TREATMENT OF LEPROSY

A REVIEW

By Ernest Muir

Working under the School of Tropical Medicine and the Indian Research Fund Association, Calcutta

INTRODUCTION

It is only recently that leprosy has been included in the list of remediable diseases, and there are still some physicians who are sceptical as to the benefits of treatment. There are two main reasons for this scepticism. One is that many advanced patients, because of their weakness and debility, cannot hope for improvement; other patients have abandoned hope and their mental attitude is an insuperable obstacle; there are others again in whom the disease has practically died out but has left only deformities and scars, and these permanent trophic effects still label them as lepers. These hopeless types are in some ways the most conspicuous, and failure to distinguish them from the cases that will respond to treatment has been largely responsible for the scepticism referred to.

The other reason is that leprosy is an exceedingly difficult disease to treat. The best results can be obtained only by a thorough understanding of the disease, and careful and continuous study of each case. Most of those who decry the treatment have dealt with only a few cases, often belonging to the hopeless ones; or they have been content to give a few injections of some special drug, failing to realize that the general treatment of the patient is of far greater importance and requires much more skill and experience.

The more effective the treatment of any disease becomes, the shorter and simpler is its description. For leprosy no highly effective or specific remedy is yet available, hence the multiple forms of treatment advocated by various workers. In this paper we review the more important of the remedies and methods recommended, especially within the last thirty years. Next, under the heading, Evaluation of Treatment, are discussed various fallacies and certain essentials for estimating the value of any drug or method of treatment. Lastly, we enunciate certain general principles and give in detail definite lines of treatment which we believe to have been proved by the widest use and in the hands of the most experienced workers to be the most effective at present available.

REVIEW OF LITERATURE

VACCINE AND SERUM INOCULATION

Various attempts have been made to treat leprosy through immunity production by injections of bacillary suspensions, sera, etc.

Autogenous vaccines have been used by many workers, but most of them have treated only a few cases. Scholtz and Klingmüller (217) injected the juice expressed from leprous nodules. Wooley (255) and N. Walker (242) used graded doses of heat-killed leprosy bacilli from ground-up nodules; the latter reported promising results in the one case treated. Nicholls (168) incubated a subcutaneous nodule in broth for 14 days, dessicated and ground it, and made a suspension which he killed by heat.

J. T. Wayson (243) produced bullae over lesions with carbon dioxide snow and aspirated, iodinized and re-injected the fluid, which he called "iodinized autogenous serum." Hasson (82) obtained bacilli from blister fluids similarly produced, incubated them for periods up to 3 months, and added a mixed culture of *B. pyocyaneus*. He, and also Little (123), reported excellent results with this suspension, but others obtained no benefit with it. Devoto (54) separated bacilli by treating triturated nodules with antiformin, and reported that in 2 out of 3 cases treated the bacteriological examination became negative while the third case improved. Callens (21) prepared a bacillary suspension by triturating leprous nodules with 60 per cent alcohol and glycerine in equal parts and centrifuging; the supernatant fluid was used subcutaneously, in combination with chaulmoogra esters.

One drawback of this form of treatment is the work required in obtaining the suspensions, especially when large numbers of patients have to be treated. It is obviously applicable only to far-advanced cases, unless nodules from such cases are used for the treatment of other patients without bacillus-rich nodules.

Tubercle bacilli and tuberculin.—Tuberculin has been used in leprosy because of the resemblance of the bacillus of tubercle to that of leprosy. Danielssen (34) treated 14 lepers; general and local reactions resulted and the ultimate effect was to aggravate the condition. Goldschmidt (73) treated 16 cases, which after temporary improvement became stationary or worse. Truhart (232) treated 6 lepers; ulcers healed promptly. Babes (12) found tuberculin dangerous, but later (14) decided that small doses with chaulmoogra oil

effected remarkable improvement. Arnaud (11) obtained improvement in 2 cases treated. Lie (122) considered that small doses gave encouraging results, and De Novaes (49) obtained good results in 2 out of 3 cases.

Row (208) used suspensions of autolysed cultures of tubercle bacilli washed free from fatty substances with petrol ether, the preparation requiring several months. He and others reported favorable results by this method; apparently the dangerous effects reported with the use of tuberculin are absent.

Girard and Ducros (72) reported negative results in 6 cases with the methylic tuberculosis antigen of Negre. Jouenne and Guillet (99) reported improvement in 2 cases after injecting doses of 0.02 gm. of the Calmette-Guerin antigen (B.C.G.), though abscesses resulted at the sites of inoculation. Delanoe (38, 39) got rapid improvement in 2 cases with B.C.G. intramuscularly and novarsenobenzol intravenously. On the other hand Souchard (223) and Remlinger and Bailly (190) did not obtain lasting improvement with B.C.G.

Other acid-fast organisms.—Various other acid-fast organisms and their products or extracts have been inoculated by various workers. Some of them considered that the organisms used were true cultures of the Hansen bacillus, and hoped to produce a specific active immunity. Others aimed rather at producing a group-immunity that might affect the leprosy bacillus.

The most widely known preparation was the "nastin" of Deycke (56). This consisted of a killed suspension of an acid-fast organism cultivated from a leprous nodule. A mixture of this with benzylchloride was called nastin B. Numerous reports appeared of favorable results with this preparation, e. g., Kupffer (103), Rodriguez (193), Smith and Bisset (221), Davidson (36), Raschid (189), Scott (218). On the other hand the majority of those who tried nastin either obtained no results or declared that there was no permanent improvement, among them being Lenz (118), Thompson (228), Teague (227), Peiper (182), Brinckerhoff and Wayson (19), Gordon Messum (140), Wise and Minett (251). The last-named, who carried out an experiment begun by Deycke himself, summarized the results of four years' experience of nastin treatment (244 cases) by saying that there was a slight temporary check to the disease during the first 6 months, but that otherwise the disease continued unchanged.

Rost (207) prepared a supposedly tuberculin-like substance, "leprolin," from an acid-fast culture obtained from leprous material, and several workers claimed favorable results with it. However, Rutherford (211) reported negative results, and it was shown later that Rost's culture was a contaminating organism.

Currie, Clegg and Hollmann (32) also attempted to produce active immunity with substances prepared from their supposed culture of the leprosy bacillus: (a) vaccine, killed bacilli; (b) vaccine, sensitized; (c) suspension, living bacilli; (d) "lepratoxine", an extract like Koch's T.O. and T.R.; (e) extracted fatty substances. They obtained no favorable results. Other attempts at treatment with cultures of acid-fast organisms have been made by various workers, but their results are similar to those quoted.

Markianos (131) digested rat leprosy bacilli with pepsin and pancreatin, washed them with water and alcohol, and defatted them. Suspensions of these organisms injected into a patient caused a sterile abscess, which was followed by some improvement in the patient.

There seems no doubt that favorable results have been obtained with many of these substances in certain patients. We shall consider the significance of this form of treatment later.

Sera, and autohemotherapy.—Various attempts have been made to produce an immune serum by injecting into horses material from lepers or supposed cultures of lepra bacilli. Carrasguilla (23) used lepers' blood and claimed complete success in 15 patients with the serum produced, but investigation by other workers showed that his claims were without foundation. Abraham and Herman (1) injected a horse with fluid contents of nodules, but obtained no favorable results in the two cases that were given the serum produced. Laverde (115) inoculated sheep and goats with the juice of nodules; sixty patients injected with the serum of these animals are said to have shown improvement, and six to have been cured. Currie, Clegg and Hollmann (32) used their culture in horses, but the serum obtained gave no encouraging results.

Dyer (60) treated 5 cases with antivenin with marked improvement in 4 cases. However, Woodson (254) after obtaining improvement in one case by a similar method, considered that the result was due to the serum alone.

Sezary (219) inoculated seven cases of leprosy subcutaneously and intravenously with their own blood, 5 to 10 cc. being given at a time. Subjective symptoms and pain are said to have decreased.

Bee-stings.—Rangel (187) reported appreciable improvement in a patient after subjecting him to bee-stings 20 to 200 at a time. Gancher and Boinet (71) treated a case for 40 days with bee-stings and salvarsan; the results were favorable, though the lesions did not disappear. This seems hardly above the category of folk treatment by cobra bites and scorpion stings, which merit no attention here.

Protein shock.—It has to be considered to what extent the good effects of the various vaccines, sera and other substances mentioned above are due to protein shock. Muir, Landeman, Roy and Santra (165) injected Kedrowsky's bacillus intravenously to produce protein shock, with favorable results. Kerr (100) also used this suspension and found that reactions lasting 48 hours produced much improvement. Manson-Bahr (129) gave Hasson's vaccine intravenously in one case and typhoid-paratyphoid vaccine in another with excellent results; he believed the benefit due to protein shock. Many others, including ourselves, have obtained improvement with intravenous injections of bacterial vaccines, milk and other protein-containing substances. The general condition of the patient is frequently much improved by such injections.

CHAULMOOGRA OIL

General.—Chaulmoogra or hydnocarpus oil has long been known as a remedy for leprosy in India and other countries. This is derived chiefly from the seeds of *Taraktogenos kurzii* from Northeast India and Burma, *Hydnocarpus wightiana* from Southwest India and *H. anthelmintica* from Siam and Indo-China. Recently *H. wightiana* seeds have been planted in different parts of Africa, South America and elsewhere. Among related oils is that from *Carpotroche braziliensis,* of South America [Horta (50), Coelho (28)].

Formerly chaulmoogra was used only by mouth or inunction, but during the last twenty or thirty years more favorable results have been obtained by injection. When injections were first used the oil was found exceedingly painful, irritating and slow of absorption. Largely on this account various emulsions and other preparations were contrived to overcome these difficulties. Later it was found that if the oil is prepared from fresh, ripe seeds the irritating factors are much reduced, so that the oil itself can satisfactorily be given intramuscularly, subcutaneously and intradermally. The question of absorbability is an important one. Pautrier, Descaux and Rabream in 1914 (181) reported that after injecting 60 cc. intramuscularly

during four months, they were able to spirate 50 cc. one month after the last injection. However, this has not been the general experience, and some workers have had complete absorption of amounts up to 20 cc. a week over long periods.

Oral administration.—Hansen and Looft (77) wrote of giving chaulmoogra oil in milk, without effect. Crocker, writing in 1900 (30), considered it valuable when the patient could take at least 100 minims a day. Leboeuf (116) gave it in emulsion, capsules and salads, and injected it when not tolerated orally; he found a variation in the samples. Heiser (86) found that nausea always was produced after a few months. Unna (234) considered the prognosis best in those cases which could stand large doses internally. Wilson (249) alternated injections with oral administration, giving 60 minims three times a day. Defillo (37) gave up to 100 drops, preceded by a tannic acid mixture, and Denney (46) gave up to 375 drops daily. Wayson and Badger (244) recommended an emulsion of chaulmoogra esters with cod liver oil. The fullest test on record appears to be that of Hopkins (96) who in fifteen years' treatment with the oil orally obtained cure or improvement in 45 per cent of 82 incipient cases, and improvement in 21 per cent of 88 advanced cases.

Travers (230) used a Chinese form of treatment consisting of *H. anthelmintica* seeds 3 parts, *Cannabis indica* 1 part, and *pak chut lai* (a demulcent Chinese seed) 1 part. Rogers (198) recommended pills of sodium hydnocarpate (higher melting-point fatty acids), giving 20 grams and upwards daily, but De Mello (42) failed to obtain good results with these pills. According to Levy (119), Unna's treatment included hydrolysed chaulmoogra oil taken in pill form, 10 pills of 0.15 gm. each being taken three times daily after food.

In many instances the above-mentioned forms of medication were combined with injections and other kinds of treatment, so that it is difficult to apportion the benefit derived.

Injections of chaulmoogra mixtures.—Heiser (86) and Mercado (139) reported good results from the use of the Mercado mixture—which consisted of chaulmoogra oil 60 cc., camphorated olive oil 60 cc., resorcin 4 gm.—and other workers had similar results. Stevenel (224) made an emulsion of the oil with normal sodium hydrate solution (5 cc. in 150 cc.) and reported that in two cases in which this was used nodules disappeared. Lamoureux (107), using the same emulsion, produced a quiescent state which lasted for 2 years. Harper (78, 79) reported from the Fiji Islands on the intravenous use of a

mixture of chaulmoogra oil and ether, equal parts, with 0.1 per cent iodine; of 265 cases treated 28 improved, 195 were unchanged, and 31 became worse. Heggs (83) found that with this treatment improvement stopped before nodules and bacilli had disappeared, though an occasional case improved greatly.

Esters of chaulmoogra oil.—McDonald (136) in 1920, reporting from Hawaii on the use of ethyl esters of chaulmoogra oil prepared by Dean, stated that in two years 78 patients had been dismissed, apparently cured. Later McDonald and Dean (138) reported results obtained with ethyl esters of fractions of the oil; on the whole better results were obtained with the hydnocarpic fraction than with the chaulmoogric. De Langen (41) after a visit to Hawaii was sceptical whether real cures had been obtained.

Rodriguez (195), reporting in 1925 on what is the largest experiment in the treatment of leprosy that has ever been known, that at the Culion Leper Colony, states that the iodized ethyl esters continued to be best, with 77.3 per cent improved, the creosoted preparation being almost as good. Both were considerably better than the plain esters or the Mercado mixture; the latter was preferable in cases complicated with nephritis, but the former had been given up because of irritation. He found the higher alcohol esters less efficacious than the ethyl ones. Lara (111) reporting in 1930 on the continuation of this work, states that since 1921 about 80 per cent of 8,520 cases have been treated intensively, chiefly with iodized ethyl esters. In recent years a better diet has improved the nutrition of the patients and helped treatment. Between 1922 and 1929 a total of 1,355 patients—19.6 per cent of all treated cases—had been paroled (i. e., discharged as having remained negative bacteriologically for 6 to 24 months) while 480 more negative (quiescent) cases were waiting for their discharge, this making a total of 27.1 per cent of the treated cases. Yet from 1906 to 1921 only 47 negative cases had been released under former treatments, 46 of these having been under the Mercado method.

It should be noted that the relative values of the iodized ethyl esters and the Mercado preparation are not to be judged by these discharge figures. During the latter nine years a much larger proportion of the patients were under treatment, this was carried out much more efficiently, and at the same time the diet of the patients had considerably improved. Also the introduction of the intradermal method, as reported by Lara (110) and to be described later, is supposed to have considerably accelerated recovery. Probably a truer relative value would be that given by Rodriguez (195), an improvement of 77.3 per cent with iodized esters as compared with 60.3 per cent with the Mercado preparation.

On the other hand Pierini (183), after treating 64 cases, half with esters and half with the Mercado formula, ascribed the better results to the latter.

The intradermal method has also modified to a certain extent the relative values of the oil and the esters, for the Calcutta workers [Lowe (127)] find that the oil with 4 per cent creosote when given intradermally may produce less irritation and induration than the esters. Also, with the intradermal method slow absorption may be an advantage, as the local action on the leproma is continued for a longer time.

