus hamper modern treatment, although it is slowly disappearing. Attention is drawn to the medical superstition that Europe was ravaged by leprosy in the Middle Ages, when in fact "leprosy" was synonymous with skin disease. The main reason why the "epidemic" burned out is that skin diseases became distinguished from leprosy, and because the terms morbus gallicus and syphilis became popular.-[From abstracts in Excerpta Med. 5 (1951) Sect. 13, 264 & 269.]

HASSELMANN, C. M. Zur Frage der Ansteckung mit Lepra. [On the question of contagiousness of leprosy.] Ztschr. f. Haut-u. Geschlechtskrkh. (1950) 8/9, 383.

The suggestion that the term "leprosy," to which a certain odium attaches, should be replaced by the term "Hansen's disease" is rejected. As soon as the general public knows that Hansen's disease and leprosy are identical, the former state of affairs will be restored. The measures for the prevention and treatment of tuberculosis would never have made such great progress if the similarly ominous words tuberculosis and consumption had been replaced by a term like "Koch's disease." The reports of direct inoculation contained in the literature, and proof against criticism, prove the direct transmissibility and contagiousness of leprosy. For this reason, from the point of view of public health and the prevention of epidemics, it is not yet possible to recommend the complete relaxation of compulsory isolation of leprosy patients. The interests of public health and human rights demand the greatest possible care. But at the same time it is naturally necessary to alleviate the lot of the patients as far as possible through generous isolation measures which avoid all similarity -ERNST KEIL with imprisonment.

QUAGLIATO, R. Dispensários regionais de lepra; cinco años na inspetoria de Bebedouro. [Regional leprosy dispensaries; five years in the Bebedouro inspectoria.] Rev. brasileira Leprol. 18 (1950) 69-83. This is a detailed account of the nature of the work and the results that have been obtained in a regional *inspectoria* located in the northern part of the state of São Paulo, toward Minas Gerais, the jurisdiction of which comprises 16 municipalities and with some 344,000 inhabitants. It is not readily susceptible to abstracting. —H. W. W.

MIRANDA, R. N. A moderna classificação anátomo-clinico-imunológicad a lepra e seu valor médico-social. [Modern anatomo-clinic-immunological classification of leprosy and its social medical value.] Rev. Méd. Paraná 19 (1950) 61-67.

The author in a lecture given at the Medical School, University of Paraná, reviews the clinical classification of leprosy beginning with the Arabic division into four types, then that of Robert Willan, and on to the Manila and Cairo classifications. The modern classification, which is ascribed to papers of Rabello (1939), is based upon fundamental criteriathe structure of the lesions and immunological condition-which will be lasting although there may be modifications. The South American classification, adopted at Rio de Janeiro in 1946 and approved by the Havana Congress in 1948, involves the polar classification of Rabello into lepromatous (anergic) and tuberculoid (hyperergic) types confirmed by the Mitsuda lepromin test. The medico-social value of the modern classification is discussed with reference to two recent laws of Brazil (1948 and 1950) which regulate the parole and release of interned patients. [As a lesson for medical students this paper was considered as a good mise-au-point of the intricate subject of leprosy classification.] -H. C. DE SOUZA-ARAUJO

CONTRERAS, F. La infección hanseniana en la infancia. [Leprosy infection in childhood.] Ann. Med. Cirug. 27 (1950) 386-396.

In this lecture, delivered before the Academy of Medical Sciences of Barcelona, mention is first made of the high susceptibility of children to the infection. Once infected, however, they resist the disease better than adults, and for this reason resistant forms predominate among them. The infection is acquired in childhood in about 80% of the cases, especially in regions of high prevalence. In areas free from the disease, however, when an opportunity for infection arises adults and children are affected with equal frequency. The different possibilities that present themselves when the organism comes into contact with the bacillus are discussed, and also the difficulties of contagion, which nevertheless is the only manner in which the disease can be acquired since congenital infection does not occur. The study of allergy and immunity is regarded as more important in children than in adults. The clinical manifestations, especially the initial ones, cutaneous and neural, are considered, and also the complementary methods of diagnosis, the essentials of therapy and prophylaxis, and the value of preventoria for children. -AUTHOR'S ABSTRACT

ANDRE-THOMAS, CHAUSSINAND, R. and DE AJURIAGUERRA, J. A propos du diagnostic clinique de la lèpre; la valeur de l'aréflexie pilomotrice en aires. [On the clinical diagnosis of leprosy; the value of the pilomotor reflexes.] Bull. Acad. nat. Méd. 134 (1950) 11-17.

Although the vasomotor and secretory disturbances seem to be of greater significance in the study of sympathetic disorders than the alteration of the pilomotor reflex, their evaluation in clinical practice is affected by the fact that they depend upon two systems, sympathetic and parasympathetic. Also, the causes which provoke them are complex: mechanical and hydraulic influences, phenomena of derivation, and the influence of circulation and temperature of the deep planes. On the contrary, the pilomotor reflex permits prompt demonstration of any disturbance, and comparison with sensitivity and motility facilitates recognizance of its value. Furthermore, the examination of the pilomotor reflex is simple: lightly touching the skin of the cervical or subaxillary region, pinching of the region of the trapezium, pricking of the ear lobe, cooling of the skin of the trunk. If need be, electric stimulation of the cervical skin or injection or ingestion of pilocarpine enhances the reaction. The authors report the observation of a case in which anesthesia of the upper extremities and of the right lower limb, sympathetic disorders superimposed upon the anesthesia, and the irregular disposition of these changes, pointed to the diagnosis of leprosy, which was confirmed by the presence of bacilli in a skin patch. During later examinations the study of the pilomotor reflex quickly demonstrated further suspicious areas in which detailed examination revealed disorders of sensitivity. The study of the pilomotor reflex is therefore regarded as a means of rapid diagnosis which can be made precise by the study of sensitivity. They have adopted the theory of Decoud, according to which the Hansen bacilli are numerous in the lepromatous type but do not penetrate the perineurium or the endoneurium; the bacilli are more rare in tuberculoid leprosy but the nerve branches are more affected, which Decoud explains on the grounds of allergic phenomena. It is concluded that the multiplication of aréflexic and anesthetic zones in a treated patient does not always represent an aggravation of the infection, but may signify an allergic reaction favorable to the organism. -R. CHAUSSINAND

ADAMS, A. R. D. Leprosy. British Med. J. 2 (1951) 106-109.

This article, by the senior lecturer in tropical medicine of Liverpool University, appears under the general heading of "refresher course for general practitioners." It evidences a good deal of familiarity with the literature—although the classification is of lepromatous and neural types and a "mixed" form—and is adequate for the intended purpose. For anyone preparing to undertake actual work with leprosy patients, however, some modifications and interpretations would be required. It is properly said that the successful treatment of leprosy requires a thorough knowledge of the disease and should therefore be left in expert hands.

-H. W. W.

FINDLAY, G. H. Indeterminate leprosy; a new clinical variety. British J. Dermat. 63 (1951) 100-104.

This is a report of a case with unprecedented features seen in the Pretoria leprosarium. The patient, a female Bantu, 24 years old, had three years previously developed lepromatous leprosy which became advanced, with symmetrical infiltrations of the ears and face and other regions; smears were positive, the lepromin reaction repeatedly negative. Two years after onset—before sulphetrone treatment was begun—a second eruption appeared, with annular lesions on the head and papular ones on the trunk resembling those of tuberculoid leprosy and distributed in inverse relation to the lepromatous infiltrations. This eruption exhibited continual out-

breaks, extensions and focal involution for about a year. A few bacilli were found in smears only after prolonged search. Cutaneous sensation and the response to histamin were normal, lepromin tests negative. The lepromatous condition was little altered by this development; histologically the infiltrate was composed almost entirely of lepra cells, with globi in moderate numbers. A typical papule of the second eruption showed in sections tuberculoid changes with sparse giant cells, but no evident nerve involvement. Low down, typical lepra cells were present in abundance, with acid-fast bacilli and globi. Passing upward in the reticular layer the character of the infiltrate gradually changed, the vacuoles becoming fewer and the cells less typically foamy until they assumed the epithelioid appearance; and in the epithelioid infiltrate bacilli could not be demonstrated. In summary, the condition was one of established and persistent lepromatous leprosy in the course of which there occurred a widespread eruption resembling tuberculoid leprosy in clinical, histological and bacteriological aspects, each of these two different sorts of leprosy practically sparing the territory of the other. The author recognizes the polar types of leprosy, tuberculoid and lepromatous, and regards the indeterminate cases as comprising all not definitely of those types, including the borderline cases of Wade and the atypical ones of Cochrane on the one hand and on the other hand lesions which are fading and on the way to extinction. "The creation of an indeterminate group puts a stop to fruitless discussions" about transition stages from one polar type to another "and gives one an opportunity to consider dispassionately a case which refused to fit comfortably into the main types," and with respect to the present case "the author is thankful that he need not regard it as a lepromatous case turned tuberculoid."

Comment .- The title of this paper is misleading. In neither the official report on classification adopted by the Havana Congress, nor the transcription of it which the author cites, is there any indication of intention that such cases should be classed as indeterminate. For that group it is specified that "the lesions histologically [are] of simple inflammatory nature"; furthermore, they "are usually flat macules." In the part of the Classification Committee's report which was rejected by the Congress, the description of the subdivisions of the indeterminate group shows that, so far as skin lesions were envisioned, they are macules; apart from them only polyneuritic conditions were considered. Other workers, including the reviewer, have encountered cases in which lesions showed histologically both lepromatous changes-foamy-celled, hence old-and the tuberculoid picture. So far as we are aware, however, no other case has been recorded in which the clinical lesions, both morphologically and bacteriologically, showed so clearly the two distinctive aspects of the disease as described and, in part, depicted in this report; hence this extensive abstract. -H. W. W.

MOTTA DE AQUINO, U. Observação e discussão de um caso de lepra tuberculoide Mitsuda negativo; reacção focal despertada pela tuberculina. [Report and discussion of a Mitsuda-negative case of tuberculoid leprosy; focal reaction induced by tuberculin.] O Hosp. 35 (1949) 745-753.

