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.

[CEYLON] Medical Annual Report for 1948 of the Medical Superintendent, Hendala Leprosy Hospital, Medical Superintendent, Mantivu Leprosy Hospital, and Medical Officer, Leprosy campaign in Ceylon.

The report deals briefly with all the antileprosy work done in the two hospitals mentioned, in the 15 outdoor leprosy clinics in the endemic areas, and by the field organization which controls and observes the non-infectious cases and the contacts. The number of admissions to the two hospitals totaled 115 and the number of discharges 12, so that 1,065 patients remained at the end of the year. Occupational, educational, social and recreational facilities are provided. The cases registered in the clinics totaled 1,307, of which 926 were for observation and 381 for treatment. In the field work 224 new cases had been detected, of which 24 were below 14 years of age, and 84 were of the lepromatous type. The deaths registered in the hospitals and outside totaled 65. Regarding the epidemiology of leprosy in Ceylon, there were 3,150 cases living at the end of the year, of which 1,065 were registered in the two hospitals, 1,882 were on parole, and 203 were discharged on parole; 774 were lepromatous and 2,376 were neural. The largest number of patients were from the Western Province. During the year, 14,401 contacts were examined and 191 new cases were detected among them. Out of 14,283 school children examined, only 4 cases were detected. —DHARMENDRA

MICHAELIDES, N. C. Leprosy in Cyprus. Cyprus Med. J. **2** (1949) 65.

A series of 53 patients—33 males and 20 females—have been treated with sulphetrone, diaminodiphenylsulfone—N:N′-didextrose sulfonate [promin], and diaminodiphenylsulfone disodium formaldehyde sulfoxylate [diasone]. The cases were classified as 17 early (macules and small nodular lesions); 26 moderate (deeper nodular lesions); and 10 advanced (leprous infiltrative plaques and/or leprous ulcerations). In 14 patients, after treatment with one or more of the above derivatives, no clinical signs remained, and bacteriological examinations were negative. In 20, no clinical signs were noted, though bacteriological examinations remained positive. Seven patients showed clinical improvement and were bacteriologicaly negative, while in 12 there was slight clinical improvement but bacteriological examinations were positive. Sulphetrone was used in a number of patients who had shown intolerance to another derivative. No severe reactions were observed with it, with the exception of slight allergic dermatitis and in some patients slight enlargement of the joints of the feet during the first two weeks. It is concluded that with the new methods of treatment disappearance of the clinical symptoms is rapid as compared with the older methods. The disappearance of anesthesia and the cure of claw-hand suggest that the sulfones have some action in tuberculoid leprosy.—[Abstract supplied by Burroughs Wellcome & Co.]

WASHBURN, W. L. Leprosy among Scandinavian settlers in the upper Mississippi Valley, 1864-1932. Bull. Hist. Med. **24** (1950) 123-148.

This is a lengthy article on leprosy among the Norwegian immigrants in the upper Mississippi Valley, beginning with the Norwegian immigration of 1825. The majority of reported cases in this region were Scandinavian immigrants to Minnesota. Most of the early work on leprosy in this territory was done by Minnesota physicians vitally interested in the public health of the state. Various visits of physicians to Minnesota from Norway were made, with attention to climatic and living conditions which would bear on the spread or decrease of the disease, it being concluded that the patients were in much better condition than they would have been had they remained in Norway. A number of case histories are given, tracing the decrease or spread of leprosy in certain families. Leprosy in Wisconsin, Illinois and Iowa is discussed. The author feels that the mysterious spontaneous disappearance of leprosy from Western Europe during the 14th, 15th and 16th centuries was paralleled in the upper Mississippi Valley within the last decades of the 19th century. This article contains many historical facts of interest. —F. A. JOHANSEN

GRAMBERG, K. P. C. A. Leprabestrijding in Indonesië straks. [The prevention of leprosy in Indonesia in the future.] Med. Maandblad. **2** (1949) 211-218.

The leprosy prevention service in Indonesia was destroyed during the Japanese occupation, and the author considers that in rebuilding it a different and better organization should be evolved. Before 1942 the service was entirely separate from the leprosaria, which were also independent of each other, most of them not under medical direction. Prevention and treatment were not coordinated. In the present state of our knowledge, it is held, a leprosy prevention service is not practicable. It is not certain that the leprosy bacillus is the sole infecting agent, nor is there any unanimity as to the route of infection. The conditions are not such as to ensure the willing and intelligent cooperation of the populace in the enforcement of stringent sanitary regulations. The best that can be hoped for is a leprosy tracing service, and this must be closely linked with a leprosy treatment service. For various reasons it will be necessary to treat many patients away from their homes, and the emphasis should be on ascertainment and treatment centers, leprosaria being only a part—though an essential part—of the whole scheme. The leprosaria are no answer either to treatment or to prevention, and should not be organized as prisons nor as the pet projects of either philanthropic organizations or officials. The author proposes the setting up of two or more ascertainment centers, linked with outlying clinics where patients could stay for 3-6 months while their cases were being assessed and disposal decided. These units should be closely associated with hospital centers having all the resources of modern medicine. For cases not requiring these facilities there should be sanatoria, under medical direction, without too great restrictions and catering for all classes and all types of leprosy. Finally, for the hopeless cases there should be leprosaria, each linked both with a sanatorium and an ascertainment center. The sanatoria and leprosaria should continue under voluntary auspices, but should be inspected by a central administration which should lay down the general lines of policy for them.—[From abstract in *Trop. Dis. Bull.* **47** (1950) 139.]