Sodium hydnocarpate.—Rogers (197) published in 1916 an account of the treatment of leprosy with sodium gynocardate[1], reporting very favorable progress and stating that the most striking phenomenon was the occurrence of reactions sometimes accompanied by fever, and later (199) reported that all lesions had disappeared in 9 cases out of 15 treated. He considered the higher melting point fatty acids of chaulmoogra oil (49°-62°C) to be more active than those of lower melting point (37°C), and such a preparation (under the proprietary name of "alepol") is extensively used.

Sodium hydnocarpate is soluble in water and can be given in solutions of 1 to 2 per cent intravenously, intramuscularly, subcutaneously and intradermally. Given intravenously it is apt to cause endophlebitis and blocking of the veins, unless used very dilute, or unless the solution is mixed with an equal quantity of blood before injection [Muir (149)].

Many workers report satisfactory results with this drug, some preferring it to the oil or esters [Welch (245), Dikshit (57)]. The latter writer diminishes its haemolytic action by dissolving it in Locke's solution. On the other hand Lara, de Vera and Eubanas (112) tried sodium hydnocarpate intravenously in 7 moderately advanced cases, but after six months saw neither improvement nor retrogression, and Eubanas (65) considers that his results did not confirm the claim of Rogers (202) concerning its effectiveness. Given intradermally, it does not appear to be as effective as the esters in clearing up skin lesions [Muir (159)]. Nolasco (170) found that its intradermal injection caused thrombosis of the subcutaneous vessels even when it is buffered, and considered it unsuitable for intradermal administration.

In the Philippines the iodized esters are chiefly used, and in Japan the oil and esters. In India and Malaya the oil and esters with 4 per cent creosote are in most common use. But in many other

[1] At that time the term "gynocardate" was mistakenly used for "hydnocarpate".

parts of the British Empire sodium hydnocarpate is preferred, partly on account of its small bulk and ease of transport.

Fractions of chaulmoogra oil.—Rogers (198, 201) found, as stated, that the sodium salts from the higher melting point fatty acids were more effective than those from the lower, and later (201, 203) decided that alepol is more effective and less irritating than the salts of the total fatty acids. Hollmann and Dean (94) prepared esters of 4 fatty-acid fractions (designated A, B, C and D according to their melting points) and obtained most benefit with C and D. McDonald and Dean (138) treated 10 patients with the ethyl esters of each of two fractions, chaulmoogric acid (melting point 68°C.) and hydnocarpic acid (melting point of 59°C.); on the whole the latter gave the better results. De Vera (53) treated for a year three comparable groups of 25 patients each with ethyl chaulmoograte, ethyl hydnocarpate and the total mixed esters. In the first group 6 became negative and 12 improved; in the second 5 became negative and 11 improved; in the third 3 became negative and 9 improved.

Most workers who use the simple oil or the mixed esters consider that the expense of preparing selected fractions outweighs any slightly increased efficiency.

Methods of use of chaulmoogra drugs.—Until recently chaulmoogra oil and esters were most commonly injected intramuscularly, subcutaneous infiltration under the lesions being an alternative method [Rogers and Muir (204)]. The sodium salts are given intravenously as well as intramuscularly and subcutaneously. The intravenous use of the oil dissolved in ether has been mentioned. Some use "antileprol", a thin preparation of chaulmoogra oil, intravenously in small doses [Treuherz (231)].

The intradermal method, formerly used occasionally by some workers [McDonald and Dean (137), Muir, Landeman, Roy and Santra (165), Rogers], was first used extensively in the Philippine Islands where it is called the *plancha* or infiltration method [Lara (110) and colleagues]. The esters are injected into the actual lesions by multiple small punctures, each raising a wheal not more than one centimeter in diameter. Muir uses a special short needle for making the injections (159).

The superiority of this method is easily shown by choosing patients with marked symmetrical lesions and infiltrating those on the one side of the body, leaving those on the other side as controls

(see Plate 2, fig. 1). Improvement is much more marked on the infiltrated side. The histological changes in the retrogressing lesion under treatment have been studied by Nolasco (169).

The question of the most suitable drug for intradermal injection is still under consideration. In the Philippines the iodized ethyl esters are used. In Calcutta the oil with 4 per cent creosote is found almost as easy to inject as the creosoted esters, provided it is heated to 50°C. before injection and a suitable needle is used. While the oil raises larger wheals than the esters the lesions infiltrated with the former show less induration seven days later. As to which produces the more rapid resolution of lesions, there is reason to believe that there is not much difference between them. It is of course necessary to use pure and non-irritating oil. As has been mentioned, the sodium salts are apparently less suitable for this method of treatment and produce less benefit. Patients do not as a rule object to the injections if these are given only where analgesia is present. They generally consider the temporary pain caused by the multiple punctures preferable to that resulting from intramuscular and subcutaneous injections, as the latter lasts far longer.

Mode of action of chaulmoogra drugs.—Various theories have been advanced regarding the way in which chaulmoogra oil and its preparations act. (a) Under the supposition that there was a direct action on the bacilli, various experiments have been made to show that dilute solutions of chaulmoogra oil preparations [Walker and Sweeny (241)] inhibit the growth of acid-fast organisms in vitro. (b) Rogers (201) discusses the idea that it is the unsaturated fatty acids which cause the chief therapeutic value of oils in leprosy (see next section). (c) The theory has been advanced by Rogers (200) that chaulmoogra oil increases the lipase content of the blood and thus acts indirectly on the lipoid content of the bacilli, which is broken down with resulting antibody formation, and Paldrock (175) uses the increase of lipase in the blood as a criterion of the effectiveness of his treatment.

The action of chaulmoogra oil given intradermally has been discussed by Muir (159), who considers that there are five possible ways in which it may act: as a local counter-irritant, by local action on the bacilli, by setting free antigens, by its general effect on the body causing an action of the nature of protein shock, and by a special action on leprosy as distinguished from that of other oils.

OTHER OILS USED IN TREATMENT

Unsaturated oils.—In accordance with the theory that the unsaturated fatty acids of chaulmoogra oil (iodine value 90.7 to 104) form the chief therapeutic factor, various other oils of high iodine

value have been tried. Chief among these are cod liver oil (iodine value 154 to 181), linseed oil (iodine value 173 to 201), and soya bean oil (iodine value 137 to 143).

Rogers (199) reported that all lesions had disappeared in 5 out of 20 cases treated with sodium morrhuate (from cod liver oil), as compared with 9 out of 15 patients treated with chaulmoogra preparations. This tended to show that though the value of cod liver oil preparations is considerable, it is not equal to that of chaulmoogra.

Muir, Landeman, et al. (165) compared linseed, olive and hydnocarpus esters, and de Vera (52) treated for six months 25 cases with cod-liver esters and seven groups of 5 cases with soya, olive and coconut oil preparations and ethyl stearate and ethyl margarate. These experiments did not tend to show better results with unsaturated than with saturated oils, but it is to be said that the duration of treatment and the numbers of cases treated were not sufficient for an adequate test.

Miscellaneous oils.—Amaral et Paranhos (3) injected a solution of eucalyptol intramuscularly; they found it apt to cause diarrhoea, but satisfactory results were obtained in 70 patients. Brocq and Pomaret (20) used a mixture of eucalyptol 30 parts and chaulmoogra 70 parts with better results than with chaulmoogra alone, the mixture being less painful and remaining liquid at all temperatures. Hansen and Looft (77) mention the use of gurgun oil, given without effect. Neff (166) reports good results, especially in relieving nerve pain in lepra reaction, from the injection of esters prepared from dilo oil, obtained from *Calophylum bigator*.

THE USE OF IODIDES [3]

Danielssen in 1886 (33) was one of the first to use potassium iodide in the treatment of leprosy. At first he considered the effects favorable, but later discontinued its use, reserving it only for testing cases that had apparently recovered. Arning in the same year (10), and Labernadie in 1930 (106) failed to get any useful results, but Wolff (252), Neisser (167), Lie (120), Babes (13), Siebert (220), Marchoux and Bourret (132), and Sorel (222) all wrote favorably, though most of them mentioned the danger of giving excessive doses. Leboeuf (116) divided cases into 3 classes (a) those who fail to react even to large doses; (b) those who react or not according to the size

[3] For a discussion of the treatment of lepra reaction and sensitization see the section on this subject, page 433.

of the dose; and (c) those who react to the smallest doses. By studying each case separately he obtained favorable results.

Aoki (5, 6, 7) speaks of the value of iodides if carefully regulated to produce slight reactions, and finds them excellent in early cases. He gives them intravenously, beginning with 1 cc. of a 5 per cent solution of sodium iodide and gradually increasing to 20 cc. as frequently as once every three days; in rare cases 40 cc. produce no reaction, in which case 15 grams might be given orally. When strong reaction occurs he gives 0.01 gm. of a 20 per cent solution of calcium chloride per kilogram of weight, and 1 to 5 cc. of a 20 per cent solution of sodium salicylate.

Rogers and Muir (204) mention that potassium iodide, even in small doses, will often enable a comparatively small injection of hydnocarpus esters to produce a reaction, and Muir (152, 153) advocates regulating the dosage by means of the erythrocyte sedimentation test. Later (160) he writes:

> I have noticed that the favorable results have generally been in out-patients and in others who are presumably undergoing a fair amount of physical exercise; whereas the bad results are generally in institutions in which the patients have insufficient regular exercise and whose general resistance is presumably low. After considerable experience of the use of iodide during the last few years, I should hesitate to give this drug to any case of leprosy without the use of the sedimentation test and except in cases showing a continuously low sedimentation index.

Lowe (125) and Cochrane (27) caution against its use except in specially resistant cases, and under strict control. Wildish and Stoute (248) give it, 10 grains orally three times a day for 10 days, but stop it as soon as there is any reaction, and give from 0.25 up to 1.0 grain of tartar emetic twice a week intravenously up to 10 injections. Alternating these drugs, producing and controlling reactions thereby, they treated 150 cases for 12 months and saw no ill effects; skin ulcers were especially benefitted.

This summary shows (a) that iodides produce reactions in most cases, sometimes a large and sometimes a small dose producing this effect; (b) that these reactions, unless carefully regulated and controlled, may be harmful to patients; (c) that when the dosage is carefully regulated to the individual case much benefit may result.

It is not known how iodides act. When infiltrated into lepromata in dilute solution they produce no focal reaction, showing that the action on the lepromata or the bacilli is not direct. It has been suggested that the effect may be due to stimulation of the thyroid; but thyroid extract itself does not produce the

same reaction. In whatever way iodides bring about reaction, there is no doubt that it passes off as the drug is eliminated from the body, except in patients who have become sensitized. This temporary reaction is often accompanied by bacillemia and may be compared therefore to an intravenous injection of lepra bacilli. The important point in treatment with iodides is to regulate the size and frequency of the dose to produce immunization and not sensitization. If that is done we can produce an effect which may be considered equal to autogeneous vaccination, by a method which is much more easily applied than such vaccine treatment. Aoki's results show that this form of treatment is worthy of further trial, but it should only be carried out by experienced physicians and with patients under careful control.

THE HEAVY METALS

Antimony.—Cawston (24) reported decided improvement in patients given tartar emetic intravenously, especially the healing of ulcers and absence of recurrence, and also used colloidal preparations of antimony. Archibald (9) obtained more striking results in four cases with stibenyl than with sodium gynocardate. Maples (130) also reported good results with tartar emetic but declared that in doses consistent with safety it does not cure, and Heggs (83) had a similar experience. On the other hand Rodriguez and Eubanas (196), at the request of Cawston, treated 30 advanced cases for six months with tartar emetic intravenously, and 22 orally. Only 0.0015 gm. once a week intravenously was tolerated, and when more than 0.015 gm. was given the patients became weak, and some of them showed albumin in the urine. No benefit was noted.

Treuherz (231) gave alternately intravenous injections of tartar emetic and antileprol; he says that the antimony does not effect a change of the skin lesions or in general improvement, but produces greater resisting powers, with longer intervals between the naturally occurring exacerbations of the disease. Hoffmann (90) finds antimony compounds useful in combination with chaulmoogra preparations. Muir (152) advises intravenous injection of tartar emetic in doses of 0.02 to 0.04 gm. thrice a week for reducing lepra reaction, whether caused by iodides or in other ways. The use of tartar emetic alternately with potassium iodide by Wildish and Stoute (248) has been noted. Kingsbury (101) treated four cases in New York with an antimony compound (M303) and records one as cured and three improved.

From the foregoing it appears that antimony compounds have the power of controlling the condition known as lepra reaction. Treuherz, Hoffmann, Muir, Wildish and Stoute definitely use them

with this in view, and the results of others can be explained on this basis. Chaulmoogra oil and its preparations are generally contraindicated in lepra reaction, as they often aggravate it. Muir found that tartar emetic in larger doses (0.06 gm.) combined with intramuscular chaulmoogra esters produced a limited reaction (204), and considers it important when using antimony to control reactions to give small doses—0.02 to 0.04 of potassium or sodium antimony tartrate two or three times a week. Larger or more frequent doses are often apt to increase rather than diminish the reaction.

Arsenic.—Hansen and Looft (77) mention that Fowler's solution, through producing diarrhoea, caused diminution of nodules; but when the gastro-intestinal symptoms subsided the leprous signs were no better. Hopkins (95) found that Fowler's solution diminished the duration and severity of lepra fever.

For some time considerable attention was given the synthetic arsenic compounds. Hallopean and Aine (75) gave *atoxyl*—4 injections in 15 days—with good results in 1 case, and Brault (18) considered it more useful in leprosy than all other forms of arsenic then available. Rocamora (192) claimed that *salvarsan* combined with chaulmoogra was the best treatment, but Paldrock (172) obtained no benefit with it and Veillon (1913) had bad results. Delanoe (39) gave *novarsenobenzol* with B.C.G. vaccine, as has been mentioned. *Eparseno* was found by Delamare (40), Legendre (117) van den Branden (237) and De Mello and Cabral (43) to produce no permanent good results. The last writer found that it aggravated symptoms.

Mercury.—Hansen and Looft (77) reported that patients did badly under mercury, but Ehlers (61) got good results, while Crocker (30) advised intermittent injections of mercury in addition to chaulmoogra oil by mouth. Muir (146) found that in patients with syphilitic complications a combined treatment with *avenyl,* a mercury preparation soluble (0.25 to 0.5 per cent) in chaulmoogra oil and esters, often rendered a positive Wassermann or Kahn test negative, with a coincident improvement in the leprous condition not obtained with chaulmoogra drugs alone. Avenyl produces no toxic symptoms and can be used in cases where the usual antisyphiltic arsenicals tend to produce lepra reaction; in fact it tends to prevent lepra reaction.

Denney, Hopkins, et al. (48) used *mercurochrome,* injecting at first 5 mgm. per kilo intravenously in 44 cases, later halving the dose because of severe reactions. After having had weekly injections for a year 7 patients remained unchanged, 6 were slightly improved, 6

moderately improved, 16 markedly improved. Rao and Roy (188), giving smaller doses (10 cc. of a 1 per cent solution) in 12 cases in reaction obtained cessation of the reaction. Muir and Chatterji (163), beginning with 3 cc. of a 1 per cent solution and increasing to 10 cc. intravenously once a week, found that: (a) septic conditions were cleared up; (b) in consequence lepra reaction resulting from such conditions could be controlled; (c) continued use of 10 cc. doses resulted in liquefying and bursting of nodules (see Plate 2, fig. 2). Short febrile reactions followed the first injections, but disappeared as the septic condition cleared up. In the Gobra Hospital, Calcutta, mercurochrome is given as a matter of routine to clear up such infections. However, Muir and Chatterji (164) emphasize the danger of prolonged use of mercurochrome, as the necrosis and liquifaction produced in the leproma tend to continue for many months and the consequent lowering of the patient's resistance cannot be controlled. As soon as the septic condition or the lepra reaction has yielded, or if after the first four or five injections no improvement is apparent, the use of this drug should be discontinued.