This is a report of a case in a male patient, 25 years old, classified as tuberculoid. There were many erythematous macules, and some that were achromic with marginal erythema; some of them were anesthetic; both hands were deformed (claw). Repeated examinations of smears from the skin and the nasal mucosa for the Hansen bacillus were negative; the sputum was also negative for acid-fast bacilli. Histopathology, "tuberculoid granuloma" (Azulay). In making the lepromin test 0.1 cc. was injected intradermally, and 40 days later 0.2 cc. of the same antigen subcutaneously; both tests gave negative results. The tuberculin test was made with 0.1 cc. of a 1:1,000 dilution intradermally and 0.2 cc. of 1:10,000 subcutaneously. Both injections caused positive (1-plus) reactions. There followed a mild general reaction lasting 48 hours, and reactivation of all leprids lasting longer. It is concluded that a negative lepromin reaction does not invalidate the diagnosis of tuberculoid leprosy, that the tuberculoid granuloma may exist in association with an anergic state, and that the histological examination is necessary to confirm the diagnosis of the clinical types of lepromatous leprosy.—H. C. DE SOUZA-ARAUJO

CHATTERJEE, S. N. Thickening of the ulnar nerve in leprosy and its treatment. Paper read at the Third All-India Leprosy Worker's Conference, October 1950; privately printed.

The condition referred to and its sequelae are discussed, and the results of its treatment are illustrated by representative cases. The methods especially recommended include subcutaneous injections of hydnocarpus oil along the nerve and in the affected hand, massage, exercise and decapsulation. —H. W. W.

SAIKAWA, K. A rare case of multiple nerve abscess in an old woman. La Lepro 19 (1950), No. 6, pp. 4-6 (in Japanese); English abstract, p. 1.

The author reports a typical case of nerve abscess in a tuberculoid macular case, a woman 66 years old. (1) There were eight abscesses in the nerves of the left arm. (2) The tissue was a highly organized tuberculoid granuloma. Extracellular lepra bacilli were found in the cheesy substance and in the pus of these abscesses, but lepra cells were not found. (3) As for the genesis of the abscess condition, it can be seen as the highly biological reaction of the nerve tissue against the lepra bacillus.—[From abstract.]

GHCHRIST, J. B. Eye complications of leprosy. Med. J. Australia 1 (1950) 8-11.

Observations regarding ocular lesions were made in Queensland on 55 leprosy patients, 64% of whom had such lesions. They are divided into four grades, and their extent is correlated with the duration and type of the disease. Loss of eyebrows, total or partial, was common, and paresis of the orbicularis oculi was fairly so. Lepromata of the eyelids, episcleral nodules, and involvement of the lacrimal apparatus causing "dry eyes" each occurred in only 3 cases. No leprotic lesions of the conjunctiva were observed. Superficial punctate keratitis, pathognomonic of leprosy, was the commonest complication. Leprotic pannus was frequent, mostly in the upper part of the cornea. There was diminished sensation of the cornea to light touch in 27%. A diffuse yellow coloration of the eyeball, seen in 8 cases, was apparently an accompaniment of deep-seated inflammation. Iritis of the plastic type occurred in 27%; no miliary tubercles were found, or lesions of the retina or choroid. Cloudiness of the crystalline lens was seen in 3 cases, and the peripheral opacities of senile cataract in 3. Treatment included intramuscular injections of lactoflavin, which seemed to help the condition. Whatever the immediate results of ocular treatments, the ultimate condition of the patient's eyes depends largely upon whether or not the disease itself is arrested.—[From abstract in *Excerpta Med.* 4 (1950) 299.]

SAMPAIO, M. Atrofías cutáneas extensas e difusas de etiología leprosa.
[Extensive, diffuse cutaneous atrophy of leprous etiology.] Trab.
Soc. portuguesa Derm. e Ven. 7 (1949) 77-90.

In a man with leprosy, aged 34 years, there were, besides important muscular trophic changes, numerous extensive areas of cutaneous atrophy, most marked on the extremities, which recalled the Pick-Herxheimer atrophic dermatitis. Histologically, tissue from these areas showed infiltrations of leprous nature, but without visible bacilli. A granuloma near one eyebrow contained bacilli of Hansen, as also did the nasal mucus.— [From abstract in Ann. Derm. et Syph. 78 (1951) 501.]

TADA, A. Statistical observations of lepra patients. La Lepro 19 (1950), No. 5, pp. 24-26 (in Japanese); English abstract, p. 2.

Analysis of statistical observations of 167 leprosy patients who visited our clinic during the past 21 years has shown that there was a tendency to an increase in the number of patients after the war; that there were three times more male patients than female; that the ages of most patients were around 20 years; that the sources of infection of only 6.6%of them were clearly known; and that as for the types, the macular form was more frequent than any other (41.9%), followed by the neural, mixed and tubercular forms.—[From abstract.]

ONISHI, K. Statistical observations of the out-patient. La Lepro 19 (1950), No. 5, pp. 27-30 (in Japanese); English abstract, p. 2.

An age curve of the 72 patients who visited our institution during 1948, showed a singular phenomenon. The peak of the outbreaking curve deviated remarkably to the right, and the morbidity curve of macular (tuberculoid) cases showed two peaks, at 21-30 years and 51-60 years. The distribution curve of the present ages suggests that it contains new cases in older people, and the right-side deviation of the age curve signifies the decrease or discontinuation of leprosy cases in the district. —[From abstract.]

SHIMIZU, Y. and KONO, M. The statistical observation of lepra patients. La Lepro 19 (1950), No. 6, pp. 16-18 (in Japanese); English abstract, p. 2.

This report concerns 159 patients in Osaka and Hyogo. (1) As for type, in Osaka was found chiefly the nerve type, 42.6%, in Hyogo the macular type, 40.2%; the nodular type constituted 31.7% of the cases in Osaka and 25% of those in Hyogo. (2) As for the ages, in Osaka 40% were between 31-45 years old, and in Hyogo 40% were more than 50 years old, both age curves therefore showing deviation to the right.—[From abstract.] NOEL, R., RIST, 7. and COTTET, J. Les sulfones en thérapeutique. [The sulfones in therapy.] Presse Méd. 57 (1949) 743-745.

After reviewing the history of the study of sulfones, the authors give their properties: the growth, *in vitro* and in animals, of a number of germs, particularly the bacillus of Koch, is inhibited by smaller doses of sulfones than of sulfamides. The combination of sulfones with streptomycin delays the appearance *in vitro* of streptomycin-resistant tubercle bacilli. It is the same in man: by using sulfones one can reduce the dosage of streptomycin, and the clinical results are better. In leprosy, therapeutic trials have demonstrated the action of the sulfones, especially in lepromatous cases. —R. CHAUSSINAND

TREFOUEL, J. and MARTIN, R. Des sulfamides aux sulfones. [From sulfamides to sulfones.] Presse Méd. 58 (1950) 1374.

The authors recall the different stages of the discovery and practical application of the antibacterial properties of the sulfamides. It has been observed with the sulfamides that the more the sulfur is oxidized, the more active they are. The same is true of the sulfones. The importance of these products is due not only to their action upon the pyogenic microbes, but especially to their bacteriostatic (but not bactericidal) action upon the acid-fast bacilli. After having been used with success in tuberculosis, the sulfones have found a place in the treatment of leprosy.—R. CHAUSSINAND

LOWE, J. Diaminodiphenyl sulphone in the treatment of leprosy. Lancet 260 (1951) 18-21.

In a previous report the writer had advocated the oral use of DDS, either daily in increasing doses from 100-300 mgm., or twice weekly in doses increasing from 100-500 mgm. Since then over 500 patients have been treated. The toxic effects seen are anemia, dermatitis, psychosis and erythema nodosum. Anemia is mainly hemolytic. The fall in hemoglobin tends to be stabilized in a few weeks, and is less if the drug is induced slowly. Iron is useful, but yeast has been found unnecessary. Nutritional liver dysfunction is a common cause of anemia among Africans and renders treatment difficult. Dermatitis, seen in 2% of the cases, always appeared within the first 6 weeks of treatment when the dosage was raised above 100 mgm. daily. The exfoliation may become severe if treatment is continued. Slow induction largely eliminates this trouble. Antihistamin drugs have proved useful. Psychosis, varying from restlessness and confusion to mania, has been recorded in 6 cases, 4 of them with psychotic backgrounds, which is rare among simple ordinary Africans. It is commoner with DDS than with sulphetrone. Symptoms usually disappear on cessation of treatment. Erythema nodosum leprosum, which occurs naturally in lepromatous leprosy, is very common during sulfone therapy. It is not of serious import, although it should be kept mild by gradual induction of treatment. Fantorin has been found useful, but antihistamin drugs are of no value except to relieve the pain of neuritis and iritis. In view of these findings it is now recommended that induction of the treatment be slow, continuing 100 mgm. daily dose for 6 weeks before increasing to 200 mgm. as a maximum 6 days a week. In the twice-weekly treatment the dosage is raised from 100 mgm. by steps of 100 mgm. weekly to 400 mgm. twice weekly and maintained at this level. With this

dosage few toxic symptoms have been noted. Years of experience may be necessary before the most effective dose can be determined.

[This article led to the following Letters to the EDITOR.]

COCHRANE, R. G. Ibid. pp. 289.

The doses of DDS recommended by Lowe are still too high for the average Indian, probably because of dietetic deficiencies. The dosage should not exceed 800 mgm. weekly. To be on the safe side, 600 mgm. weekly divided into daily or twice-weekly doses is recommended. Sulphetrone is still held to be the sulfone of choice for mass treatment. Given parenterally, the cost compares favorably with DDS. Dosage: 3 gm. weekly, i.e., 3 ml. of a 50% solution in water twice weekly.

Lowe, J. Ibid. pp. 469-470.

There is general agreement that the maximum tolerated dose of DDS is 200-300 mgm. daily. In Nigeria the standard dose for mass treatment is now 800 mgm. weekly (400 mgm. twice weekly). Sulphetrone is not only more costly, but it is also wasteful because its action is due largely to its hydrolysis into DDS in the stomach. Given parenterally, its action is probably largely due to DDS as impurity in the sulphetrone. COCHRANE, R. G. Ibid. p. 799.

In answer to Lowe's letter it is stated that, "No worker, as far as I know, has been using DDS under 800 mgm. weekly for more than a year. Let us wait until at least two years have passed before accepting the efficacy of small doses of DDS. If, as Lowe suggests, sulphetrone only acts by virtue of its DDS content as an impurity or after hydrolysis in the autoclave, how does he explain the beneficial action of sulphetrone given parenterally?" Both DDS and sulphetrone are best given in twice weekly doses.