BAILEY, W. From "Cities of Refuge" to "Villages of Hope." Lep. India **21** (1949) 176-179.

Applied to antileprosy work, the title describes accurately the development that has been taking place in India for a number of years in thought and policy regarding the control of this disease. The author compares the present leprosy homes to "Cities of Refuge," a place of shelter from ostracism, persecution and hostility on the part of erstwhile friends and neighbors. For the future development of antileprosy work the author thinks in terms of village isolation centers. Such institutions would provide occupation to the inmates according to their abilities, and would give a new meaning to their lives. The concept involved is the one which offers the greatest likelihood of success in the campaign against this disease.
—DHARMENDRA

[EDITORIAL].. The place of village isolation centre in the control of leprosy in India. Lep. India **22** (1950) 1-3.

India, with its vast leprosy problem and limited institutional accommodation, is in need of developing inexpensive and efficient alternative methods of isolation of infective patients. Home isolation, though possible in intelligent families with ample resources, is not applicable on a wide scale in India. The other alternative, which is considered suitable for Indian conditions, is the isolation of infective patients in rural isolation centers, each serving one village or a group of villages. Some details are given regarding the organization of such centers.
—DHARMENDRA

DOULL, J. A. Modern concepts of leprosy. Texas State J. Med. **46** (1950) 315-319.

The author points out the failures in attempts to cultivate *M. leprae*. Early diagnosis is important, but no advances have been made in the recognition of the disease since physicians do not have leprosy in mind, and the disease is so protean in character that lesions may resemble a variety of other diseases. Three cardinal points in the diagnosis of leprosy are emphasized: (1) finding of acid-fast bacilli, (2) thickening and tenderness of nerves, (3) impairment of skin sensation. The clinical classification of leprosy is described, as is modern therapeutic treatment with the sulfone group of drugs. Public health measures are discussed with respect to methods of control, stressing the education of physicians in endemic areas as to ways of detecting the disease, lessening sensational newspaper publicity when cases are discovered, and judgment as to whether the patient should be isolated or hospitalized. Household associates of patients should be examined, and contacts who are free from the disease should be subjected to no restrictions other than the re-examinations which may be required.
—F. A. JOHANSEN

DHARMENDRA. Diet and susceptibility to leprosy. Lep. India **21** (1949) 180-192.

This is a reprint of a paper presented at the first session of the National Nutrition Conference, held in Calcutta in September 1949. It is a critical analysis of the available literature referring to diet in relation to infectious diseases, especially tuberculosis and leprosy. The hypothesis that a well-balanced diet is important in maintaining the defense against infection is supported by the evidence in laboratory animals and, to some

extent, in human beings. Regarding diet and experimental tuberculosis in animals, there is some evidence that deficiency of vitamins, proteins and caloric value increases susceptibility. Tuberculosis workers believe, on both epidemiological and clinical evidence, that malnutrition—especially a low protein intake—is correlated with increase in mortality rate in that disease. Regarding diet and leprosy, while modern thought does not support the idea that any one particular diet is responsible for susceptibility, most modern workers consider undernutrition to be one of the important nonspecific factors which tend to lower resistance. The belief that defective diet predisposes to leprosy is mainly based on the observations (*a*) that in countries where leprosy is common the diet is poor in protein, vitamins, calcium, etc.; (*b*) that in such countries there appears to be a relationship between incidence and the nature of the dietary practices in different parts of the country, and (*c*) that floods and famines, conditions which interfere with the nutrition of the people, are known to be followed by an increase in the incidence of the disease in countries where it is common. The available evidence on these three points is dealt with, and it is concluded that there is some evidence that malnutrition plays a role in predisposing to leprosy although this evidence is not conclusive. —AUTHOR'S ABSTRACT

RYRIE, G. A. Elicitation and interpretation of tactile anesthesia. Lep. Rev. **20** (1949) 114-118.

The writer draws attention to mistakes that are made in the diagnosis of leprosy when faulty technique is used in estimating tactile anesthesia. The most effective test for anesthesia in leprosy, he holds, is a point of cotton wool. If necessary the skin should be shaved, as the hairs are often sensitive when the underlying skin is not. For the skin of the face a single hair of cotton wool should be used. The outer aspects of joints in normal individuals are often relatively insensitive. In cases of doubt leprosy should not be diagnosed where there is no skin lesions, thickened nerve, or wasting of muscle. —G. O. TEICHMANN

LAI, SHANG-HO. On the value of superficial nerve hypertrophia in the diagnosis of leprosy. Chinese Rev. Trop. Med. **1** (1948) 29-42.

This paper, which comes from the Division of Leprosy of the Department of Pathology, Institute of Tropical Medicine of the National University of Taiwan (Formosa), deals first with the frequency with which the nerves examined—listed in the following table—could be palpated, without regard to size. The investigation involved a total of 3,072 children in elementary schools, aged 8 to 15 years, 8,990 healthy adults (where seen not stated), and 541 patients in the Lao-sheng Leprosy Colony; 51 Japanese patients were also examined but of them it is merely said that they did not differ from the Formosans. The frequencies with which one or the other or both of the individual nerves sought for could be palpated, set forth in detailed tables, are summarized as follows:

Nerve	Healthy children		Healthy adults		Leprosy patients	
	Males (1,872)	Females (1,200)	Males (4,833)	Females (4,157)	Males (356)	Females (134)
Auricular	32%	16%	70%	20%	82%	56%
Supraorbital	10%	2%	0.8%	0.5%	7%	5.2%
Infraorbital	1.3%	1.2%	1%	0.6%	5.1%	3.7%
Ulnar	56%	50%	80%	35%	90%	67%
Median	50%	36%	50%	32%	60%	36%
Radial	23%	20%	45%	28%	54%	46%
Peroneal	30%	15%	40%	31%	46%	35%
Tibial	10%	16%	36%	20%	41%	34%

It is noted that in the school girls nerves were usually less frequently palpable than in the boys, especially the auriculars and the peroneals. Of the healthy adults, the males gave high frequencies for most nerves, especially muscular laborers. As for the figures for leprosy patients, even those for the females, the author remarks, "Still we can not say it is extraordinary." By tactile perception the author compared the sizes of palpable nerves with a wire gauge, finding in all instances a wider range and somewhat larger averages in the leprosy patients than in others, but not as great a difference on the whole as might be expected. The incidence of facial paralysis in healthy and patient groups was also investigated; in the former it was 0.88 per cent, in the latter 48 per cent. —H. W. W.

LAI SHANG-HO. On the differential diagnosis of leprosy, especially the cases of erroneous diagnosis of the disease. J. Formosan Med. Assoc. **48** (1949) 215-220.

Pointing out the wrong to the individuals and their families when leprosy is erroneously diagnosed the author describes, with photographs, cases of ulcerative tertiary syphillis, pruriginous pemphigus, neurofibromatoses, lupus, and gout—the last in a 70-year-old day worker. [The reviewer does not recall having seen gout mentioned in this connection in the literature, and is reminded of two cases of it in Igorotes of the Mountain Province sent to Manila so misdiagnosed nearly thirty years ago.] —H. W. W.

LOWE, J. Treatment of leprosy with diamino-diphenyl sulphone by mouth. Lancet **1** (1950) 145-150.

This article commences with a short historical account of the synthesis of diaminodiphenyl sulfone (DDS, "DADPS" in the original) in 1908 and the discovery of its remarkable antibacterial and therapeutic effects in 1937. Although it was adopted for use in veterinary medicine, it was found to be too toxic for use in man and less toxic derivatives were developed, and until recently no attempt was made to use the simpler and cheaper parent substance in leprosy. In 1949 Cochrane started its use by

giving twice-weekly injections of 1.25 gm., but found toxic effects too frequent and serious to make this treatment widely applicable. To rationalize the use of DDS it was necessary first to find out whether the complex sulfones acted as such or after breaking down to that substance, either in the gut or in the tissues. It is regarded as well established that complex sulfones given in doses which produce blood-concentrations of the order of 5 mgm. per cent—and often less than that—are therapeutically active; that most of what is in the blood is not degraded to DDS and is therefore probably not active; and that the minimum therapeutic blood level of DDS itself in leprosy is perhaps 1 mgm. per cent or even less. A preliminary trial on 9 patients showed that by giving it by mouth that blood level could be reached without toxic effects and with remarkable benefit, and further work has led to the employment of a regimen beginning with 100 mgm. a day and slowly increasing to 300 mgm. a day, in 5 weeks, the treatment being continuous. This regimen does not produce toxic effects of any consequence and will maintain a blood level of about 1 mgm. per cent. The almost complete absorption from the gut and slow elimination by the kidney explain the relatively high blood levels attained with such small doses, and also the toxic effects caused by the much higher doses used by others. Slow induction of the treatment is of paramount importance in the avoidance of toxic effects. The results obtained in 88 cases so treated for periods up to 1 year are described. Of 50 lepromatous cases treated for more than 6 months none shows deterioration and 72 per cent show clinical improvement; 62 per cent have improved bacteriologically, and 3 have become negative. In the 15 tuberculoid cases treated for 4 to 10 months the response was apparent within a month and sometimes earlier, with complete subsidence of activity of the skin lesions within 6 months; nerve involvement has taken longer to subside. The results are similar to those obtained with other sulfones, but they appear to be more rapid. The cost of DDS per patient per year on this basis is 14/— i.e., about one-twentieth that of the proprietary sulfones. —G. O. TEICHMANN

WEISS, W. and BOGEN, E. The clinical toxicity of sulphetrone. American Rev. Tuberc. **62** (1950) 160-169.

Sulfone therapy of tuberculosis has been encouraging in experimental animals, but thus far remains discouraging in humans from the standpoint of both results and toxicity. Sulfones prolong life and diminish the extent of tuberculous infection in guinea pigs with little toxic effects except for splenic enlargement and cyanosis. On the other hand, the infecting organisms are not killed and the retarding effect disappears when the drug is withdrawn. In humans, the therapeutic effect is slight, and toxicity has been of such a degree as to militate against the use of sulfones except with extreme caution. The present study has confirmed the finding that what is true of previous sulfones is also true of sulphetrone. In guinea pigs, the combined use of sulfones and streptomycin yields better results than those achieved by streptomycin alone. Clinically, such treatment has been tried in a small number of cases. Sulfones in low dosage combined with streptomycin may produce better results than streptomycin alone and perhaps delay the emergence of streptomycin-resistant strains of tubercle bacilli. The use of sulphetrone is fraught with danger unless administration is cautious and subject to careful observation, with frequent checks on the sulphetrone blood concentration, hemoglobin concentration,

and urinalysis. Other less toxic agents with tuberculostatic properties, such as para-aminosalicylic acid, appear more promising as therapeutic agents. The toxic effects of sulphetrone in the treatment of human tuberculosis appear to outweigh any beneficial effects that result from the use of this drug. —AUTHORS' SUMMARY

DHARMENDRA. Two cases of leprosy treated with para-amino-salicylic acid. Lep. India **22** (1950) 4-5.

This is a short note on the experimental treatment of two cases of leprosy of the advanced lepromatous type with sodium para-amino-salicylate. The cases treated were strongly positive bacteriologically, and were subject to frequent reactions which in one of the cases were especially severe and frequent. The treatment was started with a daily dose of 20 gm., which had to be reduced to 15 gm. on account of intolerance, given in divided doses every 3 hours as a 20 per cent solution mixed with a flavoring agent. The treatment was continued for 30 weeks with occasional interruptions. The total dose given to each patient was about 3,000 gm. The blood concentration of PAS varied from 7 to 12 mgm. per cent. Both cases showed some clinical improvement, the reactions being less frequent and less severe than before, but there was no appreciable bacteriological improvement. —AUTHOR'S ABSTRACT

TOLENTINO, J. G. Synergistic action of chaulmoogra and sulfone drugs. J. Philippine Med. Assoc. **26** (1950) 315-318.

The author, not one of those who holds that chaulmoogra should be "discarded as useless, or junked as obsolete," has previously (unpublished report) observed that the sulfone drugs gave better and more impressive clinical results while chaulmoogra gave more rapid bacteriological improvement. The present report is of an experimental observation, over a period of 6 months, of three groups of cases treated as follows: (*a*), 153 cases, given chaulmoogra alone, purified oil or iodized esters, intramuscularly or intradermally; (*b*), 40 cases, given sulfone alone, diasone or promin; and (*c*), 33 cases, given chaulmoogra and a sulfone in combination. Considering only those cases who received at least one-half as much of the drugs as expected in the period of treatment, the results were:

Clinically improved:
- Chaulmoogra, 57 patients, 37%
- Sulfone alone, 27 patients, 68%
- Combination, 14 patients, 42%

Bacteriologically improved:
- Chaulmoogra, 66 patients, 43%
- Sulfone alone, 12 patients, 30%
- Combination, 19 patients, 58%

It is concluded, subject to verification with more cases and over a longer period of time, that sulfone therapy gives the best clinical but the poorest bacteriological results, and that the combined treatment gives the best bacteriological improvement and better clinical improvement than chaulmoogra alone. The hastening of bacteriological improvement is regarded as an especially important advantage, in a feature where the results of sulfone treatment seem anomalous and most discouraging to the patients. Why the combination should be less effective clinically than sulfone alone

is not apparent, and the author hopes that this apparent discrepancy will be resolved in the future. At any rate, chaulmoogra is regarded as far from being the obsolete drug that many regard it to be, especially in the elimination of bacilli from the lesions. —H. W. W.

JOHANSEN, F. A. and GRAY H. H. The modern treatment of leprosy. Med. Woman's J. **56** (1949) 19-24.

This article is a clear-cut summary, obviously written for an audience quite unfamiliar with the subject and strictly from the Carville point of view. In a long experience with chaulmoogra some improvement had been seen, and a few cases had been discharged as bacteriologically negative, but chaulmoogra drugs were abandoned in 1947 in favor of the sulfones. Work with promin was started in 1941, with diasone—at Carville—in 1943, and with promizole—the manufacture of which has been discontinued—in 1945. Anemia is mentioned as the most frequent toxic manifestation; and it is also said that, although severe granulocytopenia had not been observed, therapy should be discontinued temporarily if the white cell count falls below 3,000. Erythema nodosum reaction, and less commonly erythema multiforme, occur in 90 per cent of the patients after 3 or 4 months of treatment with sulfones. Promin has the effect of eliminating bacillary infection from the blood stream and small blood vessels, whereby the formation of new lesions is prevented. —H. W. W.

GRILLO, J. Ueber die Wirkung des Streptomycins auf Lepra. [The action of streptomycin in leprosy.] Ztschr. f. Hyg. u. Infektionskr. **127** (1948) 588-591.

This is a report of the successful treatment of an advanced lepromatous case of leprosy by streptomycin. The drug was first given in daily doses of 2 to 3 gm. and produced a strong febrile reaction with deterioration in all the skin lesions, which increased in size and became softened, while bacilli in the nasal mucus and the lymphatics appeared to be increased in numbers. The reaction lasted ten days and was followed by definite and progressive improvement, with steady retrogression of the lepromas and gradual healing of suppurating ulcers, and favorable effects with respect to all the other symptoms of the disease. After a total of 300 gm. had been given the daily dose was increased to 4 gm., then reduced to 3 and 2 gm. The intervals between the injections were from 4 to 6 hours. The total amount given was 360 gm. The toxic symptoms noticed included slight febrile reactions, skin eruptions, nausea, giddiness, and albumin and casts in the urine, but they were not sufficiently severe to necessitate interruption of treatment or decrease in the dosage. The deterioration in the lesions during the early strong reaction was followed by steady fading of the reactionary symptoms and substance of the lesions, until after three months a majority of the lepromas had completely disappeared. The bacilli showed changes in morphology and staining properties, gradually losing their acid-fastness, so that at the end of the treatment only exceptional, weakly-staining involution forms were evident and they were very difficult to stain, which is regarded as due to protoplasmic changes.—[From abstract in *Trop. Dis. Bull.* **46** (1949) 749.]

ELLIOTT, D. C. Effects of aureomycin in ocular complications of leprosy. American J. Ophth. **33** (1950) 1029.

Favorable reports of rapid improvement in several forms of conjunc-

tivitis and keratitis following the use of ophthalmic aureomycin solution prompted the author to try this treatment in some of the complications associated with leprosy. Thirty patients were treated by the installation of aureomycin hydrochloride ophthalmic solution, administered twice daily in the clinic, followed by the instillation of aureomycin ointment by the patient before retiring at night. The progress was compared with that of a control group of 20 patients who received the routine daily mercurial and boric-acid eye washes. Cultures from the eyes were made on a total of 50 patients (30 being treated with aureomycin and 20 controls not treated with that substance). The secondary invading organisms found were Gram-positive *Bacillus subtilis* in pure culture, *Staphylococcus aureus* in pure culture, a Gram-negative bacillus of the proteus group, a Gram-negative bacillus of the aerobacter group, and several forms of yeasts. Three tables illustrate the cases and the culture results before and after treatment. The author feels that improvement followed the use of aureomycin ophthalmic solution, and that many of the harmful effects which follow secondary infections in leprosy patients can be prevented if the eyes can be kept relatively free from invaders. —F. A. JOHANSEN

JOSEPH, W. F. Massage in leprosy. Lep. India **21** (1949) 179-180.

The author holds that massage is helpful not only in preventing the development of deformities but also, to a certain extent, in correcting those which have occurred, especially when this measure is supplemented by the judicious splinting of fingers. It also helps absorption of infiltrates in the skin and nerves. For the extremities he advises the usual three types of movements, viz., effleurage, petrissage and topotement; and hydnocarpus oil with 1 per cent iodine is advocated as an embrocation during the massage. For the body, only effleurage is recommended. The massage is followed by a warm bath or cold sponge. —DHARMENDRA

SMITH, M. A pharmacological study of three sulphones. Part II. Hydrolysis and the specific toxic phenomena. Lep. Rev. **20** (1949) 128-134.

In Part I of these studies, reviewed earlier [THE JOURNAL **18** (1950) 122], the writer showed that diaminodiphenyl sulfone possesses definite advantages over the proprietary sulfones in the matter of absorption and persistence in the body as well as in its cheapness. In the present article he describes experiments undertaken to estimate how far the action of the proprietary sulfones is due to a breaking down of these drugs in the body into the parent substance. Should the breakdown be complete, on a molecular basis a daily dose of 6-8 gm. of sulphetrone, which gives a blood level of 5 mgm. per cent, is equivalent to a daily dose of 0.2-0.3 gm. of DDS, which gives a blood level of 1 mgm. per cent. Actually the breakdown of sulphetrone is much less, although the fact that DDS can be extracted from the urine of patients receiving the proprietary sulfones shows that there is partial hydrolysis of them in the body. No information is available at present as to the optimum blood levels of any of the sulfones with respect to therapeutic results. Recent work has shown that extremely small doses of DDS, i.e., 0.05 gm. every other day, giving blood levels of less than 0.1 mgm. per cent, produce good results. In this article, also, is begun a discussion of the toxic effects of sulfones, with respect to the anemia produced. It is concluded that it is not one of simple hemolysis, although—not generally realized—the anemias may differ quantitatively with the type of sulfone used and the mode of administration. With sulphe-

trone, properly administered, the anemia produced is usually not severe. It is hypochromic in type, and evidence of marked hemolysis has not been found. Diasone tends to produce rather more anemia, and with doses above 2 gm. a day there is evidence of definite hemolytic effect. With DDS in the doses used (0.2-0.3 gm. daily) the anemia, although of hemolytic nature, is of a mild and self-correcting type. With parenteral administration of a dose of diasone equivalent to the oral dose (e.g., 0.7 gm. daily against 1.5 gm.), the degree of anemia produced is of nothing like the same degree; and the same holds true for sulphetrone. In short, if one gives parenterally the amount of a sulfone calculated to be equivalent to the amount absorbed after oral administration, no significant degree of anemia is produced. —G. O. TEICHMAN.

SMITH, M. A pharmacological study of three sulphones. Part III. The specific toxic phenomena. Lep. Rev. **21** (1950) 17-29.

This article begins with a continuation of the discussion of the blood dyscrasias [see preceeding item]. An effort is made to discover how far a direct toxic hemolysis is responsible for the sulfone anemias, and it is concluded that evidence for a hemolytic process is clear-cut only in the case of DDS, in doses greater than 300 mgm. daily, although it is also seen with diasone above 2.4. gm. a day. The anemias actually produced are regarded as dyshemopoietic in nature. No significant changes have been seen in the white-cell blood picture, nor has methemoglobin been encountered in 50 examinations. The rest of this article has to do with (1) liver function, not found to be affected by the sulfones, so that even in the case of patients with liver dysfunction prior to treatment—which was very commonly the case in Nigeria—sulfones should be given; (2) kidney function, the main point being that no cases of crystalluria, hematuria or anuria have been encountered; and (3) a pharmacological report on diaminodiphenyl sulfone. In this last section a report of data on 6 cases studied experimentally ends with the statement that rapid exhibition of the drug is strongly contraindicated because it induces higher blood levels than usual and toxic manifestations including methemoglobinemia with frank jaundice, effects which do not occur when the drug is exhibited slowly.
—G. O. TEICHMANN

RELWICZ, A. L. Some experiments with injected sulphetrone. Lep. Rev. **20** (1950) 30-34.

Tests were made to see whether appropriate blood levels could be maintained by giving sulphetrone subcutaneously. It was found that 4 hours after giving 7-10 cc. of a 20 per cent aqueous solution, blood levels averaged only 5.5 mgm. per cent, which was judged too low for effective treatment. After 72 hours practically all of the drug had been eliminated. Further tests were done with 33 per cent solutions. The rate of absorption was found to be directly proportional to the strength of solution. Adequate blood levels were reached during the first 24 hours but fell on the second day to 3.5 mgm. per cent. Daily injections of 5 cc. would therefore keep up the necessary blood concentration for treatment, but it would be unbearable to the patients to have such daily injections made for years. It is therefore suggested that if, for financial reasons, patients could not be given the drug orally they might have the injections on alternate days.
—G. O. TEICHMANN

SIMPSON, I. A. and MOLESWORTH, B. D. The fate of injected 4:4′ diamino diphenyl sulfone in humans and guinea-pigs. Lep. Rev. **21** (1950) 5-16.

A technical article giving full details of methods used for estimating the amounts of sulfone present in the tissue and urine in guinea-pigs and humans receiving sulfone injections, to be studied in the original by those interested. The tests seem to show that a labile conjugated form of sulfone is formed in the body and that this compound is decomposed, liberating the unchanged sulfone in the presence of dilute acid or alkali.

—G. O. TEICHMANN

GOMES, J. M. Ação do promin, in vitro, sobre mycobacteria isoladas de lepromas humanos. [Action of promin *in vitro* on mycobacteria isolated from human leproma.] Arq. mineiros Leprol. **9** (1949) 9-16.

Continuing studies on the morphology of mycobacteria [see THE JOURNAL **16** (1948) 298], cultures of acid-resistant bacteria isolated from human and murine lepromas were submitted to the action of promin, in tubes of 5 per cent glycerinated broth, in various concentrations more or less like those found in the blood of patients undergoing treatment. There was no formation of membrane, but the germs maintained viability for more than 30 days. When transferred to Petragnani's medium all developed, those exposed to the larger amounts of promin taking longer than the others. Smears of material from the promin media stained by Ziehl-Neelsen showed profound alteration of morphology, most marked in the tubes with the most promin. In the growths on Petragnani medium the bacilli showed much dark granulation, regarded as a morphological expression of promin resistance. In the therapeutic doses employed the drug is bacteriostatic; with higher dosage a bactericidal effect was obtained. The practical significance of these observations is discussed.—[From author's summary.]

DHARMENDRA and MUKHERJEE, N. Intradermal reaction with lepromin inside and outside the leprous macules. Lep. India **22** (1950) 5-10.

A detailed study is reported of the results of lepromin test both inside and outside the macules of leprosy of the different types. Dharmendra's refined lepromin was used and the results were read 24 hours after injection. In the lepromatous cases no marked differences were seen in the reactions inside and outside the patches, the reaction being usually negative. The thickness of the patch does not influence the degree of reaction. In a majority of the neural cases the reactions were stronger inside than outside the macules, though in a few cases the reverse was seen. In these cases the thickness of the patch appreciably influenced the degree of reaction, the thicker the patch the stronger the reactions.

—AUTHOR'S ABSTRACT.

ROSEMBERG, J., SOUZA CAMPOS, N. and AUN, J. N. Da relação imunobiológica entre tuberculose e lepra. I. Ação positivante do BCG sobre a leprominoreação. [Immunobiological relation between tuberculosis and leprosy. I. Induction of the positive Mitsuda reaction to lepromin by BCG.] Rev. brasileira Leprol. **18** (1950) 3-23.

This report is the first of a series concerning the immunobiologic relation between tuberculosis and leprosy. It deals with the induction of positivity to lepromin by oral administration of BCG in inmates of one

of the institutions for children of leprous parents in the State of São Paulo. The 39 children involved, aged 1 to 18 months old, had been separated from their parents at birth and were all negative to the Mantoux tuberculin test (1:10 dilution) and to lepromin. Group A, 12 children, received a single dose of 0.10 gm. of BCG 40 days after having been tested with lepromin. Nine became tuberculin sensitive, and in 8 of them the lepromin reaction turned from negative to positive between the 70th and 112th days. In the 9th case, despite the induced tuberculin allergy, the old Mitsuda test did not turn positive; nor did that occur in the 3 cases which did not develop tuberculin allergy. These 4 Mitsuda-negative cases were given a second test with lepromin 49 days after the BCG vaccination, with equally negative results. Thus 66.6 per cent of this group became reactive to lepromin because of the BCG vaccination. Group B, 27 children, received daily, progressive doses of BCG for 28 days, reaching a total of 1.19 gm. The Mantoux test became clearly positive in 24, and doubtful in 3. Of this group 25 (93%) showed change from negative to positive of the lepromin reaction which, as in the first group, had been performed 40 days before starting vaccination. A second Mitsuda test, performed 23 days after the end of the vaccination, showed positive results in all cases, including those which had not shown activation of the test made before the ingestion of BCG. Thus this group showed 100 per cent induced positivity. Attention is called to the close concordance of this reaction with the Mantoux test. Of the 39 children treated, 36 became reactive to tuberculin (33 clearly so and 3 doubtfully), and of these 36 all but 1 proved lepromin positive, whereas the 3 which remained tuberculin negative also remained negative to lepromin. Thus, a definite discordance between the two tests has been observed in only one case, in which the Mantoux reaction was positive whereas the Mitsuda test remained negative. In connection with the probable relation between these two reactions, there is an apparently contradictory aspect of their concordance and parallelism since the tuberculin reaction, in tuberculosis, expresses a state of allergic hypersensitiveness, whereas the lepromin reaction, in leprosy, expresses a state of immunity or resistance. This matter will be returned to in future contributions. The fundamental fact of immediate practical interest is that oral BCG vaccination induces Mitsuda positivity in young children. This is a further demonstration of the capacity of absorption of the BCG through the digestive tract and of the efficiency of the technique of oral calmetization. In view of the present concept of the significance of the positive lepromin reaction, with respect to resistance to leprosy, the authors believe that vaccination with BCG, to be performed during the first days of life, should be recommended for all children of leprous parents as a prophylactic measure.—[From authors' summary.]

LEIDER, M. and SULZBERGER, M. B. Studies in the allergy of infection. I. Response of the skin to BCG vaccination in various categories of tuberculin sensitivity. J. Invest. Dermat. **13** (1949) 249-264.

The authors recall first the trend of frequencies of positive tuberculin reactions in a modern city population, from very few in individuals under 2 years of age to a significant majority in those between 20 and 40 years, and a somewhat smaller proportion in older people. They then point out that, whereas there is one essential kind of positive reactivity (with three grades, normal, high and low), there are three established kinds of non-

reactivity or anergy: (*a*) the "natural" (or innate, or inherent) anergy of the preinfected ("aboriginal") state; (*b*) the "negative" (or nonspecific) anergy of the febrile, cachectic, etc., states; and (*c*) the "positive" anergy, that insensitivity which is a specifically acquired alteration of capacity to react seen in sarcoid cases. The first and the last of these types of anergy may be differentiated by the course of events after intracutaneous inoculation of BCG vaccine. Little precise information is obtainable about what happens in the "natural" (preinfection) type after such vaccination, but evidently it is a replica of the first (or infection) part of Koch's fundamental experiment. Equally unsatisfactory is the literature with respect to what happens in tuberculin-positive individuals, but from information gathered and reactions actually observed it is clear that it is the abrupt, ulcerative "Koch phenomenon"—the accelerated second, or reinoculation, stage of his fundamental experiment. The course of events in cases with "positive" anergy (sarcoid) is something quite different, as was reported by Lemming (1940, 1942) and by Warfvinge (1943). After a latent period of 5-7 days there appears a slowly-growing papule which tends to last indefinitely as a papule or plaque and presents both clinical and histological characteristics of sarcoid. The individuals do not become tuberculin positive with this development, nor does repeated vaccination induce any change in the form of the reaction. (In one of the authors' cases revaccination was done once, in two 3 times, and in one 5 times.) Possible mechanisms of this peculiarity of response are postulated, but they are not discussed in any detail.

In the discussion of this paper, CORNBLEET suggested that the persistence of tuberculin negativity after the appearance of the BCG lesions in sarcoid cases suggests the existence in that syndrome of a special immune state which suppresses a reaction to tuberculin in the presence of infection with the tubercle bacillus. BERNSTEIN spoke of the introduction of BCG tests for reason of diagnosis as of great importance. SULZBERGER, remarking that this work is just a beginning in a vast field, said that sarcoid cases due to syphilis which they had tested had shown an accelerated response and not the one characteristic of "idiopathic sarcoidosis"; in the latter there is what corresponds to the "immune response" to vaccinia, namely, "a very torpid, non-acute, foreign body-type of reaction." Further work planned includes the study of "leprous and other sarcoids." —H. W. W.

LEIDER, M. and HYMAN, A. B. Studies in the allergy of infection. II. Histologic responses of the skin to BCG vaccination in various categories of tuberculin sensitivity. J. Invest. Dermat. **14** (1950) 459-470.

The first article of this series [see preceding item] dealt with the different reactions to intradermal injection of BCG shown by individuals with various conditions of reactivity to tuberculin (i.e., the natural anergy which exists before infection; the normal allergy of infection; the negative, nonspecific anergy of febrile diseases or cachectic states; and the acquired, positive anergy or relative hypoergy of specific nature such as is seen in sarcoid), and emphasis was given the distinctive delayed and persistent lesion induced by BCG in the last of these conditions. The present article discusses firstly the phases of the tissue reaction to tuberculous infection of normal animals and man, beginning with banal inflammatory and progressing to tuberculoid changes with necrosis, and secondly the reaction

in tuberculin-positive individuals, which is described as an "accelerated replica" of the other with consequent earlier appearance of the tuberculoid structure. Regarding the reaction in acquired positive anergy characteristic of sarcoid, a little-studied matter, the authors have confirmed the findings of Scandinavian investigators and believe that their diverse and contradictory conclusions can be reconciled in a "unitary immunologic formulation." The nonulcerating papular or nodular lesion produced in such cases shows essentially and predominantly tuberculoid structures ("proliferative, productive and infiltrative with epithelioid cells"), with a certain amount of banal inflammation but without suggestion of necrosis, the whole being strongly like the changes of sarcoid disease itself. It may well be, it is held, that the allergenic fractions of the BCG vaccine responsible for sarcoid pictures are something different from those which evoke the necrotizing reactions of tuberculin sensitivity. [According to a personal communication, a third article will present a synthetic unitary theory of the allergy of infection as it applies to all of the granulomatous diseases.] —H. W. W.

DHARMENDRA and MUKERJEE. Effect of sunlight on the staining properties of the leprosy bacillus. Lep. Rev. **20** (1949) 111-114.

[This was a Havana Congress article, published in full in the *Memoria* of the Congress, pp. 689-692, and abstracted in THE JOURNAL (**16** (1948) 298).]

CUTTINO, J. T. and MCCABE, A. M. Pure granulomatous nocardiosis: New fungus disease distinguished by intracellular parasitism. Description of a new disease in man due to hitherto undescribed organism, *Nocardia intracellularis*, n. sp., including a study of the biologic and pathogenic properties of this species. American J. Path. **25** (1949) 1-48.

Report of the case of a 34 month old girl whose illness began with anorexia, nausea, vomiting and progressive loss of weight about 4½ months before her death. Shortly after the onset a mass, thought to be a lymphosarcoma, was noted in the abdomen. High voltage roentgen therapy caused an unfavorable reaction. An enlarged inguinal node removed during an exploratory operation showed complete alteration of its architecture with proliferation of foamy and granular macrophages resembling Gaucher's cells. Lipodystrophy was considered, but the Ziehl-Neelsen stain demonstrated that these cells contained massive numbers of an acid-fast, bacilliform organism, which was isolated in pure culture. Proctoscopic examination revealed irregular ulcers, a biopsy of which showed proliferation of macrophages containing many acid-fast organisms. The patient grew progressively weaker despite supportive measures and died. The morphologic, cultural and biochemical characteristics of the etiologic agent led the authors to designate it as a new species to which the name *Nocardia intracellularis*, n. sp., has been given. The disease produced by it in man is a pure form of granulomatous inflammation, characterized by phagocytosis of the pathogen by reticulo-endothelial cells and proliferation of these cells. In the spleen and lymph nodes the proliferation of macrophages is of such proportion as to displace completely the normal structure. In guinea pigs, rats and mice a nonlethal disease is produced, with changes which differ sharply from those in man.—[From abstract in *J. American Med. Assoc.* **140** (1949) 837.]