Gold.—Puente and Pierini (185) used *sanocrysin* on five patients with slight improvement in some cases, but Paldrock and Rangel (179) found that it gave no improvement but caused a rise of temperature with general and cutaneous reaction. Hoffmann (91) and Kupffer (104) got good results in eye conditions with *krysolgan.* Eubanas and de Vera (67) used it and *triphal* in five cases; none became worse but the trial was too short to test more than immediate effects. Paldrock (175, 176, 177, 178) used *solganol* in combination with applications of carbon dioxide snow to nodules, giving treatment in courses with intervals of six months between them. He considers that the solganol is able to attack the granules of bacilli after their "envelopes" have been removed by effect of the freezing. The number of patients treated was small (6 or 7), but Paldrock claims that his treatment is the only one which gives "specific" results. He also used *lopion,* another gold preparation. Amies (4) is more conservative about solganol. Of 8 cases treated intravenously for from 6 months to 2 years, 4 were improved and 3 others showed slight progress; treatment of 1 had to be stopped because of toxic symptoms. Muir (158) reports trials made by Rao with solganol B, which gave unfavorable results, though dosage was carefully regulated by means of the erythrocyte sedimentation test; the effects on eye lesions were especially harmful. On the other hand Alfred (2) reports no harm from

solganol, while in 6 out of 11 cases there was improvement of eye lesions. Heimburger, in the Tsinan Hospital Report for 1926-1932, says that gold preparations used intravenously in combination with chaulmoogra ethyl esters are of greater value than the latter alone. F'eldt (69) on reviewing the use of gold concludes that the compounds used act by stimulating the natural defensive processes through the reticulo-endothelium.

In the writer's experience solganol produced unfavorable reactions. Paldrock found it necessary to give his patients six months to recuperate from the effects of a course. The advisability of such a form of treatment is questionable; the question of the advisability of reaction-production and lowering of the general health of patients in the course of treatment is discussed later. Gold treatment may be of value when carried out carefully with doses which do not weaken the patient; but considerable superiority over other, cheaper forms of treatment would have to be well established before this very expensive drug could be brought into general use.

Copper.—Sugai (225) used copper cyanide with apparently excellent results, and Takano (226) used cyanocuprol, carefully, with similar benefit; in 6 cases macules faded, sensation returned, and nodules became absorbed. Valvedre (236) used copper combined with carpotroche oil of *Carpotroche brazilensis* and obtained definite amelioration. Rho (191), following these workers, used cuprocyanide and also cuproiodase, a lipoid compound of copper. In 20 cases he obtained healing of all ulcers except perforating ones, fibrosis of nodules, and diminution and granulation of the bacilli. He considers that copper preparations should be given in combination with chaulmoogra. Palmer (180) used copper citrate and tartrate of bismuth intravenously in 3 cases; fresh nodules broke out but improvement resulted. Henderson and Chatterji (87) reported trials with another copper preparation which lessened nerve pain but had little beneficial effect on the disease.

Other metals.—Sandes (215) gave 239 grains of *lead* salts in 6 months, inducing symptoms of lead poisoning but not improvement. We ourselves gave 12 injections of lead selenide to each of two patients, with no benefit; in one there was vomiting, rise of temperature and loss of sleep for 24 hours after each injection. *Bismuth* was used by Matta (134) in the form of tripol. There was a local reaction after each of the first few injections and distinct reduction

of the nodules up to the 7th injection, but thereafter there was no further improvement, though 18 or 20 injections were given.

The action of heavy metals.—Most of the heavy metals appear to have a double action. In large doses they can produce lepra reaction, with beneficial effects in some cases if carefully regulated. In small doses they have the property of controlling or limiting lepra reaction. This has already been pointed out with regard to antimony; Hopkins mentions it for arsenic, and Feltd for gold preparations. Ray and Roy, and Muir notice the same effect with mercurochrome, and Muir mentions it with avenyl.

OTHER DRUGS USED

In addition to the classified remedies discussed, a considerable number of other drugs have been employed, a few of which will be considered here.

Carbolic acid in dilute solution by mouth was used by Hansen (77). It produced no effect on the disease in the 53 cases treated, though Bertarelli (17) writes of a case treated with benefit. Leboeuf (116) injected a 2 per cent solution in doses of 0.5 to 6 cc. twice weekly. Unna (234) found that when tuberculous patients were phenolized by giving 250 mgm. daily of phenol in cod liver oil they could stand a diet of animal protein which was harmful without this drug, and he believed that the same would hold good in leprosy.

Sodium salicylate was considered as a tonic by Danielssen (35), and others have found it useful in controlling lepra reaction. We have found that 0.25 gm. dissolved in 2 cc. of normal saline and injected intravenously relieves the bone and joint pains common in leprosy.

Creosote was given orally by Hansen and Looft (77) without effect. Unna (234) used it in an ointment along with caustic potash and salicylic acid. Muir, Landeman, et al. (165) injected it in combination with hydnocarpus esters, adding also camphor. Later Muir (204) used it (4 per cent) with hydnocarpus oil and esters. It decreases the viscosity of the oil, and is antiseptic, antifebrile and tonic. Samson (214) in four experimental groups obtained the best results with creosoted chaulmoogra esters, finding that they stimulate the appetite.

Thymol.—Hamzah (76) injected 4 cc. of 10 per cent thymol in cod liver oil, with marked improvement in the 14 cases treated. On

the other hand Van Heijningen (238) injected solutions of thymol in alcohol and also in anise oil for 7 months, without results.

Ichthyol.—Haslund (81), Moraitis (141), Unna (234), Aoki (7) used icthyol ointments. Hansen and Looft (77) gave it internally without benefit.

Resorcin was used by Unna (234) together with pyrogallol in an ointment. It was adopted by Mercado (139) as a constituent of his chaulmoogra mixture.

Iodoform was injected in a 20 per cent solution in olive oil subcutaneously by Diesing-Duala (58), who found that improvement was slow. Amaral and Paranhos (3) injected it intramuscularly, but it was badly tolerated; Leboeuf (116) also used it intramuscularly, and Courtney (29) gave a solution in ether, intravenously and into nodules.

Aniline dyes.—These have recently been used in the treatment of leprosy by various workers: methylene blue, trypan blue, carbolfuchsin, etc. Ryrie (212) uses trypan blue, brilliant green and fluorescein. Some workers claim promising results, but it is too soon to make any definite pronouncement.

Miscellaneous.—A preparation called *javanin*, said to be an extract of pig or beef pancreas free from protein, lipoids and insulin, and which is supposed to accelerate the action of lipase in vitro, was tried by Eubanas (64) in five cases without appreciable benefit. *Succinol,* a preparation of unrevealed composition, was tested by Henderson and Chatterji (87) without beneficial results. *Fibrolysin* was also tried by the same workers, and also by Figueredo (70), with negative results.

There are many *native remedies* in use in various tropical countries, most of which are of a tonic nature and appear to control lepra reaction rather than destroy bacilli or eliminate lepromata.

LOCAL TREATMENT AND PHYSICAL THERAPY

Surgical removal of lepromata.—Several workers have tried to eradicate the infection when the lesions were small and single by excising them, but apparent primary lesions are commonly only the first manifestations of disease which is already generalized. Unna (234) recommended shaving off the surface of nodules with a razor, and applying caustics. Muir (145) recommends for cosmetic effect the trimming of the ears when these are enlarged by diffuse leproma or nodules, it being often possible in this way to remove one of the most unsightly features of the disease.

Caustics and counter-irritants.—Leboeuf (116) applied carbon dioxide snow to leprous nodules. McCoy (135) used it in 31 cases, of which 1 became bacteriologically negative while in 17 others there was diminution of the lesions. J. T. Wayson (243) applied it to produce bullae, the fluid of which he injected into the patients. Paldrock (173, 174, 178) recommends it, as has been said, and Unna (235) does likewise. Paldrock found that it produces leucopenia in advanced cases and leucocytosis in longstanding ones, and that it causes disappearance of nodules in parts of the body distant from those treated; he concluded that it removes the "envelopes" of bacilli and produces active immunization. He found that it causes immediate retardation of erythrocyte sedimentation, followed by acceleration 7 or 8 days later.

Lie (121) used ethyl chloride for repeated freezing of leprous lesions. This produced reddening and blistering; improvement was noted in almost all cases with disappearance in some.

In India trichloracetic acid has been used extensively to supplement other treatment [Muir (145)] and is popular in spite of the temporary burning sensation caused. A 50 per cent solution in water is applied to nodules and a 25 per cent solution to diffuse or macular lesions. The solution is applied, once every week or two, until the surface shows a mild degree of whitening; excessive painting may produce ulceration. Marked improvement generally results, both in the lesion painted and in distant ones. Lowe[1] in three cases applied carbon dioxide snow on the lesions of one side of the body and trichloracetic acid on the other side and found them equally efficacious in removing nodules. The acid has the great advantage that it is easily obtained and applied, whereas carbon dioxide snow is not always easily obtained, and involves the use of an expensive apparatus, while its application requires considerable time and is specially difficult in hot climates.

Cauterization with hot irons or with vegetable juice is a common popular remedy in India. However, the leprous infection generally extends beyond the apparent margin of a lesion and may thus escape the effect of the scarifying remedy; as a result one frequently finds a large macule with a central scar and a peripheral spreading lesion beyond it.

Local injections.—Various medicinal substances may be injected into skin lesions. As has been said, Unna (234) injected carbolic

[1] Personal communication.

acid and Courtney (29) idoform. The intradermal infiltration of hydnocarpus oil and esters is probably the best form of local treatment, as there is a direct effect on the lesion as well as a general effect. We are at present carrying out a series of control experiments with various drugs.

Pressure.—Denney (46) recommends local heating (to 50°-52°C.) accompanied by considerable pressure for 2 to 6 minutes daily. This has caused the absorption of lepromata in one to six months. We have noticed frequently that in Bengalis, who apply their loin cloth tightly round the waist, the region pressed upon is free from leproma while the skin above and below is affected. The form of treatment described by Denney should be more extensively tried.

Baths.—Hot mineral baths have been recommended by Ehlers (62), Unna (234), Aoki (7) and others. Most experienced workers are unanimous as to their beneficial effects in combination with some form of special treatment.

X-rays and radium.—Several workers have reported the use of X-rays, either without favorable results or with only slight improvement [Lassar, Siegfried and Urbanowitz (1905), Matthews (133), Heiser (84)]. De Vertenil (55) obtained improvement by using a varnish containing *radium bromide.*

Ultra-violet radiation.—Denney (45) found that these relieved pains and healed perforating ulcers, though Cruz (31) obtained no benefit to leprosy, while Rose (205), combining such treatments with zinc ionization, found it of great value in healing old perforating ulcers. Muir (155) found that ultra-violet rays improve the general resistance of patients, lower the sedimentation rate and are useful in clearing up the common complicating tinea and streptococcal infections. They do not appear to have any direct effect on leprous lesions.

Hirst (89) suggested that the effectiveness of chaulmoogra oil might be increased by irradiating it with sun or other rays. Labernadie (105) irradiated *H. wightiana* oil by means of a mercury quartz lamp and added ergosterol to another sample. Only 2 cases were tried, but he thought the treated oil was more effective than the untreated.

Diathermy.—This was used by Unna (233) in the treatment of diseased nerves; infiltration became less, neuralgia was alleviated, and paraesthesia diminished, but anesthesia usually remained the same. Fredell (68) and Rodriguez (194) found that it relieves painful neuralgias. Muir, with Ghosh (unpublished), found that diathermy

could not be used on acutely reacting nerves, but that in subacute or chronic cases with markedly thickened nerves the pain was relieved and the thickening became less; in cases with drop-foot due to infiltration of the peroneal nerve much benefit resulted; in cases where the process had gone on to fibrosis no improvement was obtained.

Fulguration—Cauterization with a high frequency current has been found useful in treating nasal lesions (214). This is referred to later in the subsection on treatment of the nose.

OTHERS FACTORS MODIFYING THE DISEASE

General health.—Many leprologists have acknowledged the importance of improving the general health of patients. Leboeuf (116) laid stress on rest, good hygiene and food, as in tuberculosis. Muir, Landeman, et al. (165) give first place to strengthening of the body resistance, emphasizing the necessity of dealing with complicating diseases and the importance of exercise and suitable diet. Wilson (250), under the title of "Industrial Therapy and Leprosy" shows the effect of mental and physical occupation on the general health and the disease in his colony in Korea, and similar effects are reported from other institutions. Wade and Rodriguez (240) say:

> The healthy adult seems very resistant. In the necessary lowering of his resistance various factors may enter, such as exposure, improper feeding or weakening disease. It should be recognized that sexual over-activity also is apt to bring out a latent infection or to aggravate an existing one. The importance of the general health in the treatment of leprosy has been increasingly emphasized during recent years.

The Leonard Wood Memorial Conference on Leprosy held in the Philippines in 1931 (257) agreed that:

> The general measures that appear to be most applicable do not differ materially from those used in other infectious diseases whose course is often of great chronicity. However, it is believed by physicians experienced in this disease that careful and persistent efforts to eliminate intercurrent affections which tend to reduce the general resistance of the patient are essential to successful therapy. Observations suggest that the adjustment of both the quality and the quantity of the diet may be an important therapeutic measure. It is also the belief of those with experience that other general measures, including personal hygiene, supervised or graduated physical exercise, occupational therapy, the stimulation of morale, and mental welfare are also of definite value.

Diet.—The importance of diet in the causation of leprosy, and consequently in its treatment, is brought out by an extensive survey by Santra in India [Muir (150), Santra (216)] which shows the bear-

ing of famine, ill-balanced and otherwise improper diet on the incidence of the disease. Embrey (63) at the Culion Leper Colony showed that with improved diet the general health of the patients improved, and Rodriguez (195) emphasizes the importance of proper diet and sufficient exercise in treatment. De Raadt (51) stresses the vegetable protein in the diet. This view corresponds with a belief popularly held throughout India that animal food should be restricted and that raw, germinating pulse (gram), rich in protein, should form an important part of the diet.

Complicating diseases.—These have two distinct effects on leprosy: in some cases they increase the condition and in others they diminish it. The former is emphasized by Lara, de Vera, Samson and Eubanas (113). Later Lara (109) pointed out that young, robust persons do best under treatment; married life in adolescents is favorable; females do better than males; febrile reactions are injurious. Muir (151) found that kala-azar brought out latent leprous infection, and pointed out (152) the importance of certain endemic diseases on its incidence. Canaan (22) mentioned the handicap to treatment imposed by malaria and other diseases.