SCOTT, D. B. Ibid. pp. 799-800.

The writer agrees with Lowe that dermatitis is common when high doses of DDS are given. He also finds that the patient becomes extremely sensitive to the drug and needs to be desensitized if treatment is to be continued. Other important reactions he had noted were hepatitis and nephritis. These cases made good recovery if the doses were reduced to 5 tablets [500 mgm.?] twice weekly. No further cases of nephritis or hepatitis had occurred, and skin reactions had become less common.

-G. O. TEICHMANN

LOWE, J. and DAVEY, T. F. Four years' experience of sulphone treatment of leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. 44 (1951) 635-662.

This paper is a report of four years' work of sulfone treatment, involving 568 cases of leprosy. Diasone, the first sulfone used, was discontinued because currency difficulties made supplies unavailable; sulphetrone and DDS have been used since then. All of the sulfones were given orally because of simplicity in administration and shortage of staff. The complex sulfones are held to owe their activity to degradation by hydrolysis into the parent substance (DDS), either in the intestinal tract or in the body after absorption. DDS is absorbed completely and eliminated slowly, whereas sulphetrone is very poorly absorbed and rapidly eliminated; diasone lies between the two. Toxic effects have been less frequently recorded with sulphetrone than with the others, but this difference almost disappears if the doses of all are adjusted to give blood levels correspond-

ing to the DDS content. The toxic effects are described as in the preceding abstract, with the addition of glandular fever, which is common in the area in which the authors work and is often precipitated by the use of sulfones. Discussing the results obtained, it is emphasized that in lepromatous cases improvement is regularly obtained but the full response is extremely slow. In no single uncomplicated case has it been impossible to establish and maintain sulfone treatment. Every case treated for more than a year has shown clinical and bacteriological improvement, but 4-plus cases may take 4 or 5 years to become negative, the explanation offered being that these drugs are bacteriostatic and not bactericidal; the multiplication of bacilli is slowed down, thus enabling the body slowly to overcome the infection. Development of sulfone-resistant forms is not considered important. Microscopic cure lags behind clinical cure, as dead bacilli disappear very slowly from the tissues. In the 50 tuberculoid cases treated results could only be judged clinically, as they were usually bacteriologically negative. Improvement was rapid, although nerve lesions subsided more slowly than skin lesions, and in the process of healing trophic lesions and paralyses often increased owing to fibrosis. The results achieved were too rapid to be attributable to spontaneous subsidence. DDS is now the sulfone of choice in Nigeria, where the prevalence of leprosy is very high; the ease of administration and the low cost are important factors. The dosage recommended is either (a) 100 mgm. daily for 6 days a week for 6 weeks followed by 200 mgm. a day afterwards, or (b) 100 mgm. twice during the first week, 200 mgm. twice during the second week, 300 mgm. similarly during the third week, and 400 mgm. during the fourth week and onwards. To desensitize patients allergic to sulfones very small and increasing doses of sulphetrone are advised, commencing with 20 mgm. in solution and increasing to 500 mgm. during the first 6 weeks before starting DDS. The sulfones only benefit active leprosy, and deformities and disabilities already produced will persist. Nodules when they disappear will leave the skin thinned and atrophic, and severely thickened nerves in healing will leave paralysis behind. For these reasons early treatment is of vital importance.

Later note (February 1951).—It had been found that twice-weekly treatment is better tolerated and no less effective than daily treatment, and it is now being used for mass therapy. DDS has been found to be well tolerated by nursing mothers. It is found in the breast milk and may possibly have a prophylactic value. About 20,000 patients are now receiving DDS in widely scattered centers. Of the early lepromatous cases treated by the authors, 57 have been discharged; only two have subsequently become bacteriologically positive, but on resumption of treatment they again became negative. A few severe lepromatous cases have become negative and are completing their negative period of 12 months before discharge. Combined treatment is also being tried with streptomycin, with good results in tuberculoid but not lepromatous cases. Thiacetone has given promising results alone, but appears to be toxic in combination. PAS has proved much less effective. —G. O. TEICHMANN

DE SOUZA LIMA, L. Importancia da sulfonoterapia nos dispensários e resultados. [Results of sulfone therapy in dispensaries for leprosy patients.] Rev. brasileira Leprol. 18 (1950) 24-32.

The patients concerned in this report were attending the Lapa dis-

pensary in São Paulo. The drugs used were diaminoxyl [not defined] and diamidine [diasone]. The cases classified as indeterminate are subdivided into (a) those of less than 4 years' observation, who were given the more intensive treatment, two or three dragées daily for 6 weeks, then 2 weeks' rest, and (b) those of more than 4 years treatment, who received one dragée daily for 6 weeks and then 2 weeks' rest. None of these cases has passed over to the lepromatous type, and the cutaneous manifestations have retrogressed and some have apparently recovered. Of the tuberculoid group, those with lesions in the reactional stages were given 3 dragées daily for the first 6 weeks, then 2 weeks' rest, this course being repeated until activity had ceased, and thereafter 2 or even 1 dragée daily. The less active cases were started with 2 and later had 1 dragée daily for the same period as in the other cases. The results were favorable in that the lesions tended to retrogress, but there was no effect on the peripheral nerve lesions. Cases of the lepromatous group were treated according to the clinical condition. Incipient cases were started on 3 dragées daily for 6 weeks, then, after a fortnight's rest, one daily; moderate cases had 2 daily for the first 6 weeks, then one daily after the usual interval, for a year; advanced cases were given 3 dragées daily, for 6 weeks, with 2 weeks' rest, and so on, usually for 2 years altogether. Patients who persevered with the treatment improved, and the erythema nodosum syndrome disappeared "in a good percentage of cases"; some exhibited, temporarily, signs of exacerbation, particularly if the treatment was stopped prematurely. [It is a little difficult to assess these results accurately because, although the details of the schemes of treatment are given and the results in general, the numbers of patients suffering from the different types are not mentioned.]-[From abstract in Trop. Dis. Bull. 47 (1950) 1098-1099.]

MATTOS DE MOURA, A. Considerações em torno da sulfonoterapia da lepra. [On sulfone therapy in leprosy.] Rev. brasileira Leprol. 18 (1950) 36-42.

This study is based on the treatment of 814 patients at the Sao Roque hospital-colony in Paraná: 747 lepromatous (26% bacteriologically negative at the beginning), 50 indeterminate and 17 tuberculoid. Treatment was discontinued in 65 cases; 19 died, 12 absented themselves or evaded treatment, while 24 showed intolerance of the drugs used, promanide and diasone [diamidine]. The mode of administration was either intravenous or oral. Response was more prompt with the intravenous route. Sideeffects observed with the oral treatment were gastritis and a more or less generalized pruritus which occurred in about 3% of the cases. The urine was examined regularly and bacteriological examinations were made monthly; the Mitsuda test was also performed. Clinical improvement, it was noticed, was not always accompanied by corresponding bacteriological changes, but in general the amelioration was such that the patients could be allowed out, without danger to others, and could then attend as ambulatory cases.—[From abstract in *Trop. Dis. Bull.* **47** (1950) 1099.]

^OCHATTERJEE, S. N. Sulphone drugs in leprosy. Internat. Med. Abst. & Rev. Calcutta) 9 (1951) 20-26 (also privately printed).

It is not known if the sulfones are chemotherapeutic drugs, in the Ehrlich's sense of direct action on the etiological agent of a disease, and they are certainly not fully chemotherapeutic as regards the further requirement that they should have that effect without injury to the cells of the body. Opinions differ regarding the mode of action of these drugs, but the fact that they have more effect on the lesions than on the bacilli is well established; and, indicative of his doubt of a bactericidal effect, the author asserts that tuberculoid lesions with repeatedly negative smears subside equally as well as strongly positive lepromatous lesions. Nevertheless, the sulfones are very useful and the best drugs available for the treatment of lepromatous and some neural cases. —H. W. W.

MARTÍNEZ, DOMÍNGUEZ, V. Quimioterapia de la lepra lepromatosa. [Chemotherapy of lepromatous leprosy.] Fontilles 2 (1950) 491-515.

This is a report of the results obtained during the first 6 months of diasone treatment of 71 cases of lepromatous leprosy, not including patients with unfavorable complications of red blood cell counts below 3,500,000. The treatment schedule recommended by the Havana congress was followed, and blood examinations were made monthly. Tolerance was excellent in 38, including one pregnant woman who had an uneventful delivery; 7 had at the beginning mild febrile reactions; 14 developed erythema nodosum reactions with fever, and in 4 of them the treatment had to be suspended temporarily; 7 developed pemphigoid dermatitis compatible with the treatment; 3 had reactivation of old ocular lesions, which in one instance necessitated stopping the treatment for 2 weeks; 2 developed severe anemia, with red cell counts below 3,000,000, but treatment could be resumed after 15 days because of the quick response to iron and liver extract. The results were good, 69 of the 71 patients showing clinical improvement: 3 had complete regression (clinical cure); 62 showed marked improvement; 4 were slightly improved; and only 2 remained without evident change. Bacteriologically, 35 patients became negative; 21 others showed notable diminution of the bacilli, with signs of bacillary degeneration; 13 showed no appreciable change; and in 2, more bacilli were encountered than before treatment. Immunologically, also, noteworthy improvements were seen: of the 62 patients who were negative to lepromin before treatment 13 became positive, 2 of them with strong reactions. Clinical, bacteriological and immunological differences in the manner of response to the treatment were observed according to whether the patients belonged to the nodular, infiltrative or macular subvariety of the lepromatous type. Improvement occurred in 23% of the nodular, 50% of the -FELIX CONTRERAS infiltrative, and 78% of the macular cases.

FLOCH, H., LECUILLER, A. and DESTOMBES, P. La sulfone-mère-retard en eau physiologique gélosée permet de ne pratiquer, pour le traitement des lépreux, qu'une injection intramusculaire par semaine. [The parent sulfone in physiological saline with agar can be given only once a week by intramuscular injection.] Inst. Pasteur Guyane et Terr. Inini, Publ. No. 228, April 1951.

Treatment of leprosy by daily administration of DDS by mouth is not ideal for all cases, and it would often be valuable if one weekly intramuscular injection of 1.20 gm. could be given. The authors have therefore experimented, in comparison with oral administration, with the *sulfonemere-retard*, i.e., suspensions which take advantage of the insolubility of DDS to obtain a delayed effect. The principal suspensions used have been in physiological saline, physiological saline with 0.2% agar; arachides

(peanut) oil, and ethyl chaulmoograte. The first three contained 1.20 gm. in 10 cc., the last 1.25 gm. in 5 cc., these amounts representing the weekly doses. Blood level determinations showed that the drug is absorbed very irregularly from the arachides oil suspension, so that is not to be recommended. On the other hand the suspensions in ethyl chaulmoograte and agar-saline produced satisfactory sulfone levels, with quite small variations. From the viewpoint of economy, the latter preparation is manifestly superior. The former one has been recommended by certain authors [see Schneider abstract, page 160], one injection of 5 cc. containing 1.25 gm. of DDS every 15 days. According to them this dose has maintained a blood level of 0.2-0.3 mgm.%-a level which they consider high but which in reality is low. In the authors' own work this preparation has given them better results, but they cannot recommend the schedule of two injections per month with either the chaulmoograte or the agar-saline suspension; they still prefer weekly injections with one week of rest every two months. They cannot credit the possibility, other than theoretic, of a therapeutic activity of the ethyl chaulmoograte because 5 cc. of that drug given weekly-let alone every 15 days-is an absolutely ineffective amount. They therefore recommend the 12% suspension of DDS in a 2% agar-saline, given in doses of 10 cc. per week. This produces sufficiently high and stable sulfone blood levels, and the material is economical and easy to prepare. The agar is dissolved in the saline on a water bath and then brought to 100°C. for several minutes; after cooling the DDS is suspended by trituration in a mortar, and the preparation is adjusted to pH 7.5; and finally it is distributed in 10 cc. ampules and sterilized in the autoclave at 105-110°C. for 20 minutes. -AUTHOR'S ABSTRACT

FRANCIS, J. and SPINKS, A. Antibacterial action and metabolism of five sulphones. British J. Pharmacol. & Chemother. 5 (1950) 565-583.

This article, a report of an extensive and diversified investigation, should be studied in the original by anyone concerned with the mode of action of the sulfones; only a few of the experiments can be mentioned. The basic thesis is that the soluble sulfone derivatives are active, whether in vivo or in vitro, in proportion to the degree to which they are broken down to DDS. Those employed in these studies were promin, diasone, sulphetrone, and also an acetaldehyde bisulfite derivative called 2196, developed in the same laboratories (I.C.I.) but never tested clinically because of the conviction that the soluble compounds have no real advantage over the parent sulfone. In Str. pyogenes infection of mice the five drugs, given in the food, showed relative potencies of the following order: DDS, 100; #2196, 43; diasone, 18; promin, 16; sulphetrone 1. The 2196 product, it is stated, has nearly the activity to be expected from its content of DDS. In an in vitro test with Str. agalactiae, the order of activity was approximately as follows: DDS, 2,187; #2196, 729; diasone, 58; promin and sulphetrone, 6.5. The greater differences, compared with the results of the in vivo test, are regarded as consistent with the view that the derivatives act by breaking down to DDS; the media used were sterilized by filtration to avoid the break-down of the drugs caused by heating. Methods developed for the estimation of DDS in the blood and urine are described. One of the 10 graphs illustrating various experiments shows the maximum blood concentrations of DDS in rabbits given the drugs by mouth: 0.1 gm. of DDS itself gave a level two times or more greater than the derivatives given in 1 gm. doses except the #2196 drug, the peak of which was nearly 3 times as high as that of DDS (from its ten times smaller dose). Another graph shows that, after intravenous injection of 1.0 gm. in rabbits, #2196 gave a DDS blood level 6 times as high as promin and 12 times as high as sulphetrone; the results with the last two could perhaps be attributed mainly to free DDS in the materials injected, whereas #2196 had been converted to DDS to a considerable degree. The findings indicate that the therapeutic effect of any of the derivatives is closely related to the blood concentrations of free DDS. The breakdown probably occurs in the stomach, only #2196 showing much liberation of DDS in the presence of blood *in vitro* or after parenteral administration; sulphetrone so administered is excreted rapidly and mostly unchanged. It is concluded that DDS is preferable to the derivatives for the treatment of leprosy. The nervous symptoms produced by DDS in some animals are described.

-H. W. W.

MUNGAVIN, J. M. A review of the relative activity of the sulphones. Internat. Med. Abst. & Rev. 9 (1951) 31-33.

The relative activity of the sulfones against streptococci was studied both in vivo and in vitro. When given to mice in food, the relative potencies were as follows: DDS, 100; "2196," 43; diasone, 18; promin, 16; sulphetrone, 1. There was a close correlation with the free sulfone levels. Intravenous administration of promin and sulphetrone to rabbits resulted in rapid excretion, with only a very small amount of either drug being converted to DDS. In vitro, sulphetrone and promin were about 250 times, diasone 27 times, and "2196" only 3 times less active than DDS, in a test so arranged as to prevent the breakdown of the soluble derivatives. When the media containing dilutions of the drugs were autoclaved before inoculation, promin and sulphetrone were only 9 and 27 times, respectively, less active than DDS, indicating that autoclaving liberated DDS. When added to blood and incubated at 37°C., "2196" was the only one of the compounds to liberate free DDS in appreciable quantities. All of the compounds broke down to some extent in the presence of 0.1 NHCl, the degree of breakdown being closely related to the blood concentrations and therapeutic effects obtained in mice with oral dosing. -DHARMENDRA

PENNEC, J. La promine intra-dermique dans le traitement de la lèpre lepromateuse. [Intradermal injection of promin in the treatment of lepromatous leprosy.] Rev. Serv. Santé publ. Guadeloupe 1 (1950) 9-13.

This note reports the treatment of 16 cases in Guadeloupe by injection of promin into the cutaneous lesions, as done by Herrera, with results that support but do not equal his. In 50% of the cases the results were satisfying after 6 to 8 weeks, especially when the lepromas were of recent origin; lesions on the nose responded best. The injections are not very painful, so they are worth trying. Brief details are given of all 16 cases. —[From abstract in *Trop. Dis. Bull.* **48** (1951) 165.]

KONO, M. and KAGEYAMA, R. On the promin level in blood and in urine. La Lepro 19 (1950), No. 6, pp. 19-21 (in Japanese); English abstract, p. 2.

We examined hourly the concentration of promin in the blood and

urine, by the Tsuda colorimetry method, after intravenous injections of leprosy patients. The blood concentration was found to increase rapidly after injection, but it also decreased quickly. It was therefore difficult to maintain high levels for any length of time. Excretion in the urine was maximum after 2 hours, and decreased rapidly until after 12 hours, then slowly. Nothing remarkable was found with respect to the differences of blood levels in the different types of the disease.—[From abstract.]

NISHIMURA, S. and KONO M. Studies on the effects and function mechanism of protomin on leprosy and rat leprosy. La Lepro 19 (1950), No. 6, pp. 22-23 (in Japanese); English abstract, p. 2.

(1) The results of from 40 to 116 subcutaneous injections of 0.1 cc. of protomin to 17 rats with leprosy were: aggravation in 6, no change in 6, improvement in 4, and recovery in 1. We recognize no effect. (2) Intravenous injections of 13 tubercular and 11 macular leprosy patients gave encouraging results, although the observation was short. (3) The concentration of protomin in the blood of both men and rats decreased rapidly after the injection. (4) The concentration of free diaminodiphenyl sulfone was much lower in rats than in men. (5) Regarding the distribution of diaminodiphenyl sulfone in the organs of a rat, the mean average value was highest in the liver and kidney, next in the skin and blood, and lowest in the lung, spleen and brain.—[From abstract.]

LAVIRON, P. and LAURET, L. Chaulmoogriques et sulfones dans la thérapeutique de la lèpre. [Chaulmoogra drugs and sulfones in the treatment of leprosy.] Bull. Soc. Path. exot. 43 (1950) 739-746.

For many years the authors have used chaulmoogra (Hydnocarpus wightiana) in the form of the neutralized oil or of the ethyl esters. The ethyl esters were administered intramuscularly, in doses of 5 cc., 2 or 3 times per week; the oil, in the same dosage, either intramuscularly, subcutaneously or intravenously. Gorli, an extract of Oncaba echinata, is applied in the form of ethyl ester in the same doses. In lepromatous patients, clinical improvement was obtained in over 80% of the cases, the intravenous route giving the best results. In tuberculoid cases improvement is the rule. Cimédone has been used for the past two years. Ill-effects (malaises) due to the medicament generally disappeared after the first few months. Anemia, when it exists, disappears during the rest periods. The results have been highly satisfactory, especially in the lepromatous cases. Disulone (DDS) administered to some patients for 6 months, in doses of 200 mgm. per day, has likewise given good results, in conformity with those obtained by other authors who have used it. The authors held for the necessity of combining chaulmoogra and sulfones.

-R. CHAUSSINAND

[©] LAVIRON, P., LAURET, L. and SCHNEIDER, J. Traitement de la lèpre par des injections espacées de D.D.S. dans le chaulmoograte d'ethyle. [Treatment of leprosy by spaced injections of DDS in ethyl chaulmoograte.] Bull. Soc. Path. exot. **44** (1951) 285-289.

Oral treatment being difficult to apply among primitive populations, 67 leprosy patients have been treated, 35 of them for over 6 months, by semimonthly intramuscular injections of DDS in ethyl chaulmoograte. The dosage was 1.25 gm. of the sulfone in 5 cc. of the chaulmoograte per injection in the adult, and 1 cc. of this solution per 10 kgm. of body weight in children. The results were comparable with those obtained by oral treatment. In particular, all of the lepromatous cases improved after the third month of treatment. The tuberculoid forms were influenced less consistently. Anemia has not been observed in the patients followed, and 26 of them showed increase in weight. Lepra reactions, however, were quite frequent (in 7 out of 35 cases), and they were perhaps related to the loss of weight noted in 17 patients. —R. CHAUSSINAND

MONTEL, L. R., LE GAC, P. and MULET, M. Nouveau cas de pian traités par l'huile de chaulmoogra; documents photographiques. [New cases of yaws treated with chaulmoogra oil; photographic demonstration.] Bull. Soc. Path. exot. 44 (1951) 173-174.

This brief report is of interest in the apparent excellent effect of treatment of two cases of yaws in young Negro children with neutralized *Taraktogenos kurzii* oil, without guiacol. The oil was given intramuscularly, in one case 7 doses of 1 cc. each in 16 days, in the other case 5 doses of 2 cc. each in 12 days. Photographs show the lesions before treatment in both cases, and the complete healing after treatment. (In previous communications the use of guiacolized chaulmoogra in this disease was reported [Ibid. 43 (1950) 681], and the way in which, through an error of diagnosis, a chaulmoogra preparation was employed with interesting results in a case of syphilis [Ibid. p. 685].) —H. W. W.

SCHNEIDER, J., LAVIRON, P., LAURET, L. and BASSET, A. Traitement de la lèpre par le thiosemicarbazone (ou TBI). [Treatment of leprosy by thiosemicarbazone or TB-1.] Bull. Soc. Path. exot. 43 (1950) 733-739.

A lepromatous patient followed for 22 years and for whom no therapy, including the sulfones, had caused improvement, was treated for 10 months with TB-1 in doses of 100 mgm. per day at first and then 150 mgm. The appearance of anemia caused interruption of the treatment, but it was resumed 6 weeks later. The result being favorable, 13 other patients were treated for from 3 to 9 months. They were given, on 6 out of 7 days, 100 mgm. in the first week, 150 mgm. in the second week, and then 200 mgm. In all of the 14 patients the clinical improvement has been very evident, from the second month of treatment. The bacteriological improvement was less marked; at times more bacilli were found than before the treatment; but the bacilli appeared granular and sometimes fragmentated, as is observed with the sulfones. The difficulties with this treatment have been headache in some cases, pruritus in 2 cases, and vomiting in 1 case, but these troubles quickly subsided. On the other hand several patients had albuminuria, persistent in one of them, but without other troubles of -R. CHAUSSINAND the renal function.

GÓMEZ ORBANEJA, J., SUCH, M. and GARCIA PEREZ, A. Resultados del tratamiento de la lepra con tiosemicarbazona. [Results of the treatment of leprosy with thiosemicarbazone.] Actas Dermo-Sif. 42 (1951) 605-612.

In February 1950, because of the resemblance between the Koch and Hansen bacilli, as well as certain aspects of the two infections and their treatment, it was decided to try out thiosemicarbazone which was being Current Literature

employed with success in the treatment of certain kinds of cutaneous tuberculosis. The first treatment was started on February 7, with a lepromatous patient with large infiltrated plaques and frequent lepra reactions; evident improvement followed, with lessening of the infiltration of the plaques and improvement of the course of the disease. In November, 7 other patients were put under this treatment; their improvement is indicated in the case histories. The results in the 8 patients treated are summarized as follows: Of the 7 bacteriologically positive cases, 5 rapidly became negative and in the other 2 the numbers of bacilli decreased notably and the globi disappeared, only a few scattered bacilli being found. The clinical manifestations had clearly regressed, with resorption of the diffuse infiltrations, softening and decrease in size of the lepromas, regression and cicatrization of some of the ulcers, disappearance of the frequent nasal obstructions, relief of cubital pain, and disappearance of the repeated reactional outbreaks which some of the patients had had. At the same time the laboratory findings had improved. The sedimentation rates gradually diminished. In some of the patients there was a slight eosinophilia and in others a tendency to neutrophilia, without alterations of the numbers of leucocytes or of the red cells. It is concluded that TB-1 has an indisputable activity in leprosy, although it is realized that the experience reported is not sufficient for any final evaluation. This report is made because of one published by Ryrie on patients treated at a later date than those on which this preliminary communication is based.

-FELIX CONTRERAS

GRAMBERG, K. P. C. A. The non-specific treatment of leprosy. Doc. Neerlandica et Indonesica Morb. Trop. 3 (1951) 75-82.

This article deals, usually briefly, with a wide range of therapeutic measures which leprosy patients require in addition to the sulfone drugs or the increasingly superceded chaulmoogra. With respect to general treatment, no food need be forbidden unless to meet local opinion on that matter. There is no point in giving vitamin B₁, since the nerve disturbances have no relation to beriberi, and vitamin D_2 and calciferol are not beneficial; there is more sense in administering vitamin A and the B₂ complex. Calcium is rational in supportive treatment. Among other things the treatment of anemia and the use of ultraviolet rays and hot baths are also discussed. Local treatment comprises injections of and applications to macules and lepromatous lesions (it is said that the "false lepromas" of tuberculoid leprosy are not affected by application of CO2 snow or other measures), scarification, and irradiation with Grenz rays. The care of trophic ulcers is considered at length. The section on surgical intervention deals with decapsulation of thickened nerves, which is recommended and described; and-after brief mention of sequestrotomies and amputations-cosmetic operations, which are more frequently necessary than is generally supposed, and excision of "primary" lesions, which is encouraged. Tracheotomy is merely mentioned; not one of more than 1,000 patients admitted to the Donorodjo leprosarium in 30 years had required that operation. The treatment of lepra reaction is one of the problems still to be solved. Conditions of the eyes and nose are considered briefly. In summary, for the proper care of leprosy patients the skills of several specialties are required, and various facilities available only in very large leprosaria or for those situated near a city. The

modern leprosy hospital cannot be set up on a remote island or on the border of a jungle. [This article is scheduled to be reprinted in full in a later issue.] —H. W. W.

BROTTO, W. Tratamento das neuralgias cubitais e ciáticas em hansenianos pelo sulfato de amônio associado à procaina. [Treatment of ulnar and sciatic neuralgias by ammonium sulfate and procaine.] Rev. brasileira Leprol. 18 (1950) 84-93.

In applying a method of treating neuralgias introduced by Melaragno and Tenuto, the author has used a mixture of 6 cc. of 0.75% ammonium sulfate and 4 cc. of 2% procaine prepared from ampoules immediately before injection, the injections repeated every 5 days. They are discontinued if there is no relief after 4 or 5 treatments, but continued until 10 have been given if there is relief. For ulnar neuralgia they are made in the paravertebral region, of the 7th and 8th cervical and the 1st dorsal roots (as shown in a diagram). For sciatic cases the injections are made by preference into the trunk of the nerve in the gluteal region except when the pain is diffuse over muscles, bones and joints, in which case paravertebral injection into the lumbar roots is preferred (also shown in diagram). The results obtained in 6 cases of each kind are given. Of those with ulnar neuralgia, 4 experienced complete disappearance of the pain, as did 5 of those with the sciatic disturbance. This treatment is of value only in "obstinate segmental neuralgias," and ineffective for pains of osseous, vascular or muscular origin .- [From abstract in Trop. Dis. Bull. 48 (1951) 47.]

 FARINA, R. Deformidades do dorso do nariz na lepra; correção com enxerto ósseo. [Deformities of the dorsum of the nose; correction by bone graft.] Rev. brasileira Leprol. 18 (1950) 101-110 (summary in English).

The author deals with the correction of deformities of the dorsum of the nose due to leprosy by autoplastic bone graft performed in 42 cases. The operation, which he believes is original, is described briefly, and the fundamental considerations of the method employed are discussed. The author no longer uses acrylics, for biological reasons. The percentage of bad results was 11.9. The good results obtained in 7 of the cases are demonstrated by multiple photographs and one radiogram of each.—[Mainly from author's summary.]

FARINA, R. Hipertrofia e ptose do lóbulo da orelha na lepra; correãço plástica. [Plastic correction of hypertrophy and ptosis of the earlobe.] Rev. braileira Leprol. 18 (1950) 177-180.

The author describes, and illustrates with two diagrams, a new surgical procedure (the "three triangles" method), of correcting this condition. Results obtained are shown in several photographs.—[Mainly from author's summary.]

KOLMER, J. A. Sulfone compounds and potassium iodide alone and in combination with streptomycin in the treatment of experimental tuberculosis of guinea pigs. American Rev. Tuberc. 64 (1951) 102-112.

The fact that, since the discovery of streptomycin, sulfone derivatives have been found to be inferior in the chemotherapy of tuberculosis does not signify that they may not be useful in combination therapy. It is now well-established that in experimental tuberculosis the sulfone derivatives act synergistically or additively with streptomycin, and there are also a few reports of favorable results in human tuberculosis. The question here dealt with is whether such drugs may have such an enhancing effect in nontoxic doses, and the four best-known sulfones and 13 new ones were used in the experiments, along with potassium iodide the properties of which are considered at some length. All of these drugs when used alone, except 3 of the new sulfones, were found to have definite degrees of therapeutic activity. Promin, promizole, sulphetrone, 5 of the new sulfones and potassium iodide were also used in combination with streptomycin, and all showed evidences of synergistic or additive activity in varying degrees. In view of these effects, the author suggests, combination chemotherapy of human tuberculosis with streptomycin and sulfone compounds is worthy of clinical trial. -H. W. W.

DONOVICK, R., BERNSTEIN, J., MCKEE, C. and RAKE, G. Chemotherapy of tuberculosis. IV. Studies with sulfones in the mouse. American Rev. Tuberc. 63 (1951) 556-567.

This is a study of the therapeutic activity of sulfones in experimental tuberculosis of the mouse, which animal some investigators regard as better for the purpose than the guinea-pig. Of 24 sulfones tested, 15 showed no significant activity. The 9 which did include p,p'-diaminodiphenyl sulfone, promin, diasone, sulphetrone, promizole and rodilone. None of the compounds compared on a molar basis was found to be more active than p,p'-diaminodiphenyl sulfone. —H. W. W.

KIRBY, W. M. M. Recent trends in antibiotic therapy. J. American Med. Assoc. 144 (1950) 233-236.

This article is a summary review which has features of interest in connection with chemotherapy in general. One concerns the lack of correlation sometimes observed between results obtained in animals and man. Chloramphenicol (chloromycetin) gives poor results in pneumococcic infections of the mouse, but has excellent effects in pneumococcic pneumonia in man. The same is true of tularemia infections in these hosts. These two instances, it is pointed out, clearly demonstrate the paramount importance of clinical studies in assaying the effectiveness of chemotherapeutic agents in man. Another is the important but largely unexplored field of combined therapy, with combinations of antibiotics or of antibiotics and sulfonamides. Few conditions have been proved to be more effectively treated by two such agents than one, partly due to the fact that one may be so effective by itself that superior results from the addition of another are difficult to demonstrate. An example is pneumococcic pneumonia treated with penicillin and a sulfonamide, the results with the former alone being so good. Another is tuberculosis, in which it is difficult to demonstrate clear-cut additive effects of PAS used with streptomycin, apart from the value of delaying the emergence of streptomycin-resistant tubercle bacilli. On the other hand, in enterococcic endocarditis the combination of penicillin and streptomycin is much better than either used alone. The value of combined sulfadiazine and streptomycin in brucellosis has also been established, although the newer antibiotics have replaced that regimen. The sulfonamides are often administered in combination with penicillin or other agents in severe infections; and triple sulfonamide mixtures, which reduce the incidence of crystalluria, appear to constitute a real advance. —H. W. W.

⁰ HERRELL, W. E. and BARBER, T. E. A new method for treatment of brucellosis. J. American Med. Assoc. 144 (1950) 519-524.

Treatment of this disease with chloramphenicol or aureomycin has been disappointing because of the high relapse rates. Laboratory studies having shown that a combination of dihydrostreptomycin with aureomycin or terramycin was much more effective in the experimental infection in mice than either antibiotic alone, 35 human cases have been treated with the former combination. In no case has there been a bacteriological relapse, and in only one a clinical relapse. Furthermore, there were none of the undesirable toxic reactions sometimes seen before the introduction of this method. In the discussion, K. F. Meyer commented on the suppression by this combination of drugs of multiplication of the microorganisms, thus enabling the complex immunity mechanism to take over the ultimate sterilization of the tissues. C. W. Eisele confirmed the findings from his own experience with a treatment in which aureomycin, dihydrostreptomycin and sulfonamides were combined, the last included on the basis of laboratory experiments and the well established potentiating effect which those drugs have on streptomycin. -H. W. W.

 DE SOUZA-ARAUJO, H. C. As sulfonas (promin e diasone, e AMGL e AMBSI do Instituto Butantan) não têm acção bacteriostática, in vitro, sobre os bacilos ácido-álcool resistentes isolados de leprosos, nem sobre o bacilo de Stefansky, in vivo. [The sulfones (promin and diasone, and AMGL and AMBSI from Instituto Butantan) have no bacteriostatic action, in vitro, on acid-fast bacilli isolated from leprosy patients, or on the Stefansky bacillus, in vivo.] Mem. Inst. Oswaldo Cruz 47 (1949) 671-677.

After the publication of the first papers on the curative effect of the sulfones in leprosy, which was attributed to their bacteriostatic or bactericidal action, we started a series of experiments to verify the accuracy of this assertion. Promin in dilutions from 1:2,000 to 1:4,000 inhibited the formation of veils in the cultures of four strains of acid-fast bacilli isolated from leprosy patients. Diasone did not inhibit the growth of the same strains of cultures under the same conditions. A mixture of a fresh suspension of Stefansky lepromas with an equal part of promin or of diasone, incubated for $2\frac{1}{2}$ hours at 37° C. and then inoculated into white rats, produced within $5\frac{1}{2}$ months characteristic tumors of murine leprosy, there being no reduction of the virulence of the Stefansky bacillus.

-AUTHOR'S ABSTRACT

TANIOKU, K. The chemical views on the blood of leprosy. La Lepro 19 (1950), No. 6, pp. 24-28 (in Japanese); English abstract, p. 3.

Investigating the chemical state of the blood for the early diagnosis of leprosy, I examined 52 leprosy patients (31 macular, 21 tubercular) who had received no treatment. The results showed a decrease of serum calcium and cholesterin and an increase of blood glucose, serum protein, globulin, rest-N, urea-N and uric acid. These changes, however, are not specific for leprosy, and moreover the quantitative differences of these substances reflected only the degrees of the disease, with no relation to its type.—[From abstract.]

REIMANN, F., LAQUER, W. and ULAGAY, I. The anti-allergic properties of para-aminosalicylic acid (PAS). Animal experiments and a discussion of clinical findings. Istanbul Contrib. Clin. Sci. 1 (1951) 171-190.

The beneficial effect of PAS in tuberculosis has usually been ascribed mainly to a bacteriostatic effect, because it has that effect in vitro. There are, however, serious objections to this simple conception, and certain writers have inferred a direct action on the host. There is evidence that, in both man and animals, the salicylates in general and acetylsalicylic acid (ASA) in particular have antiallergic effects. The authors report the results of experiments which show that both ASA and PAS, when properly administered, have a marked antianaphylactic effect in rabbits sensitized with egg white. Clinically PAS has been found most useful in the acute exudative type of tuberculosis, in which hypersensitivity is in play, and various authorities regard treatment with PAS as a valuable auxiliary measure rather than a curative one. Regarding combined therapy with streptomycin and PAS, the suggestion is made that it is the former which has the antibiotic effect while the latter influences the patients through an antiallergic effect. -H. W. W.

CASULA, D. Il neutrogranulogramma di Benda nella lepra. [Benda's neutrogranulogram in cases of leprosy.] Acta Méd. italica Mal. infett. e Paras. 5 (1950) 294-295.

Studying the neutrogranulogram in 8 cases of leprosy the author observed in a high percentage of neutrocytes an increased number of pathological granulations, as already described by Benda in cases of tuberculosis.—[Abstract from *Excerpta Med.*, Sect. XIII, (Derm. & Venereol.) 5 (1951) 267.]

BINAGHI, G. Il mielogramma nella lebbra. [The myelogram in leprosy.] Arch. italiano Sci. med. trop. e Parasit. 31 (1950) 46-56.

The author presents in a table the constituent cells of the sternal marrow and of the peripheral blood in 10 leprosy patients. The findings in the latter indicated a slight tendency to anemia, although the red cell count was below 4 million in only 4 cases. The hemoglobin values mostly ranged between 75 and 85. All showed eosinophilia, one as high as 14%, although in none were intestinal parasites found. Leucocytes were usually about normal with, perhaps, a leaning towards the lower limit; four were below 6,000 per cmm. In the marrow the point most noticed was the "advanced maturation of the nuclei with immaturity of the protoplasm" of the erythroblasts. This was also noticed particularly in the myelocytes ond promyelocytes, and in two of the patients many free nuclei were seen. The relative increase in basophilic erythroblasts is interpreted as evidence of medullary hypoplasia. These changes, says the author, are observable in diseases other than leprosy and are, therefore, not characteristic. [Nothing is said as to the stage or form of the disease in these cases.]-[From abstract in Trop. Dis. Bull. 47 (1950) 755.]

(Bucco, G. La fine struttura del reticolo precollageno nel granuloma leproso. [The fine structure of the precollagen reticulum of the leproma.]
Acta Med. Italica 5 (1950) 307-314.

The precollagen reticulum is shown at first to increase almost pari passu, but later, if retrograde processes supervene, its fibrils become more and more slender and break up. If, however, the granuloma becomes denser the reticular fibers increase in size and blend with the surrounding connective tissue. These processes are shown in a series of photomicrographs.—[From abstract in *Trop. Dis. Bull.* 48 (1951) 161.]

J ISHIWARA, S. Amyloid degeneration in 3 cases of lepra patients. La Lepro 19 (1950), No. 6, pp. 11-15 (in Japanese); English abstract, p. 1.

The clinical and anatomical state and the histological picture of amyloid degeneration in three cases of leprosy are described. (1) One case showed the bacon spleen, and the other two cases the sago spleen. All three showed panamyloidosis, the liver, adrenal gland, accessory spleen and other organs being involved. (2) The cause of amyloid degeneration in two of the cases was attributed to an anomaly of metabolism caused by the destruction of lepromatous tissues. Since the other case was one of lepra nervosa, the cause was not clearly decided. (3) The amyloid substance was located chiefly in the connective tissues or reticular fibers of the vessel walls, and those fibers in which this substance was deposited became gradually degenerated and disappeared, and finally replaced by the amyloid substance.—[From abstract.]

LIPPI, M. Le reazioni di Takata-Ara, di Takata-Damhoto e la bilirubinemia nella lepra. [The Takata-Ara and Takata-Damhoto reactions and estimation of bilirubinemia in leprosy.] Arch. italiano Sci. Med. Trop. e Paras. 31 (1950) 520-523 (summary in English).

The Takata-Ara and Takata-Dhomoto [shown in title as Damhoto] reactions, and estimations of the blood bilirubin were made in 18 cases of leprosy of various clinical forms. The results were normal in 14 cases, whereas the Takata reaction proved to be slightly positive in 4 cases.— [From author's summary, in *Trop. Dis. Bull.* 48 (1951) 162.]

ISHIWARA, S. Study on serum in leprosy. La Lepro 19 (1950), No. 6, pp. 7-10 (in Japanese); English abstract, p. 1.

The results of our studies to discover what changes in the serum of leprosy causes the positive Takada reaction are reported. (1) The factor of the reaction is the euglobulin of the serum, and the reaction is manifested by the precipitation of this euglobulin and by the condition of balance of the protective function of albumin and other substances. (2) Albumin controls the reaction. (3) It could not be decided if pseudoglobulin alone may be a factor of the manifestation of the reaction.—[From abstract.]

ARGUELLO PITT, L. and CONSIGLI, A. Estudio comparativo de lepromino reacciones efectuadas con antígeno bacilar común y con antígeno visceral cadavérico en enfermos de lepra. [Comparative study of lepromin reactions with bacillary and cadaveric visceral antigens in leprosy patients.] Fontilles 2 (1950) 516-519.

The authors employed visceral lepromins prepared from the livers and

spleens of recently dead patients which had been proved rich in bacilli, which had been prepared in Fontilles by the Mitsuda-Hayashi technique and which had been in storage for 6 months at room temperature. The comparison was made with two bacillary lepromins made from cutaneous lepromas by the Fernández-Olmos technique, one prepared in Rosario, Argentina, and the other in Córdoba, which gave identical results. The test was made in 20 cases, 19 tuberculoid and 1 indeterminate, 0.2 cc. of the antigens being given in the skin of the back and the readings being made after 48 hours and in the fourth week. In the Fernández reactions there were 50% discrepancies, whereas in the Mitsuda reactions there was 90% concordance, although in general the results were weaker with the visceral lepromin than with the bacillary ones. This difference was probably due to a lower bacillary content of the former. The discordance between the Fernández and Mitsuda reactions may be due to less liberation of bacillary antigenic substances during the process of preparation.

-FELIX CONTRERAS

RAFFEL, S. The relationship of acquired resistance, allergy, antibodies and tissue reactivities to the components of the tubercle bacillus. American Rev. Tuberc. 54 (1946) 564-573.

This is the first of a series of articles which has much of significance for students of the immunology of mycobacterial diseases. In experiments with guinea-pigs the author used, besides living BCG and heat-killed bacilli, also defatted bacilli (phosphatide and wax extracted), the separated protein (high molecular weight, unheated), wax (chloroform soluble, acidfast), phosphatide (crude and purified), and polysaccharide, these things alone and in certain combinations. A table shows the results obtained. (a) Sensitivity to tuberculin (OT) was induced by only four of the antigens: BCG, heat-killed bacilli, defatted bacilli plus wax, and the wax alone; not by the defatted bacilli, alone or with phosphatide added, nor the protein alone or with phosphatide (although these animals were sensitive to the unheated protein itself), nor the phosphatide alone or the polysaccharide. (b) Resistance to infection was seen only after BCG inoculation, which is further evidence of dissociation of that condition from hypersensitiveness. (c) Skin tests with the other fractions gave varied results. With the protein extract the tuberculin-sensitive animals responded in the same way as they did to OT. On the other hand, the animals injected with the protein alone or in admixture with the phosphatide gave only responses of the "immediate" anaphylactic (Arthus) type. The polysaccharide caused reactions in animals sensitive to OT and a few of certain other groups, but not those responsive to the protein; these reactions, also, were of the anaphylactic type. All skin tests with the phosphatide gave negative results. (d) In complement-fixation tests for serum antibodies, the polysaccharide used as the antigen was ineffective; tuberculin, the phosphatide, and the wax gave positive results in only some of the animals treated with BCG and the heat-killed bacilli; with the protein, on the other hand, positive results were obtained in all groups but those treated with phosphatide and the polysaccharide (almost 100% of the protein-treated animals). A whole bacillary suspension gave positive reactions with sera from all groups of animals except those treated with the phosphatide, the polysaccharide, and the protein alone; the protein-phosphatide group is recorded as ±. Because the sera of the animals treated with the wax alone gave positive

results with the protein and with the bacillus suspension, and because these animals were tuberculin positive and showed a (modified) Koch reaction on inoculation, it is regarded as obvious that protein in antigenic form persists in the chloroform extracts which contain the wax. These results all point to the wax as the important element in "artificial" production of tuberculin-type allergy. That fraction restored that effect to the extracted bacilli when it was re-added to them; when it was added to the protein it changed the type of response from immediate to delayed; and it induced that kind of reaction when used alone. Various tests applied demonstrated that the sensitivity induced by the wax is not of the anaphylactic type. —H. W. W.

RAFFEL, S. Components of the tubercle bacillus responsible for the delayed type of "infectious" allergy. J. Infect. Dis. 82 (1948) 267-293.

This article has not been seen, but it is evidently concerned primarily with a further study designed to establish the fact that the hypersensitiveness induced in the guinea-pig by injections of the antigens containing the tubercle-bacillus wax is of the delayed or tuberculin type. It appears from later publications that the work was with tissue-culture explants of bone marrow from guinea-pigs which had been prepared (a) with tuberculoprotein alone, (b) with the protein plus the tubercle-bacillus wax, and (c) by infection. When exposed to tuberculin (OT), the explants from the animals treated with the protein, like those from normal animals, showed no injurious effect, because the "shock tissues" for anaphylactic reactivity—smooth muscle and blood vessels—were absent. On the other hand, those from animals given the protein-wax mixture were highly vulnerable, precisely as are those from infected ones, for in both cases the tissue cells themselves are involved in the "infectious" or tuberculin type of sensitivity. The results are demonstrated by photomicrographs.

-H. W. W.

RAFFEL, S. and FORNEY, J. E. The role of the "wax" of the tubercle bacillus in establishing delayed hypersensitivity. I. Hypersensitivity to a simple chemical substance, picryl chloride. J. Exper. Med. 88 (1948) 485-502.

Believing that if a particular lipid of the tubercle bacillus can induce the delayed type of hypersensitivity with the isolated tuberculoprotein, instead of the immediate type, it might also do so with other and nonrelated antigens, appropriate experiments were performed with picryl chloride, one of the simple chemical substances which serve as haptens. When picryl chloride is introduced parenterally the resulting reactivity is of the immediate or anaphylactic type, with antibodies demonstrable in the serum; when it is applied upon or introduced into the skin it establishes the delayed type of reactivity, without demonstrable antibodies. It has been shown, however, that when injected intraperitoneally along with killed tubercle bacilli, the delayed type of reactivity ensues instead of the immediate one. The authors have found that a mixture of picryl chloride and the tubercle-bacillus wax, given intraperitoneally, caused marked delayed sensitivity to subsequent contact and intradermal tests with the chemical. Picryl chloride in a water-in-oil emulsion (paraffin oil) had no such effect. The delayed nature of the reactivity induced by the picryl chloride-wax preparation is evidenced by the chronological and morphological character of the cutaneous response and the results of other experiments described. The effect of the wax is not as an adjuvant, which would merely increase the degree of the response which the other substance alone would produce—as paraffin oil sometimes does—without changing its nature, but the mechanism of its activity is not known. Consideration of the possibility that the presence of active tuberculosis in the body may result in the production of the delayed type of reactivity with antigens which normally induce the immediate type leads to speculation regarding "heteroallergic" reactivity of the Koch form to other bacteria, a condition sometimes observed in tuberculous animals and man, and to other related questions. One of them is whether the fact that picryl chloride induces the delayed reactivity, when placed upon or introduced into the skin, unlike the effect after parenteral introduction, may signify that lipid substances normally present in the skin may have a part in that phenomenon.

-H. W. W.

RAFFEL, S. ARNAUD, L. E., DUKES, C. D. and HUANG, J. S. The role of the "wax" of the tubercle bacillus in establishing delayed hypersensitivity. II. Hypersensitivity to a protein antigen, egg albumin. J. Exper. Med. 90 (1949) 53-71.

It is known that when egg white is injected into tuberculous guineapigs, or into those receiving injections of killed tubercle bacilli, the skin reactions to the protein persist for 48 hours and are often necrotic, very different from the usual brief, edematous (Arthus) type of reaction which occurs in animals sensitized with egg white alone. The authors have investigated the influence of the tubercle-bacillus wax on the response to crystalline egg albumin. Animals treated with the albumin-wax mixture, but not albumin-phosphatide, gave more prolonged skin reactions to the albumin than did the albumin-sensitized controls. The results were less clear-cut than in the experiments with tuberculoprotein and picryl chloride because, as usual when egg proteins have been used in such work, all animals developed the Arthus reactivity; but in those treated with the wax the persistent type of reaction developed in addition. Various investigations were made to determine whether or not the persistent effect actually represented the delayed type of reaction superimposed on the immediate one, including that of the relationship of the cutaneous reactions to anaphylactic responses, tests of corneal reactivity, and tissue culture studies. Other procedures failed to provide definite evidence, and the authors comment on the fact that methods which are definitive in one instance are without effect in another. In the anaphylaxis experiment treated animals were given the albumin intraperitoneally. Those which had received albumin alone (whether in solution or in a water-in-oil emulsion) suffered severe shock, while those given the albumin plus wax (whether or not in emulsion) showed no ill effects. In the tissue-culture experiment the explants of bone marrow from albumin-treated animals when exposed to the antigen suffered no harm, whereas those from animals sensitized to albumin plus wax deteriorated badly, as in the tuberculoprotein experiments (photomicrographs). The results of the corneal reaction test were equally striking. This tissue, like bone-marrow explants, has no blood vessels or smooth muscle to give the anaphylaxis response, whereas the tissue cells themselves are sensitized in well-established "infectious" sensitivity. The animals treated with albumin alone showed no response to intracorneal

injection of that antigen, nor did a group given albumin plus phosphatide, whereas those treated with albumin-wax showed opacity and marked microscopic changes after 48 hours (photomicrographs). It is stated that in another experiment involving tuberculous animals with marked cutaneous sensitivity and BCG-treated animals with moderate sensitivity, only the former showed this corneal response to tuberculoprotein, and it is inferred that a high degree of delayed hypersensitivity is necessary for it to occur. The mechanism by which the bacillary wax induces the effects which have been observed remains unexplained. As before, presenting the materials in a water-in-oil emulsion had no effect, nor did the presence of the phosphatide, hence the effect is not a general property possessed by any lipid or liquid hydrocarbon, nor is it an adjuvant effect in the ordinary immunological sense. —H. W. W.

RAFFEL, S. Chemical factors involved in the induction of infectious allergy. Experientia (Basel) 6 (1950) 410-419.

The first part of this article, which is based on a lecture delivered at a meeting of the Naturforschende Gesellschraft of Basel, reviews work which has been done on the chemistry of the tubercle bacillus. Its principal constituents are proteins, lipids (mainly a phosphatide, fatty acids, a complex "wax," and firmly bound lipids, the whole constituting about 35% of the weight of the bacilli of the H37 strain) and polysaccharides. The histological tubercle is due chiefly to the phosphatide element, and in the main to its phthioic acid component. A detailed analysis of the chemical constituents of the human bacillus as determined by various workers is presented in a diagrammatic scheme. This cannot be reproduced here, but because it is unique the following attempt to reduce it to text is made. Starting with (A) the living bacillus, the filtrate of the synthetic medium on which it has been grown contains proteins and polysaccharide A. Ether-alcohol extraction of the bacilli themselves gives (1) lipids and (2) polysaccharide A. The lipids are separable by acetone into (a) a soluble fraction containing fatty acids and phthioic acid, and (b) an insoluble phosphatide fraction which on hydrolysis is resolved into phthioic, palmitic, oleic, mycocerosic and glycerophosphoric acids and an unidentified nitrogenous base. Returning to (B) the bacterial residue left from the etheralcohol extraction, treatment with chloroform removes (C) the crude wax. This, when the ether solution is treated with methyl alcohol, resolves into (1) a soluble soft wax which on hydrolysis gives phthioic, tuberculostearic, stearic and palmitic acids and an unsaponifiable wax, and (2) an insoluble purified wax. This important latter substance has been examined in two ways. By hydrolysis (Anderson), there are obtained (a) phthioic, mycolic, mycocerosic, tuberculostearic and fatty acids, and phthiocerol and an unsaponifiable wax. By chromatography with alumina columns from boiling acetone (Lederer), there are isolated (a) a soluble fraction which is mycolic acid, and (b) an insoluble one which by treatment with methyl alcohol followed by alumina absorption gives a lipopolysaccharide; and from this, by hydrolysis, there are obtained mycolic, fatty and amino acids and polysaccharide W. Returning again (D) to what remains of the bacterial residue, (1) extraction with 25% alcohol gives polysaccharide A, while (2) further extraction with alcohol-ether HCl removes (E) the firmly bound lipids. This material contains (1) an unsaponifiable wax which does not pass the bacterial filter, and (2) a filterable fraction containing

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polysaccharide and fatty acids. In the diagram the proteins, the phthioic acid, the crude wax and the purified fraction of it, and the lipopolysaccharide are indicated as possessing "activity as described in the text." The major portion of the text reviews summarily the author's experiments dealt with in the preceding abstracts. First there is a lucid discussion of the differences, as regards mode of induction and the responses exhibited, between the anaphylactic type of sensitivity induced by antigens such as bland proteins which gain access to the tissues, and the "infectious" (or tuberculin-like) type which requires the presence of an infectious organism. With regard to tuberculosis, the specific antigen is the bacillary protein, but for inducing the state of infectious hypersensitivity the presence of bacilli, living or killed, in the body is required. It has now been shown that association of the protein and the wax is responsible for the establishment of that type of allergy. It is said (not seen in other reports) that none of the individual substances obtained by Anderson on hydrolysis of the purified wax has the same "directive" activity in the induction of tuberculous allergy as the whole wax itself. On the other hand, the lipopolysaccharide isolated by Lederer by chromatography appears to be the active ingredient; this substance is described. It appears that the cornea test has also been used in experiments with tuberculosis materials. In normal animals and those sensitized (anaphylactically) with tuberculoprotein, intracorneal injection of tuberculin had no effect, whereas in tuberculous animals and those injected with the protein-wax the response was positive. The question of whether other infectious agents may contain lipids with biological properties which determine the delayed type of hypersensitivity is under study, and there are indications that that may be the case. The mechanism by which the tubercle-bacillus wax exercises its effects still remains unknown. The idea that it may be ascribable to epithelioid and giant-cell formation is discounted because the phosphatide has a more marked effect than the wax in altering cells, to the extent of simulating tubercles, but does not influence the hypersensitive response. The work has not thrown any light on the question of the nature of the bacillary substance which is responsible for the development of relative resistance when it is produced. The Koch response is obtained in both the resistant BCG animals and those sensitized by protein-wax, which are not resistant, although it is materially less marked in the latter. Nor is there a definite answer to the question of the nature of resistance, but it is at least evident that tuberculosis allergy and resistance to tuberculosis are not synonymous. -H. W. W.

LURIE, M. B., ZAPPASODI, P., DANNENBERG, A. M., JR., and SWARTZ, I. B. Constitutional factors in resistance to infection. The effect of cortisone on the pathogenesis of tuberculosis. Science 113 (1951) 234-237.

Rabbits of a strain which genetically is highly susceptible to tuberculosis were employed in an intensive study of the effects of cortisone (2 mgm./kgm. of the acetate, given intramuscularly on alternate days) on resistance to experimental infection. Three days after this treatment was begun, when the number of circulating lymphocytes had been markedly decreased and the fasting blood sugar had been increased, all of the treated animals and an equal number of controls received measured quantities of tubercle bacilli by inhalation. In the cortisone treated animals intracu-

taneous injection of India ink or hemoglobin induced less inflammation than in the controls, due to reduction of permeability of the vessels, and the response to tuberculin was markedly reduced. On the other hand, phagocytosis by the liver and spleen of India ink injected intravenously was markedly increased. The livers of the treated animals were twice as heavy as those of the controls due to large deposits of glycogen and fat from the physiological effects of the cortisone, while the spleens were much reduced in size because of its lympholytic effect. The adrenals were markedly atrophied because of suppression of the secretion of ACTH by the pituitary, and also the male gonads but not the ovaries. The treated rabbits consistently showed more tubercles in the lungs-on the average four times as many-as the controls, but the lesions were uniformly and strikingly smaller and the spread of the infection to the adjacent lymph nodes and other organs was greatly reduced. The lesions in the treated animals were sharply delimited and showed more caseation, but the caseous pneumonic foci swarmed with bacilli; whereas the more widely spreading interstitial tuberculomas in the controls contained much fewer bacilli, despite which fact the controls showed much more dissemination. The drug had "markedly and fundamentally affected the essential mechanism of the pathogenesis of tuberculosis" in these susceptible animals, the outcome-at least insofar as the lesions are concerned-being more like what occurs normally in animals of resistant strains. The simplest explanation is that cortisone increased the phagocytic activity of the reticu--H. W. W. loendothelial cells.

SIGNORINI, F. L. and TERNI, M. Ricerche culturali e sierologiche sulla lepra. [Cultural and serological researches in leprosy.] Boll. Ist. Sieroterap. milanese 29 (1950) 70-116.

This long article covers a vast ground, and will be of great interest and help to the medical historian and the bacteriologist. In the account of the many attempts to cultivate the leprosy bacillus more than a hundred names are mentioned and data on their work are tabulated. Various serological reactions in leprosy are then discussed. In their own work the authors used various media and the larvae of *Galleria mellonella*. In several of the larvae injected with leprous material acid-fast bacteria were seen at autopsy 2 to 11 days after the inoculation, but attempts to transmit them to other larvae were unsuccessful. So were those to grow them on artificial media except in one tube of several inoculated from one of the larvae; one colony developed. This microorganism proved not pathogenic to laboratory animals. A serological study indicated that it is more closely related to the Hansen bacillus than the tubercle bacilli [as reported in THE JOURNAL 18 (1950) 161-167]. There is a bibliography of well over 400 references.—[In part from abstract in *Trop. Dis. Bull.* 48 (1951) 44.]

MONTEL, M. L. R. Affinités tinctoriales du bacille de la tuberculose aviaire (méthode de Macchiavello). Comparaison avec le bacille de Koch, avec le bacille de Hansen et le bacille de Stefansky. [Tinctorial affinities of the avian tubercle bacillus, Macchiavello method; comparison with the Koch, Hansen and Stefansky bacilli.] Bull. Soc. Path. exot. 44 (1951) 47-49.

Avian tubercle bacilli, obtained in abundance from the spleen and liver of a rabbit inoculated intravenously, have been studied in smears stained by the method of Macchiavello, and a comparison is made with previous observations of the Hansen and Stefansky bacilli, and with the bovine tubercle bacillus also obtained from an inoculated rabbit. These acid-fast microorganisms, it is stated, can be arranged in a descending curve at the top of which is the Hansen bacillus, easily seen in negative and highly refringent; then the Stefansky bacillus, also easily seen but less refringent; and at the bottom the tubercle bacilli, which are perceived with difficulty and show very little refringence. —H. W. W.

BOLLIGER, A., FORBES, B. R. V. and KIRKLAND, W. B. Transmission of a recently isolated mycobacterium to phalangers (*Trichosurus vulpe-cula*). Australian J. Sci. 12 (1950) 146-147; reprinted in Leprosy Briefs (Leonard Wood Memorial), 2 (1951) 37.

The common phalanger, or oppossum, having been found highly susceptible to the tubercle bacillus (but not to the leprosy bacillus), inoculations were made with acid-fast bacilli from an indolent lesion of the foot similar to that described by MacCallum and others [see THE JOURNAL 18 (1948) 127] and with a culture obtained from that ulcer. The infection was established, and proved to be transmissible in series. Ulcerating lesions containing acid-fast bacilli developed after 2 to 6 months, at various sites independent of the route or place of inoculation. In a few animals the ulcers healed, but those which did not heal increased rapidly in size and led to sloughing, weeping areas with ultimate exposure and even destruction of the underlying muscles. Three uninoculated contact animals developed lesions with the relevant mycobacterium, the infection in one case being wide-spread and progressive. —H. W. W.

DE SOUZA-ARAUJO, H. C. Lepra murina. Nova série de pesquisas feitas com o bacilo de Stefansky, amostra do Instituto Pasteur de Paris. Quatro amostras de culturas de bacilos ácido-álcool resistentes isoladas de ratos brancos e camondongos pretos inoculados com esse material. [Murine leprosy. New series of investigations with the Stefansky bacillus, Pasteur Institute strain. Four strains of cultures of acid- and alcohol-fast bacilli isolated from white rats and black mice inoculated with this material.] Mem. Inst. Oswaldo Cruz **48** (1950) 113-123.

The author refers to previous work on rat leprosy done with three strains of Stefansky lepromas from Berlin (Ficker), London (Laidlow) and Paris (Marchoux), in which he proved that the Stefansky bacillus produces classical globi. The new work here reported was done with two lepromas of rats from the Pasteur Institute (Chaussinand). The black mouse (North American race) was found to be highly susceptible, there being produced large areas of alopecia and lepromas, some of them of the muscle-skin type, within 22 days. (The principal part of this paper regarding the high susceptibility of the black mouse to the Stefansky bacillus was published in THE JOURNAL [18 (1950) 49-52]). From white rats inoculated with this material two strains of chromogenic cultures of acidfast bacilli have been cultivated, both of them gram-positive and fluorescent but negative to the Dubos test of virulence, notwithstanding which fact the cultures produced infection in rats from the lesions of which both cultures were recovered. From the tumors or lymph nodes of black mice. there were obtained two nonchromogenic cultures of strongly acid-fast

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organisms, one of them bacillary and the other one coccoid, both producing on Loewenstein's medium dry, granular colonies, the subcultures becoming creamy-yellow. Both strains are gram-positive and strongly fluorescent, and both are positive for Dubos test; both are infectious for rats and mice, from which the cultures were recovered. With the cultures obtained from these animals the author has produced the two types of lesions described in 1903 by Stefansky in spontaneous rat leprosy: the lymph-node type in rats (less susceptible), and the musculocutaneous type in mice (much more susceptible). —AUTHOR'S ABSTRACT

NAKAMURA, M. The effects of protomin and vitamin K on rat leprosy. La Lepro 19 (1950) No. 5, pp. 21-23 (in Japanese); English abstract, p. 2.

The effects on the growth of the leproma of intravenous injection of protomin alone or with vitamin K were determined. It was found that the intravenous injection of protomin controls the onset of rat leprosy, and the result was better when it was used with vitamin K.—[From abstract.]