LEPROSY REVIEW.

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EDITOR - R. G. COCHRANE, M.D.

Contents.

The Association does not accept responsibility for views expressed by the writers. Communications may be sent to the Editor, at 29, Dorset Square, London, N.W.1.

NOTES ON CONTRIBUTORS.

T. F. G. MAYER, M.R.C.S., L.R.C.P., has just resigned his position as Secretary of the Nigerian Branch of the Association. He has served for over 20 years in the West African Medical Service.

J. RODRIGUEZ, M.D., is an officer of the Philippine Health Service and is in charge of the Leprosy Treatment Centre at Cebu. He was until lately Chief Physician of the Culion Leprosy Colony.

P. H. MANSON-BAHR, D.S.O., M.D., F.R.C.P., is one of the Physicians to the Hospital for Tropical Diseases, London, and Lecturer at the School of Tropical Medicine.

Sir LEONARD ROGERS, M.D., F.R.S., was Professor of Pathology at the School of Tropical Medicine and Hygiene in Calcutta, is a Physician of the School of Tropical Medicine in London, is Hon. Medical Adviser to the British Empire Leprosy Relief Association, and is on the Council of the International Leprosy Association.

H. I. COLE, PH.D., is Chief Chemist at the Culion Leprosy Settlement.

Editorial.

ON account of the importance of the recent International Conference held under the auspices of the Leonard Wood Memorial for the Eradication of Leprosy, it was felt that it would be profitable to devote most of this number of the REVIEW to matters concerning this gathering. We therefore feel certain that our contributors will forgive us for holding over their articles until the next issue. The Editor is very grateful to all who have so generously contributed to the pages of the REVIEW, and we would urge that the success of this journal depends on the constant supply of articles. While articles of a practical nature are most welcomed, those of a descriptive or topical nature will be gladly considered. In view of the expected publication of the International Journal of Leprosy in the near future it might be well to state that LEPROSY REVIEW endeavours to meet the need of a quarterly periodical of a practical nature dealing with aspects of the subject which will interest and instruct the worker who wishes to be kept up to date with the latest developments; it does not attempt to deal with the highly technical or scientific sides. This want, we feel sure, will be filled by the proposed quarterly of the International Leprosy Association.

In this number in addition to the valuable Review of the Report of the Manila Conference by Dr. T. F. G. Mayer, we are publishing a paper by Sir Leonard Rogers, which, for lack of space, has unfortunately had to be abridged. This paper represents Sir Leonard's considered views, and we are certain that it will be welcomed by a large circle of workers. While in this paper compulsory segregation in backward and primitive countries is condemned, and we think rightly, Sir Leonard is careful to point out that local conditions vary to such an extent that it may be impossible at present entirely to eliminate compulsion. Further, Sir Leonard mentions that compulsion may be a useful measure for the purpose of bringing pressure to bear on those early cases who refuse to attend for regular treatment, and on open cases who are unable or unwilling to take the necessary precautions.

It has more than once been stressed in this journal that while the ideal system is one which treats closed cases under a suitable dispensary system, and open cases under some sort of isolation, either home or institutional, we have not failed to point out that local conditions, and the state of public opinion, may cause some modification of the general

principle, and that the existing systems have to be modified rather than abolished. The ideal is to bring as many cases as possible under treatment and, if necessary, segregation, with the minimum amount of cost. It is only by a careful study of epidemiology and local conditions that a system can be devised in any country which will combine the maximum degree of efficiency with the minimum amount of expenditure. We trust that the section of the Report on the Manila Conference on Epidemiology will be carefully studied and acted upon, for, in no field is there more need for careful and prolonged study, and we feel sure that the stress laid on this aspect of leprosy work will stimulate further researches in the epidemiology of the disease, and will result in valuable contributions to our only too scanty knowledge of the etiology of the disease.

As the ethyl esters are being used to a great extent in the intradermal method of treatment, the method of preparation is described. The cold and hot processes are so simple, and the apparatus required uncomplicated, that it is hoped that the account of the manufacture of the esters will encourage those who wish to use them to make them locally. The intradermal method of injection is being very widely used, and is a distinct help in clearing up skin lesions. We trust workers will try out this method, and should they wish a supply of special needles they can be had either through the Association or directly from J. Gardner and Son of Edinburgh. There has been a great deal of discussion as to the action of the hydnocarpus preparations; to what extent they act only by virtue of their irritant affect on tissue cannot at present be estimated. It is felt by many workers, however, that the hydnocarpus group of remedies have in addition some special action on the processes of the disease.

While we have had to hold over much material, it was felt that the continuation of the valuable and instructive article by Dr. Manson-Bahr should be published in this issue, and we are sure that it will be of very great assistance to workers in the field. It is hoped to deal occasionally in the REVIEW with the treatment of other diseases which workers in leprosy may be called upon to manage. As far as possible, well known authorities will be asked to help us in this matter, so that those in the field may have authoritative guidance as to the treatment of the diseases which frequently complicate and make the healing of leprosy such a difficult problem.

Report of the Leonard Wood Memorial Conference on Leprosy held in Manila, Philippine Islands,

JANUARY 9TH TO 23RD, 1931.

(PHILIPPINE JOURNAL OF SCIENCE, Vol. 44, No. 4 April 1931, pages 449-480.)

REVIEW OF REPORT.

T. F. G. MAYER.

THIS is a unanimous report of a conference of leprosy workers, among whom were some of the best known in the world. It was possible to hold it in such a highly organised centre of anti-leprosy work as the Philippine Islands owing to the generosity and foresight of The Leonard Wood Memorial for the Eradication of Leprosy.

The following attended the conference :—

Drs. Et. Burnet, Secretary, Leprosy Commission, League of Nations ; R. G. Cochrane, Secretary, British Empire Leprosy Relief Association : Dr. H. I. Cole, Chief Chemist, Culion Leper Colony ; J. Fajardo, Director of Health, Philippine Health Service ; Maj.-Gen. J. D. Graham, I.M.S., Public Health Commissioner, Government of India ; ; Dr. G. Gushue-Taylor, Superintendent, Mackay Memorial Hospital, Taihoku, Formosa ; Dr. V. G. Heiser, Director for the Far East, Rockefeller Foundation ; Lee S. Huizenga, Superintendent, Mission Hospital Jukao Ku, China ; A. N. Kingsbury, Director, Research Institute, Kuala Lumpur, Federated Malay States ; P. H. J. Lampe, Director of Health, Dutch Guiana ; C. B. Lara, Chief Physician, Culion Leper Colony ; J. Lowe, Medical Superintendent, Dichpali Leprosy Hospital, India ; J. L. Maxwell, Henry Lester Institute of Medical Research, Shanghai ; E. Muir, Leprosy Research Worker, Calcutta School of Tropical Medicine ; E. A. Neff, Superintendent, Makogai Central Leper Hospital, Fiji ; B. Nocht, President, Leprosy Commission, League of Nations ; M. Ota, Tohoku Imperial University, Japan ; J. N. Rodriguez, Supervisor of Leprosy Treatment Stations; Philippine Health Service ; J. C. Tull, Government Pathologist, Singapore , H. W. Wade, Chief Pathologist, Culion Leper Colony, and Medical Director, Leonard Wood Memorial ; N. E. Wayson, Director, United States Leprosy Investigation Station, Hawaii ; Le Roy-Desbarres and H. Joyeux, of French Indo-China.

The main part of the report is concerned with recommendations calculated to deal with the confusion in the use of technical terms connected with leprosy to be met with in the world's literature.

The conference thought that there might be differences in the symptoms of the disease due to variations in strain of the causations organism, to racial peculiarities, or to such local conditions as diet, manner of life and so forth.

They considered that under the present differences of procedure and indiscriminate usage of terms, it was difficult to appraise and compare results as between one worker and another in different parts of the world.

It was desirable that this confusion should end and with this object in view the conference strongly urged an interchange of visits by serious students and workers in leprosy, so that they might be able to correlate their work.

The conference also recommends the compilation and keeping up-to-date of a comprehensive leprosy survey including information as to the extent and distribution of the disease in various parts of the world, the predominating types, factors affecting anti-leprosy work, the laws and regulations obtaining as well as the measures taken to combat the disease, including a description of the various forms of institution established. They consider the Leprosy Commission of the League of Nations, or an Association of Leprologists, suitable bodies to undertake such work.

The conference recommended that, in future, epidemiological data with regard to leprosy be given according to the following tabular form :—

Outline of Data to be Obtained.

I. Community. Name and type (village, town, district, country, &c.).

(*a*) Geography, Location, topography, geology, soils, &c.

(*b*) Climatology. Temperature (maximum, minimum, mean); humidity (relative, absolute); rainfall (minimum, maximum, mean, seasonal) winds (velocity, prevailing, hurricanes, typhoons, &c.).

(*c*) Population. Total number and variation in numbers; censuses or estimates; migrations; number of families.

(1) Racial, numbers of each; types of each (aborigines, natives, recent immigrants); mixtures (numbers and types).

(2) Social. Religions, castes, &c., numbers of each, types of each; marriage laws, food laws, &c., housing; types and sanitary surroundings.

(*d*) Occupation. Industrial; agriculture (crops, amounts and types); tenant system (serfdom, overcrowding, communal system, family or larger units); husbandry, fisheries.

(*e*) Diseases (general, not leprosy). Prevailing types, incidence of these and frequency of epidemics; endemicity, diseases probably due to faulty diets, types of diseases and prevalence.

(*f*) Leprosy. Incidence; distribution (geographically and by house within the community; note any unusual prevalence along lines of communication or in other districts.)

(*g*) School survey. Children; number of children from one to four years of age (inclusive); number of children of school age; number attending school; number of cases of leprosy in these groups.

2. Family.

(*a*) Blood relations. Name of head of family; number in family; age of members, sex of members; race; number, age and sex of breadwinners; age of individuals and total for family.