On the other hand Denney and Hopkins (47) referred to the effect of vaccination on 118 leprous patients; there were febrile reactions in 51 out of 71 nodular cases, but they appeared to improve after the reactions passed off. Muir (151) recorded cases in which kala-azar complicated fairly advanced leprosy; the patients later recovered from the complicating disease under treatment and the improvement in the leprosy caused by the kala-azar was so striking that other leprous patients volunteered to have themselves inoculated. Pinard (184) mentioned temporary amelioration of leprosy following an artificial infection with benign tertian malaria. Balina (15) recorded benefit from severe pneumonia; rapid clearing of the leprous patches was ascribed largely to the acute febrile condition.

The effect of aggravating the condition seems undoubtedly due to lowering of the patient's general resistance; and is most noticeable in early cases. The beneficial effect is more difficult to explain. It is noticed in advanced cases of the skin type, but not in early or in neural cases. As a general principle acute febrile diseases frequently cause marked diminution in advanced cutaneous cases. The writer has seen a patient of this type who developed acute exfoliative dermatitis of which he died after 3 months' illness; at the autopsy not a single acid-fast organism could be found, though they had been present in huge numbers when the terminal illness began. It may be asked whether leprosy might not be treated by the induction of acute diseases, just as certain

diseases are treated by inducing malaria. The writer, after inducing such diseases as malaria, kala-azar and rat bite fever, is of the opinion that, though the signs of leprosy may be diminished safely to a certain extent in this way, ultimate recovery is in the long run not accelerated but delayed because of the lowered general health caused by the induced diseases.

Self-healing.—Hansen and Looft (77) and Impey (97), in 1895, mentioned the frequency with which leprous infection dies out, leaving the patients no longer infective. Tonkin in 1904 (229) said that although in a sense leprosy is incurable, it can be arrested and practically cured; that the average duration of the disease does not usually exceed a dozen years, so that if a leper outlives this period it will be quiescent, and if he survives twenty years it will be unrecognizable. Ehlers (62) speaks of *vis medicatrix naturae,* and Muir (144) writes of the tendency of leprosy to die out in the third stage of the disease. Bargehr (16) believes that his leprolin test demonstrated the existence of an immunity in cases in which the disease had died out. On the other hand Roy (210) mentions patients whose suppurating feet he amputated, after which lesions which had apparently died out reappeared. The apparent arrest of the disease was probably due to the acute septic infection, which acted on the leprous condition in the manner mentioned in the foregoing, and removal of these foci allowed the lingering leprous infection to show itself clinically once more.

Muir (156) has shown that leprosy dies out without treatment in many early cases, because of the removal of predisposing causes and restoration of the natural resistance.

A survey in Madras (1930) showed, in a population of 146,853 inhabitants, 1,251 patients suffering from leprosy—0.85 per cent. Of these, 633 were early neural (N-1) and 257 advanced, while 159 were early skin cases (C-1), only 202 being of the C-2 and C-3 types. Thus only 16 per cent were advanced and highly infectious. If leprosy were always a progressive disease we should expect a far larger proportion of advanced cases, unless the disease had recently been introduced, which was not the case. Evidently, in a large number of infected persons the disease never produces more than slight clinical lesions and disappears. It is probable also that many persons are infected who never even develop clinical signs. In these respects leprosy resembles tuberculosis.

At the other end of the picture we have the gradual disappearance of gross infections. In some this appears to be spontaneous, because of improved general health; in others complicating diseases seem to play a part; while in still others trophic ulcers and septic conditions are undoubtedly concerned.

LEPRA REACTION (LEPRA FEVER)

Signs of lepra reaction.—Lepra reaction is one of the best known phenomena in leprosy, and the literature of leprosy treatment is full of references to it. The clinical signs of it are a general febrile condition, swelling of formerly apparent lesions and the appearance of lesions where they were not formerly visible. Hollmann (93) states that reaction is not a fresh manifestation of the disease, but an inflammatory reaction in previously unrecognized foci. Bacillemia is present, at least in the more advanced skin cases. In neural leprosy the involved nerves become swollen and painful. Lepra reaction may occur apparently spontaneously, but it is generally associated with some condition that lowers the general health, and may also be caused by treatment. For the sake of convenience we designate two types: (a) that which is of a toxic nature and subsides when the cause disappears or is removed by treatment; and (b) that in which in addition to the presence of toxemia the patient has become sensitized and the reaction tends to continue indefinitely or to recur at intervals. The former type may pass on into the latter unless precautions are taken.

Effect on leprosy treatment.—That excessive treatment may produce reactions of the second type is well known. Special drugs commonly are pushed until signs of reaction appear and then stopped until after the patient recovers, as has been noted in discussing various treatments [Ehlers (61), Crocker (30), Heiser (86), Paldrock (176)].

Concerning the effect of such reactions on the disease, many confusing and contradictory statements have been made. Some authors hold that they are beneficial, and others that they are harmful. It may be mentioned incidentally that a patient may be first seen in a state of lepra reaction. If this is of the first type, it may disappear spontaneously and simulate a spectacular "cure", credit for which may be attributed to whatever remedy may have been used. Photographs showing spectacular improvement after treatment sometimes represent only the passing off of lepra reaction (see Plate 1, figs. 1-4).

Of those who consider lepra reaction favorable, Rogers (197) stated that the most striking result of his treatment was the occurrence of definite local reactions, sometimes accompanied by fever. Hollmann and Dean (94) mention that with fractional esters there were local reactions in the leprous lesions in all nodular cases. Denney and Hopkins (47) write that after vaccination febrile attacks occurred,

followed by improvement. Wheatley (246) mentions that a succession of small reactions under treatment best maintained progress. It is well known that lepra reaction, spontaneous or induced, has the effect of causing granulation, or breaking up of bacilli into acid-fast dots [Walker (242)]—the severer the reaction the greater the granulation—and some workers have considered this a criterion of improvement.

Of those holding reactions unfavorable, McDonald and Dean (138) say that 10 per cent of the patients are unable to take treatment continuously owing to a tendency to reaction. Rodriguez (194) states that during a limited period lepra fever was met with in 23.6 per cent of the cases under treatment at Culion, and he and Lara (109) agree that improvement is greater in the cases not showing reaction. Lowe (125) preferred hydnocarpus esters to potassium iodide for treatment as they caused fewer reactions. Muir (156) pointed out that the lesions in C-3 cases can often be greatly reduced by remedies which produce marked reactions, but that the residual disease was rendered the more difficult of removal as the general health of the patient was lowered and he was sensitized. He contended that it was better first to raise the general resistance and then give special treatment in maximum doses consistent with the maintenance of a high standard of general health.

Treatment of lepra reaction.—Treatment of lepra reaction depends on its type. In the first type treatment consists in removing the cause. A reaction from potassium iodide in an unsensitized patient subsides with the excretion of the drug. An attack of malaria may cause a reaction which subsides after a few days of quinine administration. In the second type a vicious circle is formed, the depression of health which it causes being sufficient to prevent its subsiding. Such a condition may continue for weeks or months, and may recur frequently. It is necessary, therefore, in addition to removing the cause, to take special means to desensitize the patient.

Numerous drugs have been used for the treatment of lepra reaction. *Fowler's solution* was advocated by Hopkins (95). Alkalis have been used by many, both orally and intravenously. Rodriguez (195) gave intravenously 20 to 25 cc. of a saturated solution of *sodium bicarbonate* daily for several days, or 2 to 3 gm. of the drug orally 4 or 5 times a day. Roy (209) records cases of severe and intractable nerve pain which yielded to two intravenous injections of 150 and 200 cc. respectively of 0.5 per cent sodium bicarbonate in normal

saline, at 5 days interval. On the other hand we know of a C-2 case which became very much worse after 20 cc. of the same solution.

Rodriguez (194) on Mitsuda's advice, gave *calcium chloride,* 2 per cent, intravenously, in doses of 20 to 30 cc. daily for a week. Hasle (80) gave 15 intravenous injections of 10 cc. of this in one month, and a second series after an interval of 15 days, with improvement in 15 of the 20 cases treated and no ill effect. *Potassium antimony tartrate* is one of the most useful drugs in the control of lepra reaction, as has been noted in discussing antimony, and *mercurochrome* is also very valuable, especially when reaction is caused by complicating septic infection.

Muir (204) recommended *adrenalin* for nerve reaction, 3 minims in saline solution being infiltrated subcutaneously along the course of the nerve. This often gives relief within a few minutes, and two minims injected intramuscularly each day is often useful in stopping lepra fever. Wheatley (247) obtained good results with this drug, and Green (74) used it to desensitize patients. Eubanas (66), for nerve reactions, used a mixture containing *cocaine* and adrenalin and usually obtained relief of pain after an average of 2 injections. *Ephedrine sulphate* was used by Muir and Chatterji (162) in place of adrenalin in nerve reaction, it having the advantage of being effective by mouth. Relief is often obtained within one-half to one hour with 0.02 gm. doses. The same dose in 10 cc. of 0.5 per cent sodium bicarbonate may also be infiltrated along the painful nerve, often with almost instant relief. However, in a certain proportion of cases neither adrenalin nor ephedrine has any effect in stopping nerve reaction.[4]

In cases of marked reaction with fever it is important to administer a saline purge and keep the patient in bed. On the other hand graduated exercises should be begun as soon as the condition subsides; reactions seldom occur in patients who are taking abundant physical exercise. There is reason to believe that one of the most potent factors in the desensitizing of patients is suprarenal secretion, a hypothesis supported by the permanent beneficial effect often produced by adrenalin and ephedrine. Possibly antimony in small doses stimulates the suprarenal glands; Chopra, Gupta and Chowdhury (26) found in Belgian hares that after intravenous injections of organic compounds of antimony there is a definite increase in the residual epinephrin content of the gland, this being nearly doubled after 10 injections. Much of the effects of other metals may be of a similar nature, though larger doses may have a contrary effect, stimulating reaction instead of reducing it.

[4] For other references to methods of treating reacting nerves see the subsection on nerves under "Regional Treatment".

EVALUATION OF TREATMENT

FALLACIES AND CRITERIA

The foregoing citations show many contradictory statements concerning the value of various treatments. Even workers of large experience differ, or appear to differ on important questions. Experience necessarily varies according to the nature of the country, its laws and customs, and many other factors, but some differences are unquestionably due to lack of clear definition of terms used. An attempt to define terms was made by the recent Leonard Wood Memorial Conference. For example, it was decided to discard the word "cure" as a term capable of misunderstanding; Scott (218), for instance, defined it as "complete restoration of health, strength and working power with loss of every symptom which causes inconvenience or incapacity", but there are patients of the advanced C-3 type to whom these terms could be applied. The task was not completed by the conference, but its report may be used as a starting point for better understanding and a basis for further discussion.

Fallacies in evaluation.—In evaluating the effect of any drug or line of treatment there are various fallacies which have to be guarded against [Muir (147)]. These are: (a) mistaking the subsidence of lepra reaction for elimination of the disease, and assuming to be an effect of the drug the granulation of bacilli that such reactions cause; (b) crediting the clearing up of leprosy manifestations to a treatment when it is really due to removal of another disease or aggravating factor; (c) ascribing a direct or "specific" effect to the results of protein shock or of counter-irritation by CO_2 snow, trichloracetic acid, etc. (d) On the other hand, the failure of drugs to remove permanent trophic lesions often has led unjustly to their discredit.

The psychological effect on patients and physicians of the laudation of some much-advertised drug often has been seen in the raising of false hopes. Messum (140), referring to his trial of nastin, told of how many of the patients soon declared themselves much benefited, and discussed the rôle of suggestion in this. The patients were much more cheerful, because of hopeful anticipations, but examination showed no definite improvement, and after some months the patients arrived at this conclusion, a few showing indignation because they were worse than before.

Criteria of effectiveness.—It is necessary to arrive at satisfactory criteria by which the effectiveness of any form of treatment may be

estimated. The signs of active leprosy as defined by the Leonard Wood Memorial Conference (257) include:

> Positive bacteriological findings in skin or mucous membrane determined by the usual methods; the presence of raised or erythematous lesions; increase or diminution of lesions in size or number; tenderness of nerves, with or without thickening.

The aim in the treatment of leprosy is to restore the general health of the patient, and to remove all active signs of the disease, thereby rendering it "quiescent." Thereafter the patient is to be kept under observation for a period of two years, during which active signs must continue to be absent. Only when the patient has stood this severe test should the disease be declared "arrested."

ESTIMATION OF PROGRESS UNDER TREATMENT

Correct estimation of progress of patients under treatment is necessary, whether for determining their prognosis or judging the effectiveness of a treatment method. This involves careful determination of the condition both before and after treatment, and requires familiarity with the disease and its natural course when untreated.

Condition before treatment.—The extent of the disease process varies widely even in cases belonging to one type or sub-type. The mass of the lesions and the number of bacilli in them are not necessarily related to their extent and number. Skin lesions are not always clinically discernible, and bacilli may be numerous in the skin without any noticeable clinical signs. On the other hand, in many cases—the majority in India—the bacteriological examination is negative, and only clinical findings are available. The clinical examination must be correspondingly thorough. It is also important to take into consideration physical, social, mental and other factors that bear on the progress of the disease.

Factors to be considered are: (a) the extent of infection and disease in the body; (b) the degree of resistance of the patient; (c) the causes of low resistance when present; (d) their nature, whether temporary and to disappear spontaneously, or removable by treatment, or not removable; (e) whether there is lepra reaction and if so its type and effects. Regardless of evident disturbances, careful examination for complicating disease should be made, including the appropriate laboratory tests.

Condition after treatment.—To estimate accurately the condition after treatment requires thorough and repeated examinations. The bacteriological examination should not be declared negative till bacilli have been sought repeatedly over the whole extent of the nasal septum, the pinnae and the former skin lesions. Even then potassium iodide may elicit scattered foci, though this procedure is not advised except in cases with continuously high resistance. In patients who have never given positive bacteriological findings the decision as to quiescence and arrest must depend on the disappearance and continued absence of clinical signs of activity. An important consideration as regards the chance of avoiding relapse is the general resistance and the likelihood of maintaining good general health. With accurate records, the progress made is determined by comparing the condition before and after treatment, but, as has been indicated, this is no easy matter and requires full familiarity with the disease.

ESTIMATING THE VALUE OF DRUGS

It is generally recognized that improvement in a patient under treatment cannot be attributed entirely to the special drug used. Under favorable conditions leprosy has a tendency towards self-healing, and improvement may be due largely to improved diet and other conditions, especially in the case of destitute patients after admission to a well-managed institution.

Controlled experiments.—Before the value of any drug can be estimated it must be tried out in a sufficient number of cases: results based upon trials in a few patients are apt to be misleading. In such trials adequate controls are necessary; many reports of therapeutic experiments are open to criticism on this score. The factors which enter into the estimation of evaluation of a drug are so many and complex that no exactly controlled experiment is possible. The best that can be done is to collect a large number of cases in whom the disease, general resistance, and other circumstances are as alike as possible and use half of them as controls and half for the treatment to be tested. Unfortunately, short experiments lasting only a few months are apt to be most misleading, and it is difficult to persuade controls to continue in that capacity, without effective treatment, for a long time. The only reliable criterion of results is a positive bacteriological finding becoming negative. The best possible experiment will give only a general impression, but with large numbers of cases treated over a period of years and by several independent workers conclusions are of real value.

With intradermal injections it is possible to test the local effect of various drugs in patients with symmetrical lesions, infiltrating those on one side with the drug to be tested, the other to serve as a control.

LINES OF TREATMENT RECOMMENDED

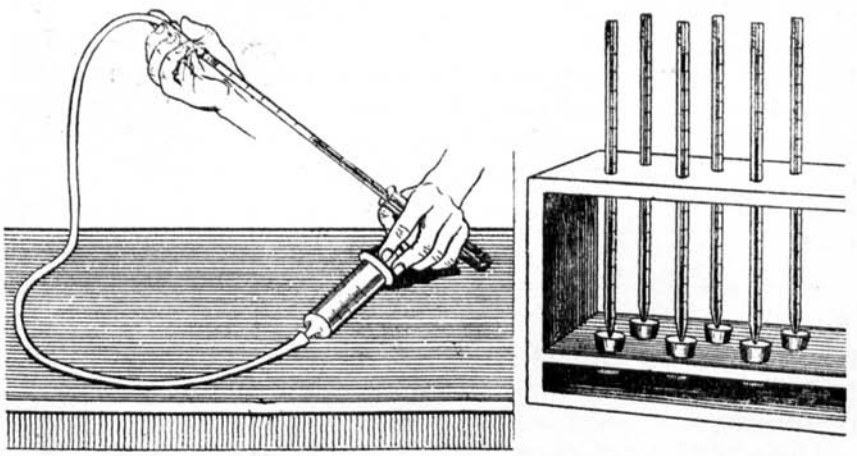
PRINCIPLES OF TREATMENT

While general principles may be laid down, it should be clear that success must depend upon careful attention to each case. The best results are obtained by: (a) raising the patient's general health and resistance to the highest possible level; and (b) giving the maximum amount of the most effective special treatment consistent with maintaining the general health. By *special treatment* is meant a drug used to clear up lesions caused by the presence of the bacillus of leprosy; by *general treatment* is meant all measures used against complicating diseases or lepra reaction and for improving the general health.

It is not intended to draw too clear a line of distinction between the general and special treatments, or to suggest that general treatment should cease when special treatment is begun, or that it is always necessary. Special methods, when carefully regulated, may often improve the general health by clearing up lesions; and general treatment will often cause a marked improvement in the leprous condition. However, in general the distinction holds, and both kinds of treatment should be employed.

Estimation of resistance.—It is clearly important to have some reliable means of estimating the patient's resistance. In discusssing lepra reaction we have mentioned that some physicians press the special treatment until a general reaction is produced, but this should be avoided. The general appearance and feelings of the patient are useful. Those who have well-developed muscles, not unduly fatigued by exercise, who have a good appetite and who sleep well seldom suffer from lepra reaction. But at the begining of treatment, especially with patients in poor condition, it is difficult to judge the resistance. It is particularly in these circumstances that we have found the erythrocyte sedimentation test invaluable [Muir, (154)]. As a general principle, everything which accelerates sedimentation lowers the resistance to leprosy. When sedimentation is slow it is possible to press the special treatment; when it is fast it is necessary to proceed with caution and to build up the general health.

The sedimentation test.—The technic advised is an adaptation which we have found advantageous. Into a syringe containing 0.3 cc. of 5 per cent sodium citrate draw 1.2 cc. of blood from the patient's vein, take in a small quantity of air, mix the contents thoroughly, and evacuate into a test tube. Sedimentation is carried out in 300 mm. pipettes of 1 cc. capacity, graduated from above downwards from zero to 100, there being a space of 3 mm. between each two marks. The pipette is attached to a 10 cc. syringe with which to aspirate the blood mixture from the test tubes to the zero mark (see Text-fig. 1). The filled pipettes are placed upright in a rack with their points inserted in small holes bored in rubber corks, and (preferably) incubated at 37°C.



TEXT-FIG. 1.—The blood sedimentation test. Showing (a) the method of filling the pipettes with the aid of a syringe, and (b) the filled pipettes in position in the special rack.

The level of the erythrocytes is read off after 1.5 hours and again after 2.5 hours, and the average of these two readings is taken as the sedimentation index. Thus, if at the first reading the level of the cells has fallen to 10 (30 mm.) and at the second to 20 (60 mm.) the index will be the average of 10 and 20, i. e., 15. The maximum reading is about 80 (240 mm.).

GENERAL TREATMENT

Complicating conditions found in the original examination (discussed under Condition before Treatment) and others arising later are to be corrected so far as possible. Malaria, chronic dysentery, pyorrhoea, helminthic and streptococcal infections and venereal diseases are among the most common complicating diseases though these will vary in different countries. In debilitated patients it may be months or years before the special treatment can be tolerated because of reactions; these cases tax the ingenuity of the physician.

In a disease like leprosy, in which the heat regulating function of the skin is interfered with, the coming of a cooler season or removal of the patient to a cooler climate is often followed by improved health.

The question of food is important: an appropriate, well balanced diet is essential. Cod liver oil, combined where possible with ultra-violet-ray treatment, is useful in some cases. In others 0.5 to 1.0 grain of dried thyroid extract daily at bed time has changed the whole aspect of the case, but care must be taken in giving this drug. The stomach content is sometimes deficient in hydrochloric acid, and such patients improve markedly with 0.5 ounce per diem of dilute acid.

An important part of general treatment consists in regulating the patient's daily time-table. He should have suitable mental and physical occupation to avoid brooding and depression. Physical training should be progressive and include special exercises to correct any trophic pareses or deformites. Taken by and large, to obtain the best results in the treatment of leprosy the greatest possible medical skill and care are necessary.

SPECIAL TREATMENT

In choosing the special treatment the best remedies and methods known at the time should be used. As a rule experimentation should be left to physicians with proper experience and facilities. The literature of leprosy is full of accounts of experiments on two or three cases made by doctors with little or no previous experience and incapable of truly evaluating the results. Treatment has progressively improved, especially during the last ten or fifteen years. In making recommendations we shall confine ourselves to drugs and methods which, after much trial and experience, are at present being used by some of the most experienced workers. The writer is naturally influenced by his own experience, but he is on the whole in line with the majority of other workers.

It is well before going further into the matter to point out that almost all effective forms of special treatments have a depressing effect; they produce a negative phase which varies in length and degree directly with the size of the dose and the frequency of injections, and must therefore be used with due regard to the resistance of the patient. The first dose must be tentative; the second should be given only when the negative phase of the first has passed off; gradually the dosage is raised till a balance is reached which indicates the limit of tolerance—this, however, may increase later, permitting the treatment to be pressed more strenuously.

In view of the discussion in the first part of this paper only passing reference will be made here to the use of vaccines of various kinds, the heavy metals, or potassium iodide—which is perhaps the most powerful method of auto-inoculation but is considered by most workers too dangerous for general use.

Of the other remedies the oils appear to give the best results, and chaulmoogra or hydnocarpus oil undoubtedly holds first place. Various forms of injection (intramuscular, subcutaneous, intravenous and intradermal) have now entirely replaced the older methods of inunction and oral administration, though these are still often used as supplementary methods.

A preparation worthy of more than passing attention is sodium hydnocarpate (alepol) which, in many countries is used as the drug for routine treatment. As has been said, it can be demonstrated to be less effective than the oil and esters in its local effects when given intradermally. It has, however, the great advantages that being a dry powder it occupies little bulk and is easily preserved, and can thus be sent to outlying places where the oil and esters are not available. For intramuscular, subcutaneous and intravenous injection it has been found very valuable by many workers, though others have failed to get equally good results.

INTRADERMAL INFILTRATION

This method, the "plancha" method of the Philippine workers, including the infiltration of subcutaneous leproma, undoubtedly gives better results than intramuscular and subcutaneous injections. It is not difficult for any leprosy worker to satisfy himself on this point by treating some of a patient's lesions and leaving others for a control. In patients in whom the skin areas involved are too small to permit giving the desired doses by the intradermal route supplementary intramuscular or subcutaneous injections may be given.

Objections have been raised that leprosy is a general disease, and that improvement in infiltrated skin lesions cannot be taken as a proof that the drug used will cause improvement in deeper lesions, but it appears that the benefits of the injections are not confined to the lesions infiltrated.

Chaulmoogra oil versus esters.—The esters were originally made to obtain a preparation less irritating and more easily absorbed than the oil. However, oil manufactured from ripe, fresh seeds causes very little irritation, and with the intradermal method the need for

quick absorption has been lessened. In patients with extensive lesions it may take several months before the whole affected area of the skin can be infiltrated, and prolonged retention may increase the local effect.

One disadvantage of the oil is that, being more viscous, it does not penetrate the intercellular spaces as readily as do the esters, but this may be overcome by heating the oil on a water bath to 55°C. The greater difficulty of injecting is overcome by using a short guarded needle (159). On the other hand, the oil is necessarily much cheaper than the esters, and it is easier to ensure a uniform quality. Painful injections may frighten away patients. The *H. wightiana* oil obtainable in India, with 4 per cent creosote, causes on the whole no more irritation than the creosoted esters. In the Philippines the esters are iodized to reduce their irritating qualities. The relative efficacy of the oil and esters given intradermally has not yet been fully tested, but our experience is that both are effective, and that if either is better than the other the difference is not great.

TECHNIC

Injection.—A small syringe is used, and, except for reaching the deeper lesions, the short, guarded needle is convenient as it cannot enter the skin too deeply. The quantity of drug to be injected is drawn up or poured into the syringe; if oil is used its temperature must be at least 55°C. The area to be injected is marked off with a grease pencil and sterilized with spirit or iodine. Infiltration is made through multiple punctures, 6 to 10 mm. apart. One-half to one minim is injected at each puncture, so that to give the maximum 5 cc. dose some 80 to 100 punctures are required. Each injection raises a wheal or, if the skin is too thick for that, causes the markings to stand out in increased relief. If a large area has to be covered the punctures may be spaced more widely. The needle should be sloped to an acute angle with the skin surface and should not enter more than 2 or 3 mm. except for deeper lesions.

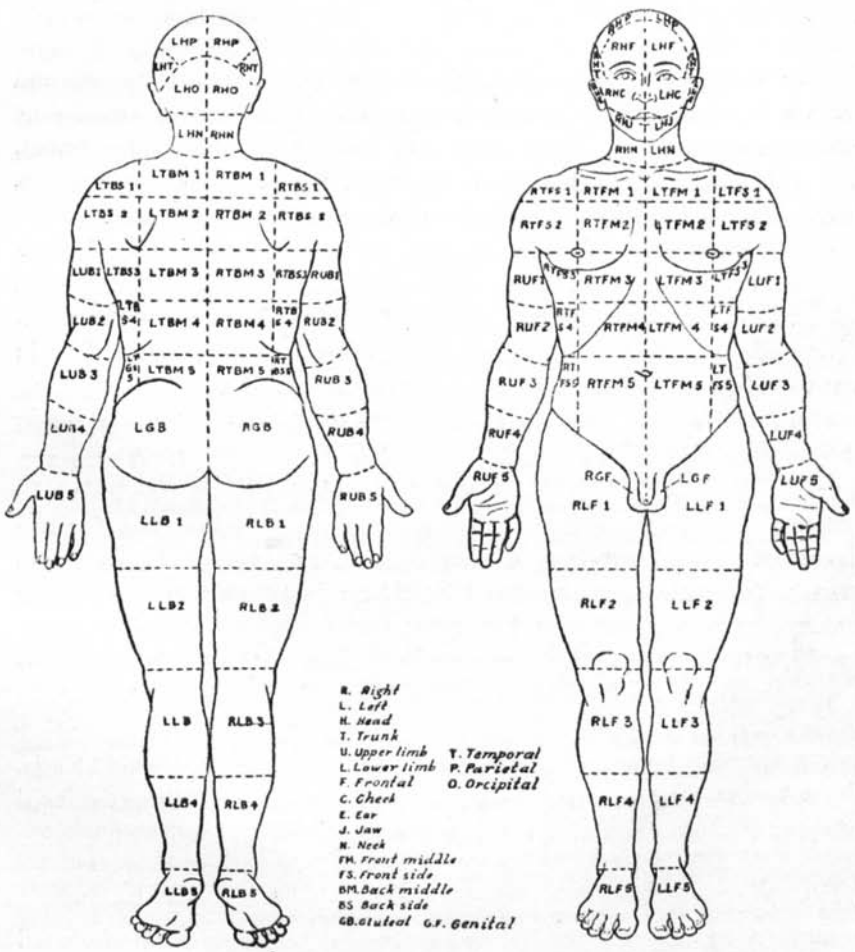
In patients with marked fibrous nodules it is sometimes well to begin treatment by infiltrating them, the more diffuse lesions being treated later. With an ordinary hypodermic needle 2 to 4 drops of the drug are slowly injected into the middle of the nodule, which will first swell and later shrink, with or without liquefaction and discharge.

Dose.—The dose will vary according to the tolerance of the patient from 0.5 to 5 cc., once or twice a week. In active patients in good condition the larger doses are tolerated, but as has been said, it is well to begin with the lower doses and gradually work up. Pain and ulceration may result if too much drug is injected at a point, or if the injection is too superficial, or if the drug is unduly irritating.

Choosing sites.—Almost all skin areas showing either visible lesions or deep analgesia due to local invasion by *Mycobacterium leprae* are suitable for infiltra-

tion. This does not apply to analgesia of the extremities due to affection of the nerve trunks supplying them, though infiltration of the skin covering a thickened, superficial nerve such as the ulnar sometimes causes marked improvement. Since lesions may be present without outward signs, one should not necessarily consider the absence of a visible lesion as a contraindication for infiltration if deep analgesia is present.

When lesions are widespread it is often well to begin with the back of the trunk as it is less sensitive and the process of injection cannot be seen; the face and other more sensitive regions are treated when the patient has become more accustomed to it. Records of treatments are kept to permit systematic



TEXT-FIG. 2.—The author's method of marking out the surface areas of the body.

covering of all the areas affected. A method of dividing the surface into 100 small, easily defined areas has been described by the writer; this is shown in Text-fig. 2, and also illustrated in Plate 2, fig. 2.

Reinfiltration.—As a rule lesions should not be infiltrated a second time within a month. The induration caused by the previous infiltration must first be absorbed lest much pain and even ulceration occur. Spots of hyperpigmentation remain at the old sites of puncture, and the new punctures should be made between them. Analgesia is generally less in areas already infiltrated, so there is more pain on each successive occasion. However, patients become accustomed to this and are willing to suffer it when they see definite improvement. With patients showing high general resistance and few lesions, we often find it sufficient to infiltrate all the lesions at one or two sittings and not repeat treatment for a month.

Supplementary treatment.—Recommendation of the intradermal infiltration method, the most effective remedy at present available, does not exclude other supplementary methods of special treatment. Hot baths, cauterization with trichloracetic acid and other caustics, heat with pressure by strapping, and many other methods will speed up the absorption of lepromata, and are therefore valuable for use in conjunction with the standard treatment. Wheatley (1923) and others have recommended a change in the special drug when the condition of the patient becomes stationary, but the change should be in the direction of raising the resistance of the patient.

Length of treatment.—Generally speaking, special treatment should continue until all active signs have disappeared. There are, however, certain factors which call for modification of this rule. In patients in whom some depressing factor was responsible for the development and progress of the disease, removal of this may so greatly facilitate improvement that, if an institution is pressed for space, such a patient may be sent home while still showing a few bacilli, with instructions to report from time to time. On the other hand, patients who have become free from all active signs but whose general health is not of a high standard, also those who on returning to unfavorable home conditions would become depressed, should continue under treatment in the institution for a longer time to avoid relapse.

Prognosis.—In a patient who can tolerate maximum treatment and maintain a sedimentation index below 10, a good prognosis can generally be given. Excluding accidents he should go forward steadily to recovery; though the time required will vary with the extent of the infection. Such patients are generally of active habits, good

physique and muscular development, and, as has been said, it should be the endeavor to bring such conditions about.

REGIONAL TREATMENT

Perforating ulcers.—The treatment of perforating ulcers depends on the depth of the lesion and on the state of the nerve supply. If the lesion is deep and involves the bones or joints, the dead tissues must be removed. Secondary infection and induration of the ulcer often prevent healing. If the supplying nerve has been destroyed healing is very difficult. Complete rest in bed and soaking the parts in mild antiseptics (water bath or repeated poultices) will cause at least temporary healing if dead bone is absent, but the new tissue is apt to break down when the patient begins to walk again. Patients may give rest to the ulcers and yet obtain exercise by using crutches, or the wooden bucket-leg with which the weight of the limb is thrown on the knee. Carefully padded shoes are also of use.

Denney (44) applied basic fuchsin to perforating and skin ulcers and obtained complete healing in 15 out of 33 cases. Lang (108) used iodoform dissolved in eucalyptus or acetone. Denney (45) and Rose (205) obtained healing by means of ultra-violet rays. Osawa and Nojima (171) got good results with sympathectomy, as did also Py and Riveros (186).

Operative treatment of the nerves.—Reference has been made to the use of adrenalin, sodium bicarbonate, etc. in the treatment of nerve troubles, and of diathermy in subacute and chronic nerve conditions. There are also certain operative measures which may be used with benefit, especially when the condition does not yield to other remedies.

The ulnar nerve as it passes behind the elbow is often bound down to the bone, and the acute swelling in reaction leads to strangulation, acute pain and sensory and motor paralysis. Incision of the constricting tissue gives relief of pain and, if the operation is performed in time, a considerable restoration of function. Furthermore, in acute reaction the ulnar nerve may be constricted by its own sheath, in which case linear incision for 3 or 4 inches above the elbow [Muir (145), Impey (98)] is very useful. Lowe (126) recommends the removal of the sheath for a few inches.

Abscesses occur in the ulnar and other nerves [Muir (142), Lowe (126)]. They are often multiple and may be central, causing swelling of the whole nerve, or may herneate through the sheath. Such abscesses should be incised and the contents scraped out; drainage is

seldom necessary. Nerve-stretching [Hansen and Looft (77)] is not satisfactory. Resection of the nerve [Loche (124)] is a useless and harmful procedure.

The eye.—Eye lesions in leprosy are due to either (a) leprotic invasions, or (b) anesthesia of the cornea and paresis of the eyelids. The former seldom occur unless there is involvement of the surrounding skin. Since there may be considerable affection of the eye without inconvenience or obvious clinical signs it is well to test with atropine all cases with lesions of the face or nose. If there is any sign of fixation or irregular dilatation atropine should be given occasionally to prevent further fixation. In giving special treatment to patients with eye lesions particular care should be taken to avoid reactions, for these are often disastrous to the eye.

Dizon (59) recommends subconjunctional injections of adrenalin and atropine to break down early adhesions of the iris. Wood (253) mentioned benefit from sodium taurocholate with bicyanide of mercury in saline. Hoffmann and others have obtained good results with krysolgan and other gold preparations. Kirwan (102), for corneal infiltration due to leprous granuloma, recommends a complete peridectomy, stating that it produces excellent results and often prevents extension of the disease. In cases in which the pupil is prevented from dilating by posterior synechiae he recommends a broad optical iridectomy. This gives at least temporary improvement in sight and in some more permanent improvement. However, in the majority of cases the final results have been disappointing; in many of them the ciliary infection is lit up afresh, with the formation of plastic exudation in the new pupil.

In our experience the best effects are from general treatment. Improvement may follow the use of gold, antimony, copper, mercurochrome and many other remedies, but they should be used carefully and with the object of improving the general health rather than of diminishing directly the intra-ocular infection. Subconjunctival injections of various well-diluted antiseptics are of use, probably as counter-irritants, if the patient's general resistance is high. Treatment should be early, and not left until the patient begins to complain of pain and photophobia. Eye infection is likely to recede gradually along with the rest of the infection of the body.

In the second type there is anesthesia of the cornea, and paralysis of the lower lid and ectropion and consequently inability to protect the eye-ball. The cornea is apt to become dry, and may ulcerate. Liquid paraffin should be dropped between the lids frequently during the day, and a pledget of cotton wool soaked in it should be tied over the eye at night. Massage of the face around the orbit and intrader-

mal infiltration of chaulmoogra esters in the periorbital region will often restore the function of the eyelids to a large extent in early cases. Heymans (88) recommended the treatment of lagophthalmus by joining the outer parts of the eyelids, raising a flap from the lower lid and fixing it to the upper lid. Kirwan (102) performs a marginal tarsorraphy in the more advanced cases.

The nose.—In the majority of advanced cases of cutaneous leprosy the nose is affected, particularly the septum. The cartilagenous part is frequently perforated and contraction may lead to depression of the nose. Since many bacilli are mixed with the nasal discharge it is probable that this is one of the most serious causes of the spread of infection. Various forms of treatment have been recommended to remedy this condition. Rose (206) used ionization with 1 per cent sodium hydnocarpate solution, finding that the number of bacilli was rapidly reduced, and that they often disappeared altogether. However, we find that while the bacilli are diminished and the patients relieved of obstruction we do not get complete elimination. The treatment recommended by Samson, Lara and Cruz (214) is much more effective: after anesthetizing the mucosa with 5 per cent cocaine they fulgurate with an insulated unipolar electrode from a diathermy apparatus, or as an alternative use 5 to 10 per cent chromic acid. In arrested cases it is often possible to improve the appearance of the deformed nose by operation.

The lungs.—Leprosy and tuberculosis of the lungs may co-exist [Muir (161)]. When there is tuberculous complication rest and suspension of special treatment are usually required, but if the pulmonary condition is leprotic the patient should be encouraged to take exercise and special treatment should be continued if the general health permits. The differential diagnosis of the acid-fast bacilli coughed up is made by injection of guinea-pigs.

CONTROL OF THE PATIENTS

Control under treatment.—One of the greatest difficulties in treating leprosy is the length of time required. Modern improvements have led to more rapid progress, and patients tend to present themselves in earlier stages, but on an average treatment of 3 to 5 years is required in well-established cases. The emphasis laid on general treatment makes it clear that without the intelligent and willing cooperation of the patient good results are impossible. Obviously, compulsory treatment is not likely to be successful, and in any circumstances careful and patient instruction is necessary.

Old patients who have made definite progress towards recovery give encouragement to the new-comers. The patient who is treated privately may lack this form of help, and the physician must make up for it by encouraging him in other ways. A careful prognosis should be arrived at, and this and also the necessity of his co-operation and persistent efforts should be explained to him.

In determining whether a patient should be treated as an in-patient or an out-patient the most important of various factors is the question of spreading infection, but as far as treatment is concerned the patient who has high resistance and is making favorable progress may profitably be dealt with at an out-door clinic. On the other hand, for the patient with low resistance or with complicating conditions it is exceedingly desirable that at least the initial treatment be in a hospital. Another factor is the condition of the patient's home —social, economic and hygienic. If there is ostracism and depression, if food is insufficient or unsuitable, or if the accommodations, surroundings or climate are unfavorable, the chances of the patient's recovery as an out-patient are considerably diminished and if possible he should be treated as an in-patient.

There are various forms of institutions for the accommodation and treatment of the leprous patient. For the hopelessly crippled the asylum or home is the most suitable. For those in good general health but requiring prolonged treatment under the safeguards of segregation, the colony or settlement supplies healthy exercise and occupation. For those suffering from lepra reaction or other depressing conditions careful treatment in a leprosy hospital is necessary. Institutions, therefore, should be of three classes, or should be divided into three sections, suited to the nature of the cases to be dealt with.

There is a difference of opinion as to the effects of promiscuous mixing of patients, e. g., of early neural and advanced skin cases. Some hold that those already showing signs of leprosy cannot be adversely affected by contact with other types. It is difficult to bring forward definite proof for or against this view. But in tuberculosis small or infrequent infections tend to produce immunity, while frequent or massive infections lead to disease, and the probability is that the same holds good in leprosy, perhaps in an even greater degree. It is wise, therefore, both in residential institutions and in out-patient clinics, to separate as far as possible the early neural from the advanced cutaneous cases. This we consider even more important for children, as it is in childhood that infection is most liable to take place.

Control after discharge.—The possibility of controlling the patient after discharge varies in different localities. In small areas it is sometimes possible to keep in touch with former patients. In India this is impossible, and few of those instructed to report after stated periods do so.

Lowe (128) found that of 84 discharged patients who reported during 1931, within an average period of 14 months after discharge, 12 showed relapse. Chiyuto and Valasco (25) were able to follow up 78 per cent of the quiescent and arrested cases released in the Philippines from 1922 to 1930. Of these 67 per cent had remained quiescent and 33 per cent had become active again. Of 735 cutaneous cases 542 remained quiescent, but of 23 neural ones 21 showed no recurrence of active signs.

These figures, while showing the undoubted value of treatment, also demonstrate the need of after-treatment and supervision if relapse is not to take place. Patients treated in the favorable circumstances of a residential institution tend to relapse when they return to the less sheltered life, the less regular routine and—as is often the case—the hardships of their home life. It is well, therefore, that patients should return for inspection at frequent intervals for a number of years, and that if any suspicious signs of recurrence appear they should report at once. During the time of treatment patients should be educated regarding the nature of leprosy, the danger of relapse, and the importance of maintaining throughout the remainder of life a high standard of general health.

REFERENCES

(1) ABRAHAM, P. S. AND HERMAN, C. L. Baumgarten's Jahresb. **14** (1897) 443.
(2) ALFRED, E. S. R. (Solganol in treatment). Lep. Rev. **4** (1933) No. 1.
(3) AMARAL AND PARANHOS. Bull. Gen. de Thérap. (1908) Jan. 23.
(4) AMIES, C. R. (Treatment with solganol). Trans. Roy. Soc. Trop. Med. and Hyg. **23** (1929) 309.
(5) AOKI, T. (Iodine in diagnosis and treatment). Japanese Jour. Derm. and Urol. **25** (1925) 95.
(6) AOKI, T. (Iodine in diagnosis and treatment). Japanese Jour. Derm. and Urol. **30** (1930) 213.
(7) AOKI, T. (Early diagnosis and treatment). Japanese Jour. Derm. and Urol. **31** (1931) No. 11.
(8) AOKI, T. AND AOKI, Y. (Intravenous sodium iodide in diagnosis and treatment). Derm. Wochenschr. **90** (1930) 438.
(9) ARCHIBALD, R. G. Jour. Trop. Med. and Hyg. (1921) Nov.
(10) ARNING, E. Report on Leprosy in Hawaii. 1886, 50.

(11) ARNAUD. (Case treated by tuberculin). Baumgarten's Jahresb. 12 (1896) 373.

(12) BABES, V. Baumgarten's Jahresb. 7 (1891) 284.

(13) BABES, V. Baumgarten's Jahresb. 17 (1901) 294.

(14) BABES, V. (Reaction of lepers to tuberculin). Compt. Rend. Soc. Biol. 67 (1909) 411.

(15) BALINA, L. (Cases). Sem. Med. 37 (1930) 777.

(16) BARGEHR, P. (Natural cure). Geneesk. Tijdschr. Nederlandsche-Indië (1926).

(17) BERTARELLI, A. Lepra 13 (1912) No. 1.

(18) BRAULT. Bull. Soc. Française de Derm. (1907).

(19) BRINCKERHOFF, W. R. AND WAYSON, J. T. (Studies on leprosy). Bull. United States Pub. Health and Marine Hosp. Serv. Washington, 1909.

(20) BROCQ AND POMARET. Bull. Soc. Française Derm. et Syph. 24 (1913) 70.

(21) CALLENS, J. (Treatment by leprolin). Bull. Soc. Path. Exot. 23 (1930) 909.

(22) CANAAN, T. (Treatment). Arch. f. Schiffs. u. Trop. Hyg. 35 (1931) 645.

(23) CARRASQUILLA. Baumgarten's Jahresb. 13 (1896) 475; 14 (1897) 438.

(24) CAWSTON, F. G. British Med. Jour. (1920) July.

(25) CHIYUTO AND VELASCO. (Observation of arrested cases). Jour. Philippine Islands Med. Assoc. 11 (1931).

(26) CHOPRA, GUPTA AND CHOWDHURY. (Antimony and adrenals). Indian Jour. Med. Res. 16 (1928) No. 2.

(27) COCHRANE, R. G. (Potassium iodide in leprosy). Jour. Christian Med. Assoc. India. (1929) 6.

(28) CEOLHO, G. (*C. braziliensis* in treatment). Presse Med. 34 (1926) 1357.

(29) COURTNEY, B. J. Lancet (1914) June 27.

(30) CROCKER, R. The Polyclinic (1900) Oct.

(31) CRUZ, M. C. (Ultraviolet rays in treatment). Jour. Philippine Islands Med. Assoc. 8 (1928) 134 and 312.

(32) CURRIE, CLEGG AND HOLLMANN. (Specific therapy). Lepra 13 (1912) No. 1.

(33) DANIELSSEN. Arch. f. Derm. u. Syph. 22 (1886) 220.

(34) DANIELSSEN. Baumgarten's Jahresb. 7 (1891) 284.

(35) DANIELSSEN. (Cited by Hansen and Looft, 1895).

(36) DAVIDSON, J. (Nastin treatment). Indian Med. Gaz. (1909) Nov., Suppl., 15.

(37) DEFILLO, F. A. (Treatment in the Dominican Republic). Presse Med. 34 (1926) 363.

(38) DELANOE, E. (Treatment by novarsenobenzol and B.C.G.). Bull. Soc. Path. Exot. 22 (1929) 898.

(39) DELANOE, E. (Treatment by novarsenobenzol and B.C.G.). Bull. Soc. Path. Exot. 23 (1930) 1005.

(40) DELAMARE, G. (Cases resistant to eparseno). Prog. Med. (1925) 896.

(41) DE LANGEN. Geneesk Tijdschr. v. Nederlandsche-Indië 62 (1922) No. 2.

(42) DE MELLO, F. Presse Med. (1921) Oct. 29.

(43) DE MELLO, F. AND CABRAL, J. (Treatment with eparseno). Bull. Soc. Path. Exot. **19** (1926) 779.

(44) DENNEY, O. E. Philippine Jour. Sci. (1915) Nov.

(45) DENNEY, O. E. (National Leper Home, Report for 1927). Pub. Health Rep. **43** (1928) 810.

(46) DENNEY, O. E. (National Leper Home, Report for 1928). Pub. Health Rep. **44** (1929) 3169.

(47) DENNEY, O. E. AND HOPKINS, R. Pub. Health Rep. (1922) Dec. 22.

(48) DENNEY, HOPKINS, WOOLEY AND BARENTINE. (Treatment with mercurochrome.) Pub. Health Rep. **40** (1925) 1795.

(49) DE NOVAES SILVA. (Treatment with tuberculin). Rev. Med. Cir. do Brasil **35** (1927) 83.

(50) DE PARREIRAS HORTA. (Treatment with braziliensis oil). Bull. Soc. Française de Derm. et Syph. (1926) 365.

(51) DE RAADT. O. L. E. (Nutrition in leprosy and tuberculosis). (1929).

(52) DE VERA. (Treatment with oils other than chaulmoogra). Jour. Philippine Islands Med. Assoc. **5** (1925) 374.

(53) DE VERA. (Treatment with various esters). Jour. Philippine Islands Med. Assoc. **9** (1929) 307.

(54) DEVOTO, A. (Treatment with vaccines from nodules). Giorn. Italiani di Derm. e. Sifil. **67** (1926) 618.

(55) DE VERTENIL. Arch. of Röntgen Ray (1913) July.

(56) DEYCKE. Monatsh. f. Prakt. Derm. (1908) Feb. 15.

(57) DIKSHIT, B. B. (Treatment with alepol). Indian Med. Gaz. **67** (1932) 7.

(58) DIESING-DUALA. Lepra **6** (1904) No. 1.

(59) DIZON. (Eye, etc., manifestations). Jour. Philippine Islands Med. Assoc. **10** (1930) 214.

(60) DYER, L. (Antivenene in treatment). Baumgarten's Jahresb. **14** (1897) 445.

(61) EHLERS. Lepra **1** (1900) Nos. 1 and 2.

(62) EHLERS. Lepra **1** (1900) No. 4.

(63) EMBREY. Philippine Jour. Sci. (1923).

(64) EUBANAS, F. (Treatment with javanin). Jour. Philippine Islands Med. Assoc. **7** (1927) 407.

(65) EUBANAS, F. Jour. Philippine Islands Med. Asso. (1930) July.

(66) EUBANAS, F. (Cocaine-adrenaline in neuritis). Bull. Philippine Health Serv. **11** (1931) 359.

(67) EUBANAS, F. AND DE VERA, B. (Treatment with gold). Jour. Philippine Islands Med. Assoc. **7** (1927) 319.

(68) FREDELL, Lancet (1914) Dec. 5.

(69) FELDT, A. (Treatment with gold). Klin. Wochenschr. **7** (1928) 73.

(70) FIGUEREDO, N. (Treatment with fibrolysin). India Med. Gaz. **64** (1929) 426.

(71) GANCHER AND BOINET. Bull. Soc. Française Derm. et Syph. (1913) 172.

(72) GIRARD, G. AND DUCROS. (Treatment with methylic tuberculosis antigen). Bull. Soc. Path. Exot. **21** (1928) 594.

(73) GOLDSCHMIDT, J. (Effect of tuberculin). Baumgarten's Jahresb.7 (1891 285.

(74) GREEN, R. (Observations on lepra reaction). Trans. Roy. Soc. Trop. Med. and Hyg. (1929) No. 4.

(75) HALLOPEAN AND AINE. Bull. Soc. Française Derm. et Syph. (1907) Dec. 7.

(76) HAMZAH, M. (Treatment with thymol). Klin. Wochenschr. 2 (1923) No. 42.

(77) HANSEN, G. A. AND LOOFT, C. Leprosy. English edition, J. Wright & Co. Bristol. 1895.

(78) HARPER, P. Jour. Trop. Med. and Hyg. (1920) Dec.

(79) HARPER, P. Jour. Trop. Med. and Hyg. (1923) Jan.

(80) HASLE, G. (Treatment with calcium chloride). Bull. Soc. Path. Exot. 22 1929) 11.

(81) HASLUND. Lepra 1 (1900) Nos 1 and 2.

(82) HASSON, J. (New method of diagnosis and vaccine treatment.) Trans. Roy. Soc. Trop. Med. and Hyg. 19 (1926) 349.

(83) HEGGS. (Note on treatment). British Med. Jour. 2 (1923) 1253.

(84) HEISER, V. G. Lepra 13 (1908) No. 1.

(85) HEISER, V. G. Pub. Health Rep. (1914) Jan. 2.

(86) HEISER, V. G. American Jour. Trop. Dis. and Prev. Med. (1914).

(87) HENDERSON AND CHATTERJI. (Note on treatment). Indian Med. Gaz. 63 (1928) 620.

(88) HEYMANS. South African Med. Rec. (1913) 246.

(89) HIRST, L. F. (Treatment). Ceylon Jour. Sci. 1 (1925) 107.

(90) HOFFMANN, W. H. (Treatment with antimony). Arch. f. Schiffs- u. Trop. Hyg. 31 (1927) 139.

(91) HOFFMANN, W. H. (Gold treatment). Munch Med. Wochenschr. 74 (1927) 405.

(92) HOFFMANN AND BACZ. (Early choroiditis). Bull. Soc. Path. Exot. 22 (1929) 11.

(93) HOLLMANN, H. F. Arch. Derm. and Syph. (1922).

(94) HOLLMANN, H. F. AND DEAN, A. L. Jour. Cutan. Dis. (1919) June.

(95) HOPKINS, R. (Treatment, especially chaulmoogra). New Orleans Med. and Surg. Jour. 69 (1916) No. 3.

(96) HOPKINS, R. (Cited by Rogers and Muir, 1925, p. 255).

(97) IMPEY. Essay, New Sydenham Society, 157 (1895).

(98) IMPEY. (Transmission and treatment). British Med. Jour. 1 (1927) 401.

(99) JOUENNE, P. AND GUILLET, R. (Treatment with B.C.G.). Bull. Soc. Path. Exot. 20 (1927) 91.

(100) KERR, I. (Chaulmoogra treatment at Dichpali). Lancet 2 (1925) 373.

(101) KINGSBURY, J. (A new antimony compound in treatment). Arch. Derm. and Syph. 24 (1931) 1053.

(102) KIRWAN. (Ocular complication). Trans. 7th Congress Far Eastern Assoc. Trop. Med., India, 1927. Calcutta, 1929, vol. 1, 295.

(103) KUPFFER, A. (Treatment with chaulmoogra and nastin). Lepra 8 (1909) 144.

(104) KUPFFER, A. (Treatment with krysolgan). Med. Klin. **23** (1927) 364.
(105) LABERNADIE, V. (Treatment with irradiated oil). Bull. Soc. Path. Exot. **22** (1929) 759.
(106) LABERNADIE, V. (Failure of potassium iodide). Ann. de. Med. et de Pharm. Colon. **28** (1930) 54.
(107) LAMOUREUX, A. Bull. Soc. Path. Exot. **16** (1923).
(108) LANG, M. C. (Local treatment of ulcers). Indian Med. Gaz. **65** (1930) 274.
(109) LARA, C. B. (Treatment with chaulmoogra derivatives). Jour. Philippine Islands Med. Assoc. **8** (1928) 56 and 263.
(110) LARA, C. B. (Plancha or infiltration method of treatment). Jour. Philippine Islands Med. Assoc. **9** (1929) 336.
(111) LARA, C. B. (Progress of treatment at Culion). Jour. Philippine Islands Med. Assoc. **10** (1930) 469.
(112) LARA, C. B., DE VERA, B. AND EUBANAS, F. (Results of trials of sodium hydnocarpate and Bruscheltini vaccine). Jour. Philippine Islands Med. Assoc. **8** (1928) 261.
(113) LARA, C. B., DE VERA, B., SAMSON, J. G. AND EUBANAS, F. G. (Causes of death at Culion). Jour. Philippine Islands Med. Assoc. **4** (1924) 289.
(114) LARA, C. B. AND NICOLAS, C. (Efficacy of the infiltration method in early cases). Jour. Philippine Islands Med. Assoc. **9** (1929) 312.
(115) LAVERDE. Twentieth Century Practice of Medicine. New York, 1897, vol. 18, 579.
(116) LEBOEUF, A. Bull. Soc. Path. Exot. (1914) June.
(117) LEGENDRE, F. (Treatment with eparseno). Ann. de. Med. et de Pharm. Colon. **23** (1925) 374.
(118) LENZ. (Treatment). Arch. f. Schiffs- u. Trop. Hyg. (1909) No. 12.
(119) LEVY, D. M. (Unna's treatment). Nederlandsche Tijdschr. v. Geneesk. (1925) 1422.
(120) LIE, H. P. (Bergen leprosy hospital). Lepra **1** (1900) 62.
(121) LIE, H. P. (Bergen hospital, 1899-1901). Lepra **4** (1904) No. 1.
(122) LIE, H. P. (Treatment). Deutsche Med. Wochenschr. **34** (1905).
(123) LITTLE, E. (Case originating in England, cured by vaccine). British Med. Jour. **2** (1926) 1034.
(124) LOCHE, H. (Surgery of nerve leprosy). Festschrift von Schjerning, 1913, 129.
(125) LOWE, J. (Lepra reaction). Indian Med. Gaz. **64** (1929) 438.
(126) LOWE, J. (Nerve abscess). Indian Med. Gaz. **64** (1929) 24.
(127) LOWE, J. (Hydnocarpous oil and ethyl esters). Lep. in India **4** (1932) No. 4.
(128) LOWE, J. (Re-examination of cases). Lep. in India **5** (1933) No. 1.
(129) MANSON-BAHR, P. (Protein shock treatment). Lancet **1** (1928) 1111.
(130) MAPLES, E. E. Nigeria Ann. Med. and Surg. Rep. 1919-1921, 33.
(131) MARKIANOS, J. (Treatment by defatted bacilli). Bull. Soc. Path. Exot. **23** (1930) 145.

(132) Marchoux, E. and Bourret, G. (Potassium iodide). Lancet 1 (1908) 1804.
(133) Mathews. Lepra 13 (1908) No. 1.
(134) Matta, C. Giorn Stat. de. Malat. Vend. Pelle. (1923).
(135) McCoy, G. W. Pub. Health Bull. (1916) Jan.
(136) Mc Donald, J. T. Jour. American Med. Assoc. (1920) Nov. 27.
(137) Mc Donald, J. T. and Dean, A. L. Pub. Health Rep. (1920).
(138) Mc Donald, J. T. and Dean, A. L. Jour. American Med. Assoc. (1921) May 28.
(139) Mercado, E. Pub. Health Rep. 28 (1913) 1855.
(140) Messum, G. (Treatment with nastin). Transvaal Med. Jour. (1910) 214.
(141) Moraitis. Lepra 4 (1903) 73.
(142) Muir, E. (Nerve abscess). Indian Med. Gaz. 59 (1924) 87.
(143) Muir, E. Leprosy. Diagnosis, Treatment, and Prevention. First edition, 1924; fifth edition 1930.
(144) Muir, E. (Leprosy self-healing). Lancet 1 (1924) 277.
(145) Muir, E. (External medication). Indian Med. Gaz. 51 (1926) 205.
(146) Muir, E. (Treatment of Wassermann-positive cases with a new mercurial). Indian Jour. Med. Res. 14 (1926) 291.
(147) Muir, E. (Fallacies in testing drugs). Indian Jour. Med. Res. 14 (1926) 125.
(148) Muir, E. Trans. 7th Congress Far Eastern Assoc. Trop. Med., India, 1927. Calcutta, 1929, vol. 2, 305.
(149) Muir, E. (Treatment with sodium hydnocarpate). Indian Jour. Med. Res. 15 (1927) 501.
(150) Muir, E. (Factors which influence incidence). Indian Jour. Med. Res. 15 (1927) 1.
(151) Muir, E. (Effects of kala-azar). Indian Jour. Med. Res. 15 (1927) 497.
(152) Muir, E. (Iodide antimony treatment). Indian Jour. Med. Res. 15 (1927) 507.
(153) Muir, E. (The sedimentation test). Indian Jour. Med. Res. 16 (1928) 135.
(154) Muir, E. (The sedimentation test). Indian Med. Gaz 64 (1929) No. 9.
(155) Muir, E. (Natural resistance). Trans. 8th Congress Far Eastern Assoc. Trop. Med., Siam, 1930. Bangkok, 1931, vol. 2, 524.
(156) Muir, E. (Treatment of residual disease). Lep. in India 2 (1930) No. 3.
(157) Muir, E. (Treatment). Trans. Roy. Soc. Trop. Med. and Hyg. 25 (1931) 87.
(158) Muir, E. (Solganol B in treatment). Lep. in India 4 (1932) No. 1.
(159) Muir, E. (The intradermal method). Indian Med. Gaz. 67 (1932) No. 3.
(160) Muir, E. (Potassium iodide in treatment). (Lep. in India 4 (1932) No. 2.
(161) Muir, E. (Leprosy of the lungs). Lep. in India 5 (1933) No. 2.
(162) Muir, E. and Chatterji, S. P. (Ephedrine in treatment). Indian Med. Gaz. 63 (1928) No. 4.
(163) Muir, E. and Chatterji, S. P. (Mercurochrome in treatment). Lep. in India 4 (1932) No. 3.

(164) MUIR, E. AND CHATTERJI, S. P. (Further on mercurochrome). Lep. in India 5 (1933) No. 1.

(165) MUIR, E., LANDEMAN, ROY AND SANTRA. (Treatment in relation to spread). Indian Jour. Med. Res. 11 (1923) No. 2.

(166) NEFF, E. A. (Ethyl esters of *Calophyllum bigator* in treatment). Jour. Trop. Med. and Hyg. 32 (1929) 241.

(167) NEISSER, A. (Therapy, especially serotherapy). Trans. 1st Internat. Lep. Conf., Berlin, 1897, vol. 2, 156.

(168) NICHOLLS. Trans. Roy. Soc. Med. (1908). Dec.

(169) NOLASCO, J. O. (Histopathology after local infiltration). Jour. Philippine Islands Med. Assoc. 9 (1929) 347.

(170) NOLASCO, J. O. Jour. Philippine Islands Med. Assoc. (1930) July.

(171) OSAWA AND NOJIMA. (Sympathectomy for trophic ulcers). Deutsche Med. Wochenschr. 53 (1927) 66.

(172) PALDROCK, A. St. Peterburgen Med. Zeitschr. (1912) 135.

(173) PALDROCK, A. (Leucopenia). Derm. Wochenschr. 81 (1925) 998.

(174) PALDROCK, A. (Complement consumption in carbon dioxide snow treatment). Derm. Wochenschr. 81 (1925) 1456.

(175) PALDROCK, A. (Carbon dioxide snow and solganol treatment). Arch. f. Schiffs- u. Trop. Hyg. 31 (1927) No. 10.

(176) PALDROCK, A. (Carbon dioxide snow and solganol treatment). Arch. f. Schiffs- u. Trop. Hyg. 32 (1928).

(177) PALDROCK, A. (Carbon dioxide snow and lopion treatment). Arch. f. Schiffs- u. Trop. Hyg. 33 (1929) 455.

(178) PALDROCK, A. (Non-specific treatment). Arch. f Schiffs- u. Trop. Hyg. 34 (1930) 237.

(179) PALDROCK AND RANGEL. (Sanocrysin treatment). American Jour. Trop. Med. 7 (1927) 214.

(180) PALMER, F. J. (Treatment with metallic salts). Ann. Meeting, Jorhat Branch British Med. Assoc., 1925.

(181) PAUTRIER, DESCAUX AND RABREAN. Bull. Soc. Française de Derm. et Syph. (1914).

(182) PEIPER. (Treatment with nastin B and B2). Arch. f. Schiffs- u. Trop. Hyg. 14 (1909) 46.

(183) PIERINI, L. E. (Treatment). Sem. Med. 35 (1928) 1183.

(184) PINARD, RABUT, GIRAND AND ABRICOSOFF. (Treatment by malaria therapy). Bull. Soc. Française de Derm. et. Syph. (1929) 648.

(185) PUENTE AND PIERINI. (Sanocrysin in treatment). Sem. Med. 33 (1926) No. 13.

(186) PY AND RIVEROS. (Treatment of ulcers by sympathectomy). 5a Reunion Soc. Argentina Patol. 1929, vol. 1, 408.

(187) RANGEL, M. (Prophylaxis and treatment). Rev. Med. Ceirurg. do Brasil 34 (1926) 113.

(188) RAO, G. R. AND ROY, A. T. (Mercurochrome in treatment). Indian Med. Gaz. 67 (1932) 124.

(189) RASCHID, F. (Nastin in treatment). British Med. Jour. 2 (1909).

(190) REMLINGER, P. AND BAILLY, J. (Treatment with B.C.G. and methylic antigen). Bull. Soc. Path. Exot. **21** (1928) 283.

(191) RHO, F. (Copper in treatment). Jour. Trop. Med. and Hyg. **27** (1924) No. 23.

(192) ROCAMORA, J. L. Lepra **13** (1912) No. 1.

(193) RODRIGUEZ. (Treatment with nastin). Therapist **19** (1909) 73.

(194) RODRIGUEZ, J. N. (Progress of treatment at Culion). Jour. Philippine Islands Med. Assoc. **5** (1925) 40.

(195) RODRIGUEZ, J. N. (Results of treatment at Culion). Trans. 6th Congress Far. Eastern Assoc. Trop. Med., Tokyo, 1925. vol. 2, 699.

(196) RODRIGUEZ, J. N. AND EUBANAS, F. B. (Treatment with antimony). Philippine Jour. Sci. **23** (1923) 576.

(197) ROGERS, L. Indian Med. Gaz. (1916).

(198) ROGERS, L. Indian Jour. Med. Res. (1917) Oct.

(199) ROGERS, L. Lancet **1** (1921) June.

(200) ROGERS, L. British Med. Jour. **2** (1923) July 7.

(201) ROGERS, L. (Croonian lectures). Ann. Trop. Med. and Parasit. **18** (1924) 267.

(202) ROGERS, L. Lancet (1928).

(203) ROGERS, L. (Treatment and prophylaxis). (1929).

(204) ROGERS, L. AND MUIR, E. Leprosy. Bristol, 1925.

(205) ROSE, F. G. (Treatment in British Guiana). Trans. Roy. Soc. Trop. Med. and Hyg. **21** (1928) 481.

(206) ROSE, F. G. (A new method of treating nasal mucosa). British Med. Jour. **1** (1929) 148.

(207) ROST, E. B. Indian Med. Gaz. (1904) May.

(208) ROW, R. (Treatment with a tubercle bacillus vaccine). Trans. Roy. Soc. Trop. Med. and Hyg. **19** (1926) 407.

(209) ROY, A. (Intravenous sodium bicarbonate for nerve pain). Indian Med. Gaz. **66** (1931) No. 4.

(210) ROY. Indian Med. Gaz. (1932).

(211) RUTHERFORD. Indian Med. Gaz. (1913) Feb.

(212) RYRIE, G. A. (Treatment with dyes). Trans. Roy. Soc. Trop. Med. and Hyg. **27** (1933) 85.

(213) SAMSON, J. G. (Creosote as an adjuvant). Philippine Jour. Sci. **23** (1923) 515.

(214) SAMSON, J. G., LARA, C. B. AND CRUZ, M. C. (Treatment of lesions of the nasal mucosa). Jour. Philippine Islands Med. Assoc. **10** (1930) 273.

(215) SANDES, T. L. South African Med. Rec. (1913) 246.

(216) SANTRA, I. (Leprosy survey). Indian Med. Gaz. **62** (1927) 442.

(217) SCHOLTZ, W. AND KLINGMÜLLER, V. (Leprosy bacillus and "leprin"). Lepra **1** (1900) No. 3.

(218) SCOTT, L. B. (Nastin treatment). Indian Jour. Med. Res. (1913) Oct.

(219) SEZARY, A. (Autohemotherpay). Bull Soc. Française Derm. et. Syph. (1930) 289.

(220) SEIBERT, C. (Iodine reaction). Baumgarten's Jahresb. **21** (1905) 410.

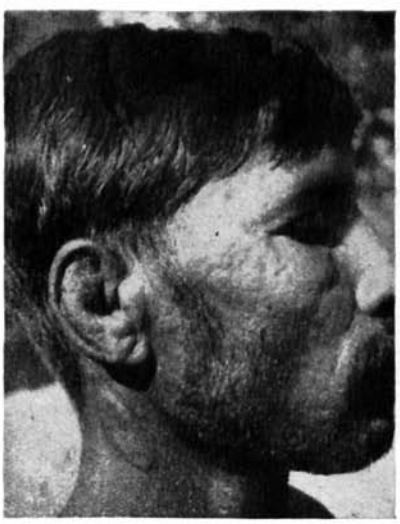
(221) SMITH, F. A. AND BISSET, E. (Bacteriology and treatment). Therapist **19** (1909) 61.
(222) SOREL, F. (Potassium iodide and tuberculin). Ann. de l'Inst. Pasteur **23** (1909) 533.
(223) SOUCHARD, L. (Treatment with B.C.G.) Arch. Inst. Pasteur d'Indochine (1926) No. 3.
(224) STEVENEL, L. Bull. Soc. Path. Exot. (1917) Oct.
(225) SUGAI, T. Mitt d. Med. Gesellsch. Tokio (1916) March.
(226) TAKANO, R. Jour. Exp. Med. (1916) Aug.
(227) TEAGUE, O. (Nastin treatment). Philippine Jour. Sci. **4** (1909).
(228) THOMPSON, J. A. Trans. 2nd Internat. Lep. Conf., Bergen, 1909.
(229) TONKIN, Jour. Trop. Med. (1904) 263.
(230) TRAVERS, E. A. O. (Treatment at Kuala Lumpur). Proc. Roy. Soc. Med. **19** (1926) 1.
(231) TREUHERZ, W. (Antileprol and tartar emetic in treatment). Derm. Wochenschr. **84** (1927) 394.
(232) TRUHART. (Treatment with tuberculin). Deutsches Med. Wochenschr. (1891) 28.
(233) UNNA, P. G. Berliner Klin. Wochenschr. (1913) Nov. 17.
(234) UNNA, P. G. Geneesk. Tijdschr. v. Nederlandsche-Indië **60** (1920) No. 5.
(235) UNNA, P. Derm. Wochenschr. **86** (1928) 383.
(236) VALVEDRE, B. Brasil Med. (1932) Dec. 2.
(237) VAN DEN BRANDEN, F. (Eparseno in treatment). Bull. Soc. Path. Exot. **18** (1925) 514.
(238) VAN HEIJNINGEN, K. (Thymol treatment). Geneesk. Tijdschr. v. Nederlandsche-Indië. **64** (1924) 932.
(239) VEILLON, A. AND LAGANE, L. Bull. Soc. Path. Exot. **6** (1913) 415.
(240) WADE, H. W. AND RODRIGUEZ, J. N. A Description of Leprosy. Philippine Health Service, Manila. (1927).
(241) WALKER, E. L. AND SWEENY, M. A. Jour. Inf. Dis. (1920).
(242) WALKER, N. (A case). Lancet **2** (1924) 542.
(243) WAYSON, J. T. (Iodine in treatment). Arch. Derm. and Syph. **3** (1921) No. 3.
(244) WAYSON, N. E. AND BADGER, L. F. (Derivatives of chaulmoogra by mouth). Pub. Health Rep. **43** (1928) 2883.
(245) WELCH, T. B. (Hydnocarpus oil and alepol). Jour. Port of Spain Med. Soc. (1927) 5.
(246) WHEATLEY, A. H. (Treatment at Pulan Jerejak). Trans. 5th Congress, Far Eastern Assoc. Trop. Med., Singapore, 1923, 252.
(247) WHEATLEY, A. H. (Treatment at Pulan Jerejak). Straits Settlements Med. Rep. for 1926, 69.
(248) WILDISH, G. H. AND STOUTE, D. G. (Combined treatment). Jour. Med. Assoc. South Africa **5** (1931) 21.
(249) WILSON, R. M. Southern Med. Jour. (1923) July.
(250) WILSON, R. M. (Industrial therapy). China Med. Jour. **43** (1929) 12.
(251) WISE AND MINETT. Jour. Trop. Med. and Hyg. (1912) Sept. 2.

(252) WOLFF, A. (Effect of potassium iodide). Baumgarten's Jahresb. 13 (1897) 519.
(253) WOOD, D. J. (Ocular leprosy). British Jour. Ophthalm. 9 (1925) 1.
(254) WOODSON, R. S. (Treatment with Calmette's antivenene). Baumgarten's Jahresb. 15 (1899) 400.
(255) WOOLEY, G. G. Science 26 (1907) 410.
(256) (Report). Tsinan (China) Hospital. 1932.
(257) (Report). Leonard Wood Memorial Conference on Leprosy. Philippine Jour. Sci. 44 (1931) 449.

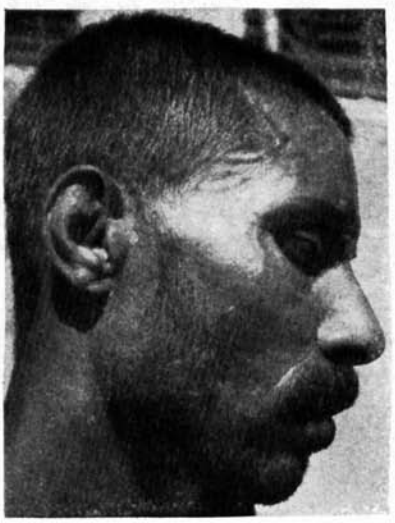
DESCRIPTION OF PLATE

PLATE 1.

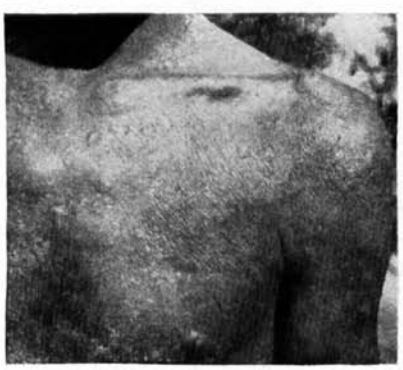
FIGS. 1 to 4. Illustrating the reduction of lesions after lepra reaction. Figs. 1 and 2, head and chest of a C-2 case during reaction. Figs. 3 and 4, the same patient three weeks later, after subsidence of reaction with treatment; clinical appearance of leprosy almost entirely gone but the case still C-2.



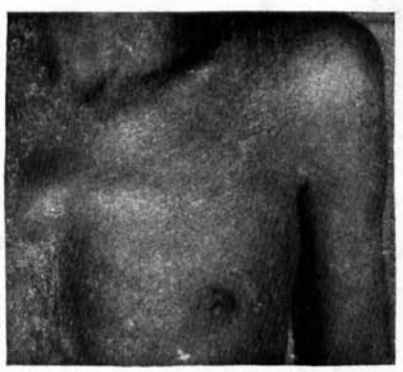
1



3



2



4

PLATE 1.

DESCRIPTION OF PLATE

PLATE 2.

FIG. 1. Effects of intradermal injections of hydnocarpus esters on the right side of the body, the left being used as a control. Note the degree of absorption of lesions in comparison with those on the left side, which were kept untreated to serve as controls.

FIG. 2. Abscess formation due to injecting mercurochrome over too long a period.

FIG. 3. Intradermal injections in marked-out areas.

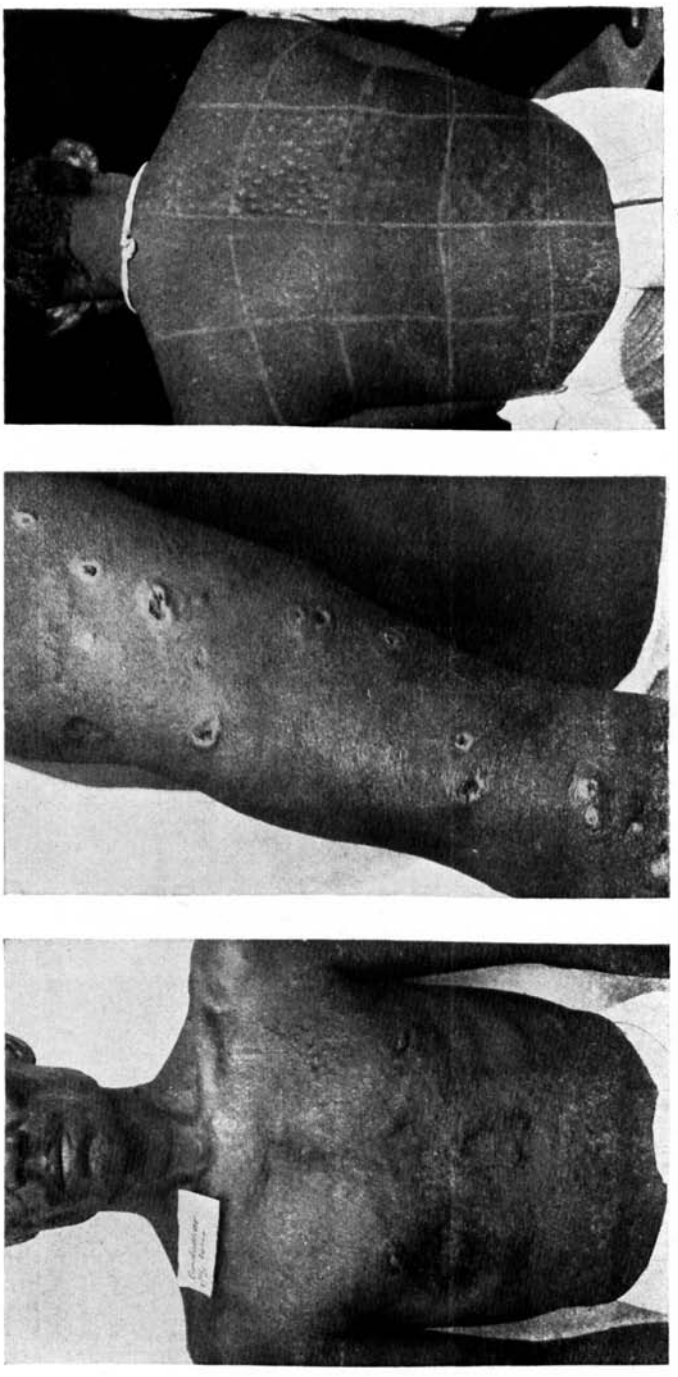


PLATE 2.