(*b*) Household family. Same data as for (*a*).

(*c*) Diseases. History of diseases other than leprosy in the family, including those prevailing in previous generation. Prevalence of disease in the habitation. Sanitary surroundings of houses.

3. Individual leprosy case.

Name: age; sex; occupation (indicate the type of the labour performed); age; economic status; marital state; race; caste; class; religion; education.

Dietary; foods and proportions of these used; manner of preparation (freshness of food).

Diseases other than leprosy; history, prevalence, &c., estimate of state of general health.

Leprosy; examine for the following: type (neural or cutaneous and degree of these); probable infectivity; source of infection; history of case; history of previous cases in the family, in relatives and previous generations; contacts, including previous cases in the family or household, as well as casual contacts.

The conference proposes the following classification of types of leprosy.

(*a*) *Main Types.*

Neural (N)—All cases showing evidence of actual or previous nerve involvement, *i.e.*, alterations of sensation with or without changes in pigmentation or circulation, trophic disturbances or paralyses and their consequent results; atrophies, contractures, ulcerations. These are not accompanied by leprotic changes in the skin.

Cutaneous (C)—All cases showing leprotic lesions in the skin. Such cases may or may not show, at any given time, clinical manifestations of nerve involvement.

(*b*) *Sub-Types* (*Indicating degree of severity*).

Neural—1 (N-1) Slight neural; cases with one or a few small areas of disturbed sensation, which may or may not show alterations of circulation or pigmentation, paralyses or trophic disturbances of minor degree.

Neural—2 (N-2)—Moderately advanced neural; cases with extensive or numerous areas of disturbed sensation, not confined to any one part of the body; with paralyses or/and visible evidences of trophic disturbances; marked depigmentation, moderate atrophy, keratosis, bullæ, &c.

Neural—3 (N-3)—Advanced neural; cases with more or less extensive areas of anæsthesia and marked motor and trophic disturbances; marked paralyses, atrophies, contractures, trophic ulcers and mutilations.

Cutaneous—1 (C-1)—Slight cutaneous; cases with one to a few leprotic macules, or a few small areas of infiltration, or nodules.

Cutaneous—2 (C-2)—Moderately advanced cutaneous: cases with numerous leprotic macules, or fairly numerous or marked areas of infiltration, or nodules, frequently with lesions of the mucosa.

Cutaneous—3 (C-3)—Advanced cutaneous: numerous or very marked involvement and such cases should be recorded to indicate the degree of this involvement, as, for example, C-2, N-1.

Secondary Neural—Neural cases that were formerly cutaneous, but from which the active leprotic lesions have disappeared.

With regard to nomenclature, the congress considered that the use of the following terms should be avoided altogether namely:—

1.—The "toxin" of leprosy or of the M. lepræ, there being no evidence to support the use of such a term.

2.—"Case of leprosy" is applied indiscriminately to all types, from those that are active, but with slight involvement, to those with marked mutilations,

but in which all evidence of activity has long since disappeared and only the permanent sequelæ remain.

The conference recommends that the term in the first column of the following list should be used instead of those in the second, *viz* :—

Mycobacterium lepræ	instead of	Bacillus lepræ
Neural case, Cutaneous case or Secondary neural case	,,	Clinical leper. / Incipient leper.
Closed case	,,	Bacteriologically negative case.
Open case	,,	Infectious case.
Arrested with deformity	,,	" Burned-out " case.
Case of Leprosy	,,	Leper.
Lepra reaction	,,	Acute exacerbation.
Arrested case	,,	Cure, negative, quiescent or relatively cured.

The conference approved the use of the terms :—

Leprotic.	Leproma.
Ulcers. Leprotic.	Ulcers. Trophic.
Infiltration.	Nodule.
Papule.	Macule.

Interrupted case=a quiescent case re-activated.
Relapsed case=an arrested case re-activated.
Suspected case.

The conference defines the following terms :—

1. " Suspected case."
   Applies to a patient who presents clinical signs suggestive of leprosy but insufficient for definite diagnosis.
2. " Clinical case."
   A case diagnosed as leprosy on clinical grounds, the bacteriological findings being negative. This term, however, is not recommended.
3. " Incipient case."
   An early or slight case in which the bacteriological findings are negative. This term, which has been used where cases of the cutaneous type predominate and those with bacteriologically positive findings are isolated, is not recommended.
4. " Leprotic."
   It is suggested that the term be applied to those changes which present clinical or microscopic evidence of inflammatory processes, typically of a granulomatous nature, which are apparently caused by M. lepræ in them.
5. " Leproma."
   Is applied in a general sense to any lesion of a leprotic nature.
6. " Leprotic ulcers."
   As those occurring in leprotic lesions which discharge the M. lepræ.
7. " Trophic ulcers."
   As those dependent on nerve changes which do not discharge the M. lepræ.
8. " Infiltration."
   A diffuse leprotic thickening of skin or mucous membrane which is not definitely of nodular, papular or macular form.

9. "Nodule."
   A definitely thickened, rounded, circumscribed mass of leprotic nature occurring in the skin, mucous membrane or subcutaneous tissue.
10. "Papule."
   A small solid elevation of the skin not more than five millimetres in diameter and of a leprotic nature.
11. "Macule."
   A circumscribed area of the skin showing a change in colour sometimes with elevation or depression. The following terms may be used further to qualify its description: hypopigmented, hyperpigmented, erythematous, circinate, marginate, zonal, raised, atrophic.
12. "Active case."
   One in which there is clinical or microscopic evidence of progressive or recessive change in lesions with or without accompanying systematic disturbances. These evidences include:—
      (*a*) positive bacteriological findings by usual methods in skin or mucous membrane.
      (*b*) the presence of raised or erythematous lesions.
      (*c*) increase or diminution of lesions in size or number.
      (*d*) tenderness of nerves with or without thickening.
13. "Quiescent case."
   One in which there is no longer clinical or microscopic evidence of activity as defined in 12.
      (The conference recommends the use of this term only in those cases from which signs of activity have been absent for at least three months; such absence to be determined by at least one examination a month. This examination to include a clinical examination as well as a microscopic examination of the nasal mucosa at more than one site and of lesions of the skin at more than two sites.)
14. "Arrested case."
   One which has remained "quiescent" for a period of at least two years.
15. "Interrupted case."
   This is one which, having been found "quiescent," has later become "active."
16. "Relapsed case."
   This is one which, having been termed "arrested," has later become "active."

There are a number of other subjects touched on in this report such as early diagnosis, treatment and the study of contacts, but they have been dealt with from time to time in LEPROSY REVIEW, so that it is not considered necessary to enlarge on them for the benefit of readers.

Possibly the most important action taken by the Conference was the formation of an International Leprosy Association the purpose of which is to encourage and facilitate mutual acquaintance and collaboration between persons of all nationalities concerned in leprosy work, and the co-ordination of their efforts; to facilitate the dissemination of the knowledge of leprosy and of its control; to aid in any other practical manner the leprosy campaign throughout the world; and to publish a scientific journal of leprosy to be called "The International Journal of Leprosy."

It is proposed that this periodical shall contain suitable original articles, reprints of important papers, abstracts, items of news, correspondence and any other suitable material.

The Editorial Board of Control will be chosen by the General Council and will consist of an Editor and two Assistant Editors.

The conference requested financial aid for the establishment of this journal from " The Leonard Wood Memorial for the Eradiction of Leprosy," this aid to be given, it is requested, for five years.

The Temporary General Council elected by the conference consisted of the following :—

President : Dr. Victor G. Heiser.

Vice-President : Western Section—Prof. Carlos Chagas.
Eastern Section—Dr. E. Muir.

General Council : Prof. Nagayo.
Sir Leonard Rogers.
Dr. Etienne Burnet.
Prof. de Langen.

Secretary : Dr. Robert G. Cochrane.

Treasurer : William H. Brown (Ph.D.).

Editor and General Councillor, ex-officio : Dr. H. W. Wade.

Associate Editors : Dr. H. P. Lie.
Dr. James L. Maxwell.

The duties of the Temporary General Council were to be directed to the formation of a permanent General Council. To this end it was charged with the duty of enrolling additional members, and on the attainment of adequate membership with the conduct through the post of an election of regular officers, and the organisation of sections.

It was thought by the conference that these objects could be obtained within a year.

It is hoped that a large amount of support will be forthcoming from medical men interested in leprosy, for only through collaboration and co-operation can progress be maintained, and further opportunities such as the Manila Conference be afforded for mutual discussion on international lines. The Far Eastern Association of Tropical Medicine has become an established institution, and those interested in research and progress in leprosy are urged to combine to make this new International Leprosy Association an outstanding success. Inquiries should be sent to the Secretary at 29, Dorset Square, London, N.W.1, from whom copies of the Constitution and By-Laws can be obtained.

DETAILS OF EXAMINATION.

Reprinted from the Report of the Leonard Wood Memorial Conference on Leprosy held in Manila, Philippine Islands.

(*a*) *Clinical Examination.*

THE whole body should be examined, in so far as is possible, in a good light and all the findings accurately recorded. While many auxiliary tests may be employed, the following methods are important :—

1.—*Sensation to light touch.*—The patient should be blindfolded. The normal skin should be repeatedly touched with some light object, such as a cotton swab, a feather, a camel's-hair brush, a spill of paper, and the patient asked to indicate accurately with the point of the finger the place touched. When the patient is responding to these stimuli the suspected skin areas should then be similarly tested, loss of sensation to light touch being indicated by repeated failure to respond. In this way anæsthetic areas may be gradually mapped out.

2.—*Sensation to pain.*—The eyes being blindfolded, a suspected skin area is alternately touched with the head of a pin and pricked with the point, a corresponding normal area being similarly examined immediately afterwards. The patient is questioned as to which prick produces more pain, the touch with the head or the prick with the point. This process should be repeated several times so as to avoid error.

3.—*Sensation to heat and cold.*—This may conveniently be tested under similar conditions by touching suspected areas with two test tubes alternately, the one containing hot (40° to 50° C) and the other cold water (20° C. or lower), the patient being asked to distinguish between them.

4.—*Thickening of the skin.*—The detection of slight degrees of skin thickening often requires considerable care. Inspection, with or without a magnifying glass, should be supplemented by palpation, the suspected area being rolled between the finger and thumb. Comparison should be made with the surrounding skin and with the corresponding area on the other side of the body.

5.—*Thickening and/or tenderness of the nerves.*—The superficial nerve trunks in normal individuals are frequently palpable and firm pressure may elicit slight pain. The determination of the thickening and abnormal tenderness should depend on careful comparison with the nerve, if

unaffected, on the other side of the body, or with the corresponding nerve in a healthy person of similar build. The superficial nerve trunks most commonly affected are the ulnar, the superficial peroneal, and the great auricular. Sensory branches supplying macules are sometimes tender and palpably thickened.

6.—*Mucous membranes.*—In examining the nasal mucosa it is advisable to use a speculum, and the field should be well illuminated.

(*b*) *Bacteriological Examination.*

Particular stress is to be laid on the need of examining smears from several sites and of making repeated examinations. Organisms may be demonstrable in one lesion or in only one part of it, while in another lesion they cannot be detected. In the early progressing cutaneous case the organisms in a lesion may be few and scattered, later becoming more numerous and generalised, while the converse may be true in the case as it improves.

Smears should contain as little diluting material (blood lymph) as possible, but the specimen should be so taken as to contain cellular material from the deeper layer in which the organisms are normally to be found.

1.—*Skin examination.*—There are two principal methods of procuring material for examination ; namely, the " scraping " and the " snip." By the former a very small cut, about 2 millimetres deep, is made with the scalpel well into the dermis, and material is scraped from the depth of this and smeared on a slide. By the latter method a small portion of the dermis, at least 2 millimetres thick is snipped off with a sharp pair of scissors, curved on the flat. The raw surface of the tissue so obtained is applied to a slide and firm pressure is exerted so as to express as much as possible of the cellular elements.

2.—*Nasal examinations.*—With the use of the nasal speculum the interior of both nares is carefully examined for infiltrations, nodules, and ulcers. If any of these is found, material should be removed therefrom with a blunt narrow-bladed scalpel, or a similar instrument, by scraping deep enough to cause a slight bleeding. Even when there is no visible lesion, a scraping should be taken from the septum, M. lepræ may be found on the septum, the inferior and middle turbinates, or the floor of the nose. The material so obtained should be smeared on a slide.

3.—*Staining.*—After drying, and fixing over a flame,

smears are stained for at least ten minutes at room temperature or heated three minutes till steam rises, in a solution of carbol fuchsin. This is prepared by mixing one part of a 10 per cent. solution of basic fuchsin in 90 per cent. alcohol with nine parts of a 5 per cent. solution of carbolic acid crystals in distilled water. This solution should be prepared at frequent intervals and be discarded when there is any trace of precipitate.

The slide is decolorised with sulphuric acid (10 per cent.) or nitric acid (10 to 20 per cent.) in water, and counterstained with methylene blue.

MANUFACTURE OF MIXED ETHYL ESTERS OF HYDNOCARPUS-GROUP OILS.

Reprinted from the Report of the Leonard Wood Memorial Conference on Leprosy held in Manila, Philippine Islands.

Preparation of esters by hot process.—Ten litres of hydnocarpus oil are boiled vigorously for forty-eight hours with 5 litres of 96 per cent. ethyl alcohol and 100 cubic centimetres of concentrated sulphuric acid under a reflux condenser. The principal advantage of vigorous boiling is undoubtedly that it keeps the two layers well mixed. The esters are then separated from the lower layer from which the excess alcohol can be recovered by distillation. The esters are washed three times with about 20 litres of water, separated from the washing water, and dried in a steam kettle or on a water bath. The yield from 10 litres of oil is about 11 litres of esters. Proportionally smaller amounts of materials may be used to prepare smaller lots of esters.

Distillation.—The washed and dried ethyl esters are then distilled at 20 to 25 millimetres pressure in a glass or iron still.

Washing with alkali.—Before neutralising the esters, the acidity is determined by titration. Five hundred grams of lye (94 per cent. sodium hydrate) are dissolved in 80 litres of hot water (90° C.) in a 160-litre steel drum. Forty-five litres of the distilled ethyl esters (2·5 to 3 per cent. acidity) are added and thoroughly mixed. If the acidity is higher than 3 per cent. a correspondingly increased amount of lye is added. After the mixture has stood for twenty-four hours the clear lower layer is drawn off through an outlet in the bottom of the tank. Hot water (90° C.) is added to the 140-litre mark, thoroughly mixed, allowed to settle for twenty-four hours, and again drawn off. The washing with water is repeated four times, and each time twenty-four hours are allowed for settling. The yield is about 96 per cent., and the acidity (as oleic acid) is usually under 0·1 per cent. If smaller lots of esters are to be neutralised

it may be found necessary to add crystals of sodium chloride to assist the separation. Heating on a boiling-water bath will also hasten the process.

Steaming and drying.—Volatile impurities, which are often irritating, may be eliminated by blowing out with steam. The esters are placed in ordinary 5 gallon oil tins to settle, poured off from the separated water, and filtered through paper. The product is a clear, very pale yellow, mobile liquid with a slight characteristic odour. Smaller quantities of esters may be refined by this method.

Ethyl esters manufactured by the above process are of constant composition and relatively non-irritating, regardless of the source or quality of the original oil.

Preparation of esters by cold process.—Four hundred twenty-five grams of cold-drawn hydnocarpus oil of good quality, 550 cubic centimetres of 96 per cent. ethyl alcohol, and 32 cubic centimetres of sulphuric acid (sp. gr. 1·845) are placed in a bottle with a tight-fitting glass stopper and left until the process of esterification is complete. The bottle should be shaken once or twice a day to mix the upper and lower layers. This, or placing the bottle in the sun or in some warm place, hastens the process. Neither shaking nor heat is, however, essential if time is not a consideration. At first the oil forms a lower and the alcohol and acid an upper layer. As esterification proceeds a point is reached at which the lower layer, now chiefly composed of esters, is of lower specific gravity than and rises above, the original upper layer, which now contains a large proportion of glycerol. To ensure the completion of esterification it is well to allow the process to continue for a further period equal to the time required for the rising of the lower layer. Thus, if the lower layer takes fourteen days to rise, the ingredients should be left in the bottle for another fourteen days. When the upper layer dissolves completely in alcohol the esterification is complete; esters, but not oil, being completely soluble in alcohol. The lower layer is then drawn off and the upper layer repeatedly washed with an equal volume of water until the water is free from acid as tested by litmus paper. A 0·1 per cent. solution of sodium hydrate in water is then added; this forms a thick emulsion. The vessel is slowly rotated and crystals of common salt are gradually added in small quantities in order to break the emulsion. The lower layer is removed; and the upper layer consisting of esters, after being washed once more with distilled water, is filtered through thick filter paper. The esters, though now clear, still contain a

certain amount of fine emulsion which makes them dark in colour. This may be removed by drying on a water bath for two or three hours while stirring constantly with a glass rod. The esters are then filtered again and the process is complete.

The esters may be washed in the bottle in which they have been prepared by substituting for the glass stopper a perforated cork with two glass tubes; one, 2 inches in length, is inserted flush with the inner end of the cork and fitted with a piece of rubber tubing compressed with a spring clamp; the other reaches to the bottom of the bottle. By inverting the bottle the esters rise to the top and the lower layer may be drained off by opening the clamp; or the lower layer may be syphoned off through the long glass tube without inverting the bottle. A separating funnel is more convenient for separating and washing the esters.

Preparation of ethyl esters by hot process without distillation.—The esters may be much more rapidly prepared by placing the ingredients mentioned under the cold process in a flask on a water bath arranged to maintain a constant level of water. A reflux condenser is connected with the flask. The water bath is kept at a temperature sufficient to maintain brisk boiling inside the flask. This is continued without stopping for eighteen hours, when it will be found that esterification is complete. Washing off the esters is then carried out as described in the cold process. The weight of the esters recovered is almost equal to that of the oil used.

In order to produce non-irritating ethyl esters by the last two processes, the original oil must be non-irritating.

**Addition of iodine.*—Addition of metallic iodine (0·5 per cent.) to the ethyl esters markedly reduces the irritating quality of the ethyl esters. Fifteen litres of the purified esters are heated in a 20 litre enamelled kettle to 140° C. The esters must be thoroughly dried before iodine is added since, if water is present, it effects by catalysis the hydrolysis of several per cent. of the esters. If the filtered esters are clear, the heating to 140° C. before adding the iodine will drive off all dissolved water. Seventy-five grams of chemically pure re-sublimed iodine are added with stirring. The temperature immediately rises to 150° C. at which point it is maintained for exactly thirty minutes, the liquid being stirred occasionally. After cooling, the iodised esters are filtered into bottles (250 cubic centimetres capacity) and sterilised for one hour in an oven at 150° C. The temperature of the contents of the bottles reaches in this time 110° C.

*Instead of iodine pure double distilled creosote to the extent of 4% may be added.—*Editor.*

The bottles are tightly corked, and sealed with paraffin or sealing wax and allowed to stand two weeks before use.

Note 1.—Smaller lots of esters can be iodised by this method provided that a shallow (pan) type of container is used.

Note 2.—It is not advisable to use esters after the lapse of two years, although samples that have stood longer than three years do not seem to have deteriorated sufficiently to become markedly irritating.

Note 3.—Iodised esters must be kept tightly corked and preferably in a dark, cool place. Repeated resterilisation should be avoided. Heat or sunlight in the presence of air produces a change in the iodised esters, which increases their irritating qualities to a marked extent.

Refining of hydnocarpus-group oils.—Crude hydnocarpus oils are sometimes found to give pain upon injection. A bland, non-irritating oil may be produced by the following methods of refining.

Volatile impurities can be removed by passing steam through the oil for about an hour, either before or after washing with alkali. Sufficient steam is used to give an aqueous distillate of about one-fifth the volume of the oil. The amount of volatile impurities is very small, but the distillate has a strong odour.

The free fatty acids are removed by washing with a solution of caustic alkali, and the only difficulty is the separation of the pure oil from the resulting emulsion. The following method has proven satisfactory. One hundred and fifty litres of hot water (about 90° C.) are run into a 400 litre steel drum provided with a faucet at the bottom ; 0·5 kilogram of lye (94 per cent. sodium hydrate) is added, followed by 100 litres of hydnocarpus oil (not over 2·5 per cent. acidity), and thoroughly mixed. With oil of higher acidity a correspondingly increased amount of lye must be used.

After the emulsion has stood twenty-four hours the clear lower layer (about 125 litres) is drawn off. Hot water is run in, while stirring, up to the 350 litre mark.

After two days the slightly opalescent lower layer (200 litres) is drawn off. The washing with water is repeated four times and twenty-four hours are allowed for separation on each occasion.

Ninety-five litres of oil are obtained, with an acidity of not over 0.2 per cent. This oil is steamed as described above and filtered, while hot, through folded filter papers. The

filtrate is dried by heating in an enamel-ware kettle, filtered again, and sterilised in bottles at 150° C.

Some provision must be made for keeping the oil hot during the separation of the emulsion if smaller quantities are refined, otherwise the mixture cools too rapidly to allow separation to take place.

A Method of Treatment by Intradermal Injection.

As this method has been in use in some of the largest centres for some time, it is felt that a general description of it might be appreciated by readers of LEPROSY REVIEW.

The intradermal or intracutaneous method has been employed by the Philippine workers for some years and it was originally described in the Journal of the Philippine Medical Association (September, 1929). The objects of this method are twofold :—

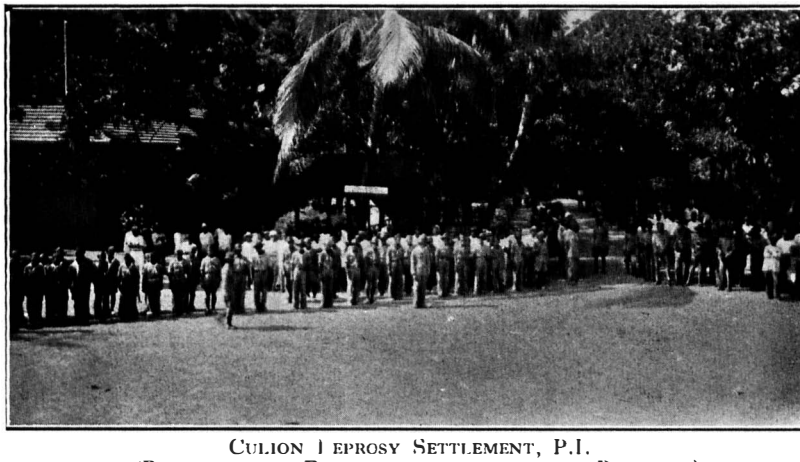
(1) To produce a degree of counter irritation and so assist in the absorption of inflammatory products.

(2) To endeavour to bring the drug in direct contact with the bacilli in the lesion.

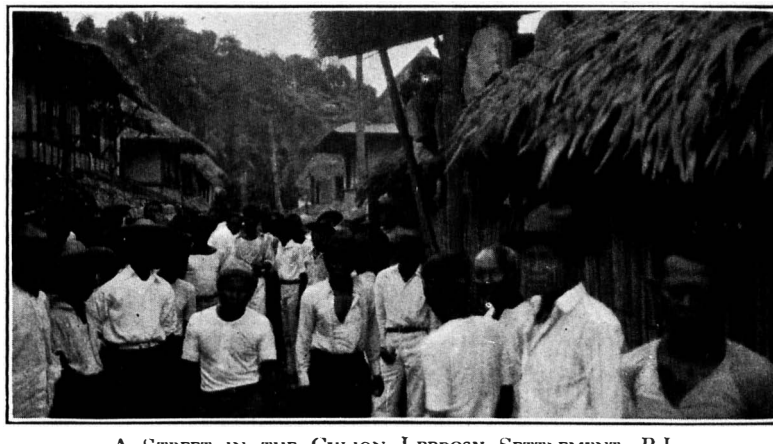
The advantages claimed are that it produces more rapid resolutions of the superficial lesions and that it is relatively free from general and local untoward results. The disadvantages are that it is more painful and takes longer to apply. As a form of counter irritation it appears to be more effective than only applying trichloracetic acid. The type of lesions that are most suitable for injection are raised macules, infiltrations and nodules. It may be impossible to inject into nodules if they are very tense; in this case they can be surrounded by a ring of injections.

Technique.

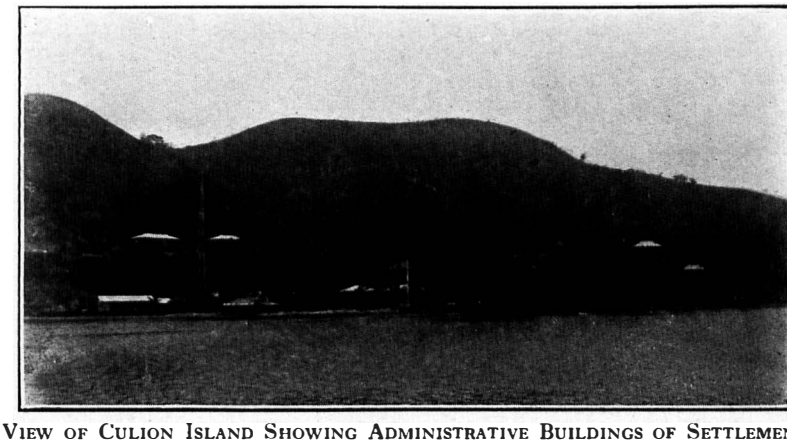
An all-glass or record syringe is used with a fine needle fitted with a guard about two mm. from the point. This prevents the needle penetrating too far into the tissue. The skin having previously been painted with iodine the needle is then introduced into and not under the skin. The thickness of the skin varies in different parts of the body ; where it is thin the needle is introduced in sloping manner so as to form an acute angle with the skin. If it is thicker then it is preferable to insert it at right angles. With a little practice the technique is soon mastered and one finds little difficulty in injecting into the corium and not into the subcutaneous tissues. An amount of the drug is injected so as to raise a



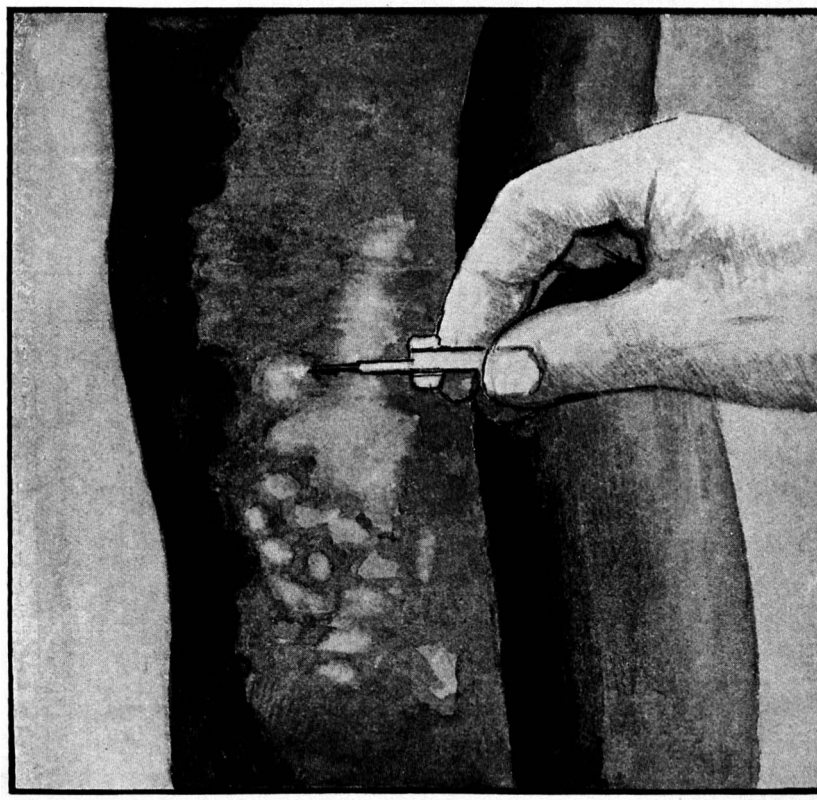
CULION LEPROSY SETTLEMENT, P.I.
(POLICEMEN ARE ENROLLED FROM AMONG THE PATIENTS.)



A STREET IN THE CULION LEPROSY SETTLEMENT, P.I.



VIEW OF CULION ISLAND SHOWING ADMINISTRATIVE BUILDINGS OF SETTLEMENT.



INTRADERMAL METHOD. NOTE THE WHEALS RAISED BY THE INJECTIONS.

(Reproduced from "Leprosy, Diagnosis, Treatment and Prevention," Fifth Edition, by E. Muir, by kind permission.)

wheal of about one-third of an inch in diameter. If a large area is to be injected it is completely infiltrated so as to produce coalescing "injection wheals." (See diagram). Some forty punctures are necessary to inject about 6 c.cs. of the esters.

The esters, alepol or oil can be used for intradermal injections. The oil, however, is inconvenient on account of its viscosity. It has been stated by some workers that alepol causes slight skin hæmorrhages (ecchymoses), but the writer has used alepol to a limited extent and as yet has found no ill effects. A certain amount of the drug is always lost by leakage (15-20 per cent.) this can be prevented to some extent by injecting down so that leakage by downward flow is reduced to a minimum.

If the lesions are small or only few in number so that only part of the drug is used the balance is given intramuscularly or by subcutaneous infiltration.

The Manila conference recommended that not more than 5 c.cs. should be given intradermally at one time and not more than 0·1 c.cs should be injected into any one point in a lesion. It is advantageous to alternate painting with trichloracetic acid and intradermal injections. The frequency of injections of any one lesion is limited by the local inflammatory reaction.

EDITOR.

Grants for Leprosy Work.

The Executive Committee of the British Empire Leprosy Relief Association have recently made the following grant :—

	£
S. RHODESIA.	
Leprosy Settlement, Gomohuru	375

This grant has been made to assist in installing a new water supply.

Applications for financial aid will be sympathetically considered by the Committee, and all applications should in the first place, be sent to the Director of Medical Services of the Colony concerned, who will forward them to the Secretary of the Association.

Some Pertinent Facts about Cebu and its Leprosy Problem.

JOSE RODRIGUEZ,

Geography.

CEBU is an elongated island barely 36 kilometres at its widest portion, with a length of 223 kilometres, and a total area of 4,836 square kilometres. The province comprises a considerable number of minor islands, of which only 14 have an area of one square mile or more. The mainland lies between 123°–17′–34″ and 124°–4′–4″ East Longitude, 9°–24′–46″ and 11°–17′–11″ North Latitude.

The highest peak is Mt. Uling, 1,013 metres, located at the central part of the island. From this peak, the land falls gradually on all sides to form the central plateau. The coastal plains are very narrow, widening only around the capital, Cebu, and at the towns of Tuburan and Bogo.

The soil is porous and so thin that the coral subsoil crops out of the surface even in the most fertile regions.

According to the 1918 census, there are 252,316 hectares of agricultural land of which only 51 per cent. were cultivated.

The principal crops are corn, coconuts, sugar-cane, peanuts, bananas, pineapples, camotes, maguey, and kapok.

The island is rich in minerals, the most important being coal and gold. The government cement plant at Naga turns out good cement, and the supply of the crude material is unlimited. Good fishing is to be had along the coast.

The estimated population of Cebu province as at December 31st, 1929, was 994,365.

Climate.

There is one first-class meteorological station located at the capital, and five rain stations distributed throughout the province.

The average means of upper and lower extremes of temperature are 35·1° C. and 19·9° C. respectively, with an absolute mean of 15·2° C. The extreme regularity in the sequence of the normal diurnal, monthly, and annual changes of temperature is most remarkable.

The average annual rainfall is low, being only 1,494·0 mm. compared to the average of 2,366·1 m.m. for the entire archipelago. This province is one of the driest in the Philippines. However, the rainfall is distributed quite evenly throughout the year, so that there is only a short dry season lasting from one to three months.

Cebu has the lowest annual mean humidity of all the stations in the Philippines. The chief characteristic of the Cebu climate is the extremely little variation in the temperature, rainfall, and humidity from month to month and from year to year.

History of Leprosy in Cebu.

The manner by which leprosy was introduced in Cebu remains to be fully established. It is now practically certain that those who ascribe the introduction of leprosy into the Philippines through the arrival of 130 Japanese lepers in 1630, are in error and that the disease was already prevalent in certain regions before that period. Guerrero is inclined to believe that the disease was introduced here by the original Malay settlers who in turn got it from their ancient Hindu colonisers.

No written records previous to the beginning of the nineteenth century regarding leprosy in Cebu are available. In 1817, a *Hospital de San Lazaro* was built by the Bishop of Cebu. An enterprising health official who advocated the forcible segregation of lepers in one of the near-by islands, estimated their number to be around three thousand in 1895.

Incidence of Leprosy.

It is, of course, next to impossible to determine the incidence of leprosy in any region with any degree of accuracy because the exact number of patients is never known.

Since 1902 to 31st December, 1929, 5,290 lepers have been discovered in this province. Of this number, 4,844 eventually reached Culion, which, however, was not established until 1906. The difference between the two figures indicates the number of those who had died between 1902 and 1906 and also those who had been released at Cebu or had been retained here. The total admissions to Culion since its establishment in 1906 to 31st December, 1929, is 19,000 cases.

Of the total of 5,290 collected in the province of Cebu, 1,393 or almost one quarter came from the capital itself.

In order to determine the relative frequency of leprosy in 52 municipalities in the province, the incidence based on the number of cases collected from each municipality since 1902, and the estimated population of each as at 31st December, 1929, was determined. The figure obtained ranged from 0·4 per 1,000 population, to 26 per 1,000 collected over a period of 28 years. The average for the province is around five lepers collected in 28 years for every 1,000 inhabitants or about one case per 1,000 inhabitants every

5½ years. It must, of course, be remembered that these figures do not represent the actual incidence of leprosy in these places, they merely serve to indicate the *relative* incidence of the disease in the different towns.

The distribution has been found to be distinctly " spotted " or focal. There are municipalities where the disease may be said to be practically non-existent ; the few cases reported from them probably came originally from the more heavily infected towns. On the other hand, there are other towns that are quite heavily infected (see table at end).

The principal focus of the disease in the province may be enclosed within a circle with a radius of about 20 kilometers, having the heart of the capital as its centre. This area with its population of around 125,000 people by the end of 1929, representing only one-eighth of that of the province and about 1 per cent. of that of the Philippines, has produced 2,349 lepers since 1902, or about three-sevenths of the total collected from the province and one-eighth of all the admissions to Culion.

The incidence was correlated with the climate whenever this could be determined for the various towns. The climatic conditions of different towns showing such marked differences of incidence were found to be so similar that the climate must play a very insignificant rôle in determining the incidence of leprosy in Cebu.

Influence of density of population on incidence of leprosy.

In preparing the data given in the table appearing at the end of this paper, the density of population was based on the population as of 1929, per hectare of cultivated territory. By simple inspection of the table, the relation of the density of the population to the incidence is not quite apparent, but when the data is treated biometrically to determine the degree of correlation, the result becomes very definite. The correlation figure was found to be ·3335–·08477, indicating a very high degree of correlation.

Future Plans.

During the present year, a thorough epidemiological survey of the more important foci of the disease in Cebu will be undertaken, in conjuction with the campaign of eradication. The former dwelling places of all the lepers collected from these foci since 1902 are now being located. Particular attention will be paid to such factors as the economic condition, habits, main occupations, and sources of food of the inhabitants, as well as the kind of soil, water supply and the flora and fauna of the heavily infected villages as compared with the uninfected ones.

Table giving the relative incidence of leprosy and the density of population per hectare of cultivated territory in each municipality.

Municipality*	Incidence per 1,000 inhabitants.	Density of population per hectare.†
Alcantara	0·4	5·8
Alcoy	1.2	5·5
Algeria	1·8	8·9
Aloguinsan	4·9	4·09
Argao	2·5	8·9
Asturias	3·5	9·99
Badian	3·4	7·99
Balamban	1·7	10·8
Bantayan	4·7	8·4
Barili	4·0	11·06
Bogo	2·4	4·9
Boljoon	5·8	5·5
Borbon	1·9	5·6
Carcar	8·7	5·8
Carmen	2·2	4·7
Catmon	0·9	4·9
Cebu	17·7	18·7
Compostela	2·1	—
Consolaciôn ..	7·3	—
Cordova	20·0	7·3
Daanbantayan ..	2·9	6·7
Dalaguete	4·3	9·1
Danao	3·1	6·3
Dumanjug	1·8	6·3
Ginatilan	2·5	9·1
Liloan	4·4	2·8
Madredijos	2·3	8·7
Malabuyoc	0·84	6·9
Mandawe	8·25	7·3
Medellin	1·7	5·3
Minglanilla	5·6	8·9
Moalbual	2·4	6·8
Naga	8·5	6·7
Opon	16·0	6·1
Oslob	2·9	10·5
Pilar	0·4	4·4
Pinamungajan ..	2·3	7·9
Poro	0·4	3·4
Ronda	1·8	14·1
Samboan	0·9	9·5
San Fernando ..	4·9	8·1
San Francisco ..	2·4	3·1
San Remegio ..	0·8	9·9
Santa Fe	3·0	7·1
Santander	0·5	10·0
Sibonga	5·2	9·3
Sogod	1·5	1·1
Tabogon	2·0	5·1
Talisay	26·4	11·1
Toledo	3·4	11·1
Tuburan	2·0	8·35
Tudela	1·1	4·84

* The municipalities of Compostela and Consolaciôn are not included because no data as to the area of their respective cultivated lands could be obtained.

† Population as of December 31st, 1929, and area of cultivated territory as per Census of 1918.

The Cebu Skin Dispensary. Cebu, Cebu.

INSTRUCTIONS TO PATIENTS WITH INCIPIENT LEPROSY.

1. You show the early signs and symptoms of leprosy. It means that unless you receive the proper treatment now, you will most likely develop the disfiguring and crippling manifestations of the disease later on. On the other hand, if you attend to your treatment at once, your chances of getting completely cured are bright.

2. The success of the treatment will depend principally upon your willingness to co-operate with your doctor. The Philippine Health Service will administer the treatment and render expert medical advice free of charge.

3. Read the following instructions carefully and follow them faithfully from day to day.

4. Eat only fresh food. Avoid stale fish, meat, vegetables—any article of food which is not perfectly fresh. Vegetables should form the bulk of your diet, but sufficient proteins should also be taken in the form of milk, eggs and meat. Avoid crabs, shrimps, lobsters, and other shell fish. If chicken makes your body itchy, it should also be eliminated from your diet. Avoid too much condiments; your food must be simply cooked and do not eat anything raw except fresh fruits.

5. Take regular daily exercise, as it is absolutely essential for your recovery. Exercise promotes the elimination of the toxic products of the disease, it gives you a healthy appetite and good sleep, and facilitates the absorption of the medicine.

Walking is one of the best form of exercise and it is suited to your condition. You must walk at least 10 miles a day; one-half of the distance may be covered in the morning and the other half in the evening.

Gymnastics, pulleys, dumb-bells, and tennis, will also keep you in good trim. Violent exertions should, however, be avoided and it is best to omit the exercise on the afternoon following your injection.

6. Keep your body clean by bathing frequently. Use plenty of soap. Whether a bath is to be taken or omitted on the day following the injection depends on how you will feel that day.

7. Your bowels must be evacuated daily. If constipation is present, correct it by eating more vegetables or by taking a proper laxative.

8. Lead a methodical life ; observe regular hours for meals, rest, exercise and for sleep. It is best to write down a fixed schedule and then follow it strictly.

9. If you are suffering from some debilitating ailment such as venereal diseases, malaria, hookworm, etc., this should be treated first before you receive the anti-leprosy treatment.

10. Come to the injection clinic at least once a week ; twice a week would be preferable. The injection days are Wednesday and Saturday ; the time is 8 o'clock in the morning. Take sufficient exercise and a good bath before coming for your injection.

11. You may do your routine work after the injection but it is best to avoid unnecessary exertions during that day.

12. Sunlight is good for your health but avoid the mid-day heat.

13. Cheerfulness is one of the best tonics. Forget your worries and be cheerful.

14. When in doubt about anything concerning your health, consult your doctor. Take him into your confidence.

15. If you know any one of your friends having symptoms similar to yours advise him to present himself to the Philppine Health Service without delay. Give him a chance !

16. The treatment will take sometime. Do not get impatient. Let perseverance be your motto and you will succeed in getting rid of your disease.

Literature.

Leprosy Review, Vol. 11, No. 2, April, 1931. Issued quarterly by the Association. Price 2s.

Leprosy in India, Vol. III, No. 2, April, 1931. Issued quarterly by the Indian Council of the Association.

Memorandum on the Present Position of Prophylaxis against Leprosy in Relation to Recent Improvement in Treatment.

(ABRIDGED.)

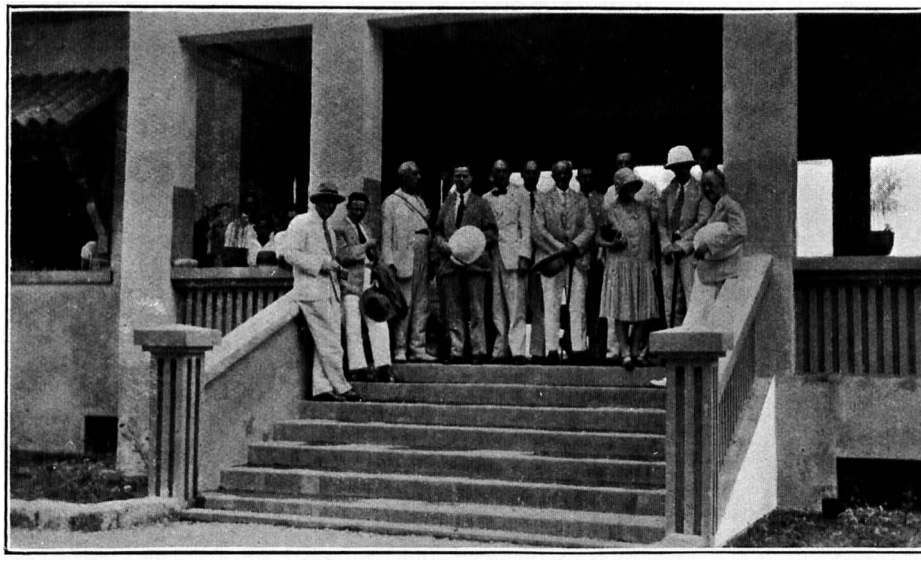
SIR LEONARD ROGERS, C.I.E., F.R.S., I.M.S. (retd.)

Prepared for the Leprosy Conference at Manila, January, 1931, and distributed to the members.

FIFTEEN years ago, in the absence of any effective treatment, even of early cases of leprosy, compulsory segregation was the only prophylactic measure in common use. The whole position requires to be reviewed in the light of the established fact that now most early cases of leprosy can be cleared of all symptoms and infectivity and prevented from going on to the more highly infective stages. If compulsory segregation inevitably leads to many of the more amenable early cases being hidden until they have reached a much more advanced and incurable stage, and have also had prolonged opportunities of infecting others before they are themselves isolated, it may do more harm than good. The question, therefore, must be fairly faced as to whether unmodified and generally applied compulsory segregation ought not to be modified to ensure that it does not result in hiding of the amenable early cases. No one has recognized more fully than I that leprosy prophylaxis must vary to a considerable extent with the local conditions, but I think the time has come when the general principles on which it should be based can be laid down in the light of our present knowledge.

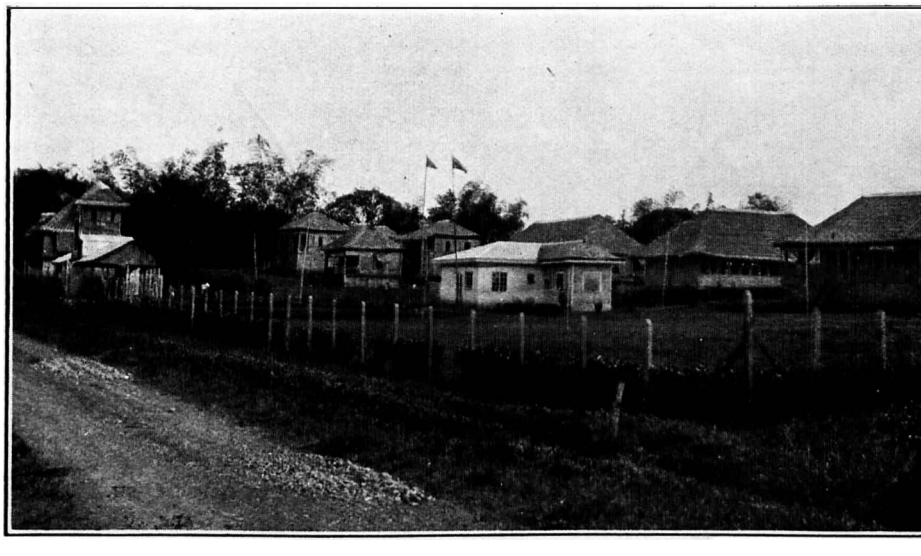
The failure of compulsory segregation to stamp out or materially to reduce the prevalence of leprosy among backward races within a reasonable time.

As a result of prolonged studies of the leprosy question, I have now come to the following general conclusions regarding the prophylactic value of compulsory segregation, which I think will meet with very general acceptance. The humane Norway system of segregation, in which compulsion was only applied to a few indigent cases during the first thirty years, and only very modified compulsion used subsequently, has undoubtedly in the course of the last seventy-five years reduced leprosy to very small proportions of the numbers in 1865, and the same system has proved of value in Sweden and Iceland under European conditions. On the other hand, among backward or uncivilised races in warm and tropical



SKIN CLINIC, CEBU, P.I.

Conference Members from Left to right: Drs. NEFF, LAMPE, MAXWELL, LOWE, GUSHUE-TAYLOR, HUIZENGA, Prof. NOCHT, Drs. WADE, COLE, and TULL.



WESTERN VISAYAN SKIN CLINIC.

countries, no such good results have yet been obtained, even after several decades of effort. Thus, in Hawaii, where compulsion was for long the sport of politics, and has been enforced for several decades under American rule, recent reports throw grave doubt on its value, and the disease is still very prevalent. In the Philippines the great Culion experiment succeeded in removing advanced cases of leprosy from the streets of the towns, but no material reduction in the number of annual admissions has been obtained, and rigid compulsory segregation has now been modified by building leprosy hospitals for the treatment of the more amenable cases near important towns, and recently the adoption of the Indian system of treating early cases as out-patients at " skin clinics " has been introduced. In the West Indies, census figures I published in " Leprosy " appeared to indicate some success of the rigid compulsory segregation there enforced, but it has since been brought to my notice that the decline was mainly due to the repatriation of considerable numbers of Indian lepers ; so here too, there is no clear evidence of the success of the plan.

Even under much more favourable conditions in South Africa and in Australia compulsory segregation has proved very disappointing in practice. Thus in Cape Colony of South Africa compulsory segregation was first enforced in the Caledon valley as early as 1817, and at Robben Island since 1845, and the data from 1891 to 1907 showed a steady increase in the numbers isolated owing to the discovery of new cases. Recently more efficient segregation has been enforced, and some decrease in the number of European sufferers appears to have taken place, but none apparently among the native races, such as the Basuto, for example, where the latest report shows an increase in the numbers isolated at very great cost. It is only fair to state that owing to paucity of medical officers and difficulties of communication the problem is very difficult in Basutoland, although not more so than in tropical African colonies such as Nigeria, but the fact remains that the very severe tax on the revenues entailed by the compulsory measures has not yet been justified in Basutoland by any definite diminution of the disease. In New South Wales, where over £2,000 per head is spent annually on each segregated case, or sufficient to allow of 1,600 lepers to be treated for a year with the efficient form of sodium hydnocarpate known as alepol, some reduction in the number of Europeans infected appears to have been obtained according to Dr. Cook, but the same authority

states that the compulsory methods have failed to reduce leprosy in the neighbouring state of Queensland.

Compulsory segregation impracticable for 99 per cent. of the world's lepers.

If compulsory segregation had been proved to be an effective method of stamping out leprosy it would still be of very little use in solving the leprosy problem as a whole, for the simple reason that it is quite impossible to carry it out for administrative and financial reasons in the areas of the greatest number of cases in India, China, and tropical Africa. Over two decades ago, Dr. Heiser estimated the world's lepers at 2,000,000, at a time when the wide prevalence in Africa was not known. More recently, as the result of three years' study of the literature, I estimated them as not less than 3,000,000. Since then, the leprosy surveys of Dr. Muir, in India, recently confirmed in British Guiana, by Dr. Rose, showed that for each typical advanced case, such as alone are enumerated under the compulsory segregation system, there are anything from two to ten early cases in existence, so the world's lepers may very easily number 10,000,000. For the sake of my argument I will place the number at the very conservative estimate of 5,000,000.

I have made out a table of the numbers recorded as being segregated at the present time in the principal countries where that measure is in force, including the data in the valuable 1930 Report of the Secretary of the League of Nations Leprosy Commission; the number comes in round numbers to 35,000. To this may be added nearly 8,000 isolated in Indian leper asylums under a voluntary system, apart from a very few indigents, although many of them are old uninfective crippled nerve cases, whose isolation is only of humanitarian value, and does nothing to reduce leprosy infections, which will bring the number up to 43,000. The fullest allowance for small numbers isolated in other countries with comparatively few lepers could not make the total segregations under the old system over 50,000—just 1 per cent. of the world's lepers.

Results of modern treatment.

It is now very generally agreed that the modern treatment is far more effective than former ones, and also that not more than 10 to 20 per cent. of the advanced cases, which form the vast proportion of cases in leper asylums under the compulsory system, can be apparently cleared up by prolonged treatment as at Culion colony, and it is still doubtful

as to how many of them relapse. Dr. Wayson has recently come to the conclusion that the last of the leprosy bacilli are rarely, if ever, eliminated from the system by the treatment in the advanced cases met with in the Hawaii leprosy institutions under the compulsory system. The same is true of tuberculosis, but the sanitorium treatment of early cases is not, on that account, considered to be useless. Under the same system in South Africa, only two years ago, the asylum medical authorities were very sceptical regarding the value of the treatment, but the latest reports record 10 to 20 per cent. of apparent recoveries.

The results in early cases are very different as shown in a table I published in 1927 (Proc. Royal Soc. Med., Vol. xx, April) with apparent recovery in 41 of my Calcutta Clinic cases, and 31 per cent. in Muir's continuation of my work there. At the Honolulu Hospital, among 486 cases treated during five years and reported on by H. M. Neil, only 8 per cent. of advanced cases, but 38 per cent. of moderately advanced ones, and no less than 64 per cent. of 45 early ones were discharged on parole as apparently recovered. Other figures might be quoted, but these will suffice to establish the generally admitted fact that good results in a large proportion of cases are only to be expected when they are discovered and treated efficiently in an early stage of the disease, and the treatment in the class of cases met with under the compulsory segregation system is not sufficiently good at present to enable their treatment alone to solve the leprosy problem. The problem, therefore, will only be solved under some system which enables the great majority of the cases to be discovered and treated regularly in quite an early stage of the disease. About 100 medical men are trained yearly in India in the modern treatment of leprosy, surveys are carried out in areas where leprosy is most prevalent, and dispensaries opened for treatment, to each of which usually 200 to 300 patients come from a wide circle. Propaganda work precedes the surveys, and in these ways a very large total of the early most amenable cases of leprosy are being treated all over India, which must prevent many of them going on to the infectious stage, and thus in time bring about a material reduction in the incidence of the disease. The cost per case is very small compared with compulsory segregation. The adoption of " skin clinics " in the Philippines for the out-patient treatment of early lepers is an important extension of the Indian system.

Voluntary colonies for the isolation and treatment of lepers in British tropical possessions.

It is only during the last decade or two that it has become evident that vast areas of tropical Africa have leprosy rates of several times that of India. This constitutes the most serious and difficult leprosy problem in the world to the solution of which the British Empire Leprosy Relief Association is devoting most of its limited funds. Already there are scores of clinics and small leprosy settlements treating very many cases with the help of numerous missionary medical men and women in the British African colonies ; several of the most important of these now have whole-time leprosy officers organising the work. How impossible compulsion is in tropical Africa, quite apart from the prohibitive cost, will be evident from the experience in the French Cameroons, where an attempt compulsorily to segregate the lepers by sending gendarmes through the villages to collect them signally failed because the cases were hidden. Yet, when cases were sent out who had improved greatly under the modern treatment they brought back numerous new voluntary patients.

Something more than clinics were found to be necessary in these areas owing to the very limited number of medical men available to staff leper dispensaries, but, fortunately, fertile land is usually obtainable for colonies, where the patients are largely self-supporting through growing their own food, and the leper colony founded by Dr. Macdonald, in South Nigeria, alone has about 1,000 lepers under treatment, with the added advantage of isolation under a voluntary and very economical plan. How successful this work has proved may be illustrated by the 1929 report of Dr. Mayer, the Nigerian expert, who records that there are now nearly 6,000 lepers under treatment in leprosy colonies and clinics under a purely voluntary and economical system. Thus within about five years, the number of sufferers now being dealt with in Nigeria alone is not far short of the total number of cases treated in settlements in India as the result of over 50 years' work. This success is entirely the result of the attraction of the improved treatment, and is a good illustration of immense advance in the possibilities of leprosy prophylaxis at the present time, as compared with the ancient compulsory segregation system alone available only about one decade ago. I am, therefore, absolutely against the introduction of compulsory segregation in any backward areas, in which it will inevitably lead to the early more

amenable cases being hidden, with resulting throwing away of the advantages now available through improved treatment.

Where compulsory segregation already exists it should be modified to allow early bacteriologically negative cases to be treated without compulsory segregation.

My views on this point have been clearly stated in several publications during the last few years, of which the following extract from my paper in the " Practitioner," of April, 1928, will suffice as an illustration :—

> " *Relaxation of compulsory isolation in the case of early uninfective lepers.*—In countries where much money has been expended in segregating lepers compulsorily, I do not advise that this plan should be abandoned for the present, but that it should be modified to prevent it doing great harm by preventing patients coming forward for treatment in the earlier stages."

What I do advocate is that early uninfective cases should be permitted to be treated by their medical men or at dispensaries and hospitals without being forcibly shut up with the advanced, and often repulsive cases in leprosy settlements.

This simple modification of compulsory laws has already been adopted in several British Colonies, such as Mauritius, and it is now being introduced into British Guiana, where the first leprosy dispensary will shortly be built at the expense of our Association as the result of the revelations of a survey proving that it is urgently required.

The periodical examination of all contacts of infective lepers and the effective treatment of the early cases thus discovered, is the only method of reducing leprosy incidence rapidly.

I now come to my last and most important point. The rapid extension of leprosy clinics and colonies on a voluntary basis is a great step in advance of the prophylactic measures available only a decade ago, but it will require many decades of unremitting work thus to reduce leprosy to small proportions. For some years past, therefore, I have advocated a further step, which is based on two important conclusions I came to as the result of my three years' study of the literature on leprosy. These are : Firstly, about 80 per cent. of new infections are derived through living in the same house with another leper, and secondly, if the cases are detected in a fairly early stage the incubation period averages about two and a half years, as in the children born at Culion, and

in about 80 per cent. of all cases it does not exceed five years. It follows that whenever a new infective leper is discovered the first step should be to examine, if possible, all his household and intimates for early cases of leprosy, and this examination should be repeated at least every six months for five years. Theoretically about 80 per cent. of possible infections from any leper should be thus discovered in the earliest stage, when the great majority of them may be expected to clear up and prevented from going on to the more infective stages under effective modern treatment. If this plan was repeated for another five year period there would be few remaining infectious lepers, for most of the advanced nodular stages die in eight to ten years or pass on into a little infective nerve stage, so that in time the necessity for isolating lepers compulsorily would nearly disappear. Where compulsion is already in force it may serve a useful purpose for a time in enabling pressure to be made on early uninfective cases to attend regularly for treatment on pain of isolation. That is why I have always advocated its being retained for a time where already in force, although I look forward to its becoming unnecessary before very long if modified in the way I have suggested.

The plan above suggested has now been proved to be feasible and successful in Nauru Island.

Within the last few months Dr. G. W. Bray has recorded the success of the above plan in Nauru Island in Oceana, (Proc. Roy. Soc. Med. July 1930) where, following an epidemic of influenza leaving great weakness, aggravated by deficient diet, leprosy increased so rapidly that by 1926, 30 per cent. of the entire small population of about 2,000 people were infected. I was consulted about this outbreak several years ago and advised frequent examinations of the whole population for early cases, with treatment of uninfective cases as out-patients. The bacteriologically positive cases were kept on one side of the island, the negative ones remained free and were treated as out-patients, but slept apart from the healthy, and all the people were examined monthly for new cases with prompt treatment of newly discovered ones. The result has been that within three years the number of cases has been reduced by 40 per cent. and Dr. Bray informs me that not a single early treated case has gone on to an advanced highly infective stage. At this rate this appalling outbreak, the worst I know of in the literature of leprosy, will be completely under control within a single decade. My plan then has already proved successful

under the very favourable conditions obtaining at Nauru, so it is clear that the nearer this method can be worked up to in other countries the more rapid will be the control and eventual elimination of leprosy, and the principles I have laid down in this memorandum furnish a reliable method of prophylaxis based on the recent advances in treatment.

Conclusion.

I have now dealt with the principles which I believe should guide the application of our present knowledge to the great problem of reducing and eventually stamping out leprosy from any country. In view of great variations in the local conditions each country must decide for itself how far these principles are applicable to their own conditions, but personally I am convinced that the nearer any area can get to carrying into effect the foregoing principles the better the results will be. The immense stimulus given to research on leprosy by the discovery of an improved treatment will doubtless place in our hands still more effective methods before long, and at the present transitionary period it will probably be advantageous for different countries to adopt. Personally, I should welcome such an area as South Africa sticking to rigid compulsory methods, as such would furnish a valuable control to more modern methods in use elsewhere. I only hope that this memorandum, which is at least the outcome of prolonged study of the leprosy problem, will be of help in focussing the attention of the conference on some points of great practical importance.

Non-Irritating Iodized Ethyl Esters of H. Wightiana.

HOWARD I. COLE.

DURING recent visits to various leprosariums, the writer was surprised to learn how many of these places had entirely given up the administration of chaulmoogra-group ethyl esters in favour of the oil because the esters had proved " too irritating and tended to produce ulcers." It is true that some years ago we also experienced trouble due to the irritating effect of the esters, but since then, we have been constantly improving this drug until we now manufacture a standardised product which never produces ulcers and which gives a very low complaint rate.

Iodized esters are to be preferred to the oil because they

are more effective, and more rapid in their action. Some places utilise a mixture of half and half esters and olive oil, with or without the addition of 4 per cent. creosote. Although this cuts down the irritation somewhat, it also necessarily reduces the effectiveness of the drug by one-half. This may be one reason why the esters have fallen into disrepute, but probably a more cogent reason is that there has been no general cognizance of the fact that the addition of iodine when properly made, greatly reduces the irritating effects of the esters. It is true that until recently, the methods of procedure found in the literature have given rather vague directions for this addition of iodine. Some laboratories have added the iodine to cold esters, and dissolved by stirring; others have heated the two together for varying lengths of time, and at varying temperatures, others still have heated the two together until a brown colour was produced. We have experimentally proved that both the temperature and the length of time of heating of the iodine with the esters, have an important influence on the irritating properties of the product. We have tested this time-temperature effect on over fifteen hundred cases, and find that too short, as well as too long a time of heating of the esters with the iodine increases markedly the irritant properties; there is a happy medium which we now follow with very gratifying results.

Over a period of years, we have also noted in thousands of cases the following causes of irritation :—

(1) Heating the esters to too high a temperature.
(2) Addition of less than one-half per cent, iodine.
(3) Presence of more than 0·2 per cent. free fatty acid.
(4) Presence of impurities.

It may be any one, or a combination of two or more of the above factors which is also partly responsible for the present disrepute of the esters. Whatever the cause, it no longer applies, for it is now perfectly feasible for any chemist to make non-irritating iodized esters if he will but follow our method. We now manufacture and use over 1,000 litres of iodized wightiana ethyl esters annually in our treatment clinics with no untoward results. Furthermore, our present method of intradermal injection would not be possible with an irritating product.

Our results with this drug surpass any other tried so far. Injection of about 8 c.c. in a number of small injections into a lesion, lead generally to remarkable reduction in the

lesion, in much shorter time than has hitherto been possible with any other leprosy drug.

We are obtaining negatives in a shorter time than ever before.

It is to be hoped that the following method of preparation of iodized ethyl esters will be tried out in other places, and that the same very encouraging results will be obtained. Complete directions for the manufacture of these esters have been described elsewhere.*

Iodized esters of low irritability, in any amount from 1 litre to 15 litres, may be prepared if the precautions given are carefully heeded.

The clear esters are placed in a shallow (pan) type of container, heated quickly to 140° C. with occasional stirring. The requisite amount of re-sublimed iodine to give a 1·5 per cent. iodine solution in the esters is added with stirring. The temperature immediately rises to 150° C. at which point, it is maintained for exactly 30 minutes, stirring the mixture frequently. After cooling, the iodized esters are filtered into bottles, sterilized, and then hermetically sealed.

PRECAUTIONS.

The ethyl esters must be thoroughly dried before the iodine is added as otherwise an irritant product will result, since the iodine will change some of the esters to free fatty acid if water is present. If the filtered esters are clear when placed in the pan, the heating to 140° C. before adding the iodine will drive off all dissolved water.

A shallow type of container must be used and the heating to 140° C. done as quickly as possible; otherwise the product may be irritating. Enamel, glass or stainless steel pans may be used.

The iodised esters will keep in a dark place for at least two years without deterioration if in hermetically sealed bottles.

Iodized esters exposed to heat or sunlight *in the presence of air* are soon changed into a product with greatly increased irritant properties, hence the need for air-tight containers. The change is generally accompanied by an increase in clarity and a change in colour from greenish brown to red brown.

Repeated re-sterilization should be avoided as it also may lead to increase in irritant properties.

*Perkins, G. A. — Journ. Ind. Eng. Chem. **19**, (1927) 939.
Cole, H. I. — Phil. Journ. Science, **40**, (1929) 503.

During the heating the esters will give off some vapour (smoke) and a slight amount of the iodine will also be volatilised by the heat, but neither of these phenomena will cause any harm to the finished product.

In order to be certain that the reaction between the iodine and the esters has gone to completion, it is wise to store the sealed bottles of iodized esters for two weeks before using.

Quinine Therapy in Malaria.

PHILIP MANSON-BAHR.

(*Continued from Vol. II, No. 2.*)

THE salt of quinine which is most commonly in use is the sulphate which is the cheapest, and in many ways, the most popular, but as it is only soluble in 800 parts of water the addition of some acid is necessary in order to keep it in solution. The hydrochloride is more expensive and at the same time more soluble—in 40 parts of water. The so-called tasteless salts of quinine, euquinine (the ethyl carbonate) the tannate and the carbonate are practically insoluble, and, therefore, should not be used except in extremeties in dealing with nervous ladies and some children who will not, or cannot, swallow the liquid preparation. The hydrochloride is regarded usually as the most useful preparation for general routine use, whilst the more soluble bihydrochloride is reserved for injection either by the intramuscular or by the intravenous route.

The most propitious moment to administer quinine during the actual attack of malaria has been the subject of speculation. It is no longer regarded as dangerous to exhibit quinine when there is a degree of pyrexia, but it is, I think, generally agreed that the drug exerts its maximum effect if given when the acute paroxysm is declining and when the patient is beginning to perspire, for at that moment the parasites have sporulated and the merozoites are free in the blood plasma, and in a condition in which they are most susceptible to the action of quinine.

Many methods have been advocated in order to mask or remove the bitter taste of quinine. An agreeable and efficacious method is to prescribe it in an effervescing mixture with citric acid gr. X to which are added four grains of ammonium carbonate and gr. XX of potassium bicarbonate. Quinine is rendered less bitter if dissolved in milk, whilst syrup of orange and glycerine disguise the

taste, and a practical method of cleansing the mouth is to chew a piece of bread.

Something must be said about the toxic effects—occasionally when given in large doses it may produce deafness and amblyopia, which may prove very persistent and occasionally permanent. The amblyopia is due to spasm of the arterioles of the retina and the deafness to the direct action of quinine upon the auditory nerve.

Quinine idiosyncrasy or quinine intolerance is occasionally met with and may be a most disturbing factor. In some people even minute doses of quinine may produce a profuse and most irritating urticaria, in others intractable dyspepsia, whilst in others again a rare, but genuine, quinine hæmoglobinuria has been noted. A useful method of determining quinine idiosyncrasy when present has been described by Dawson and Garbaile, who have shown that if a solution of 1 : 10 quinine is applied to a scratch on the forearm a zone of ædema and erythema immediately appears in a susceptible person.

Quinine in Benign Tertian Malaria.

The most dramatic results of quinine therapy are seen in this form of malaria, so striking is the cutting short of the fever and the disappearance of the parasites from the bloodstream that the effect of quinine upon the temperature curve is often used as a method of differential diagnosis from other fevers, in the absence of a microscopical examination. Whatever the exact explanation may be, it has been established as a scientific fact that quinine has a selective action for the trophozoites of this infection and a much less marked action upon the sexual forms. This phenomenon is much more striking in subtertian infections as will be noted later. A benign tertian malaria attack is usually ushered in with a rigor and a high temperature.

Vomiting is not usually a special feature, so that quinine may be readily exhibited by the mouth. Directly the patient commences to perspire the first dose should be administered and, to promote sweating, it is advantageous to combine it with 10 grains of aspirin. For an adult male European the optimum dosage, as laid down originally by Manson (a rule which followed at the present day) is 30 grains a day, divided into three doses of 10 grains each. There appears to be no special advantage in giving larger doses than this; but I have frequently observed that smaller doses, such as 15 grains daily, do not control the fever, nor cause the parasites to disappear from the circulation. This,

the maximum dosage, should be kept up for the next four days and then subsequently dropped to 20 grains daily for the next week. I am convinced that the generally held belief that it is only necessary to exhibit quinine for a short period subsequent to the fever attack is a great mistake and actually predisposes towards further relapse, so that it is necessary to institute an anti-relapse treatment. Personally, I favour the method of giving 10 grains of quinine daily for six weeks following the more massive treatment described. Others, I know, favour the week-end treatment, which consists of 15 grains daily for three days in the week. The underlying principle is by daily bombardments with quinine to extirpate the last remaining malaria germ in the system. Unfortunately, this *desideratum* is by no means always obtained.

Smaller doses of quinine are given to women, the maximum being 20 grains a day, whilst children tolerate the drug well—one-twentieth of the adult dose should be given for each year of age, so that a child of five years would receive one quarter of the adult dose.

It is to be regretted that even by continuous therapy the occurrence of subsequent relapses cannot be absolutely guaranteed; as James has shown, they may occur from nine months to one year after the apparent cure of the infection. In order to avoid this disagreeable possibility, one should endeavour to build up the resistance of the body by good food, fresh air and moderate exercise. There is some reason to suppose in the quiescent stage that salvarsan has some action on the parasite, or at least, exerts a definite tonic action on the body, so that I am in the habit of combining one or more injections of neosalvarsan 0·3 grains as an adjuvant to quinine therapy. Then there are iron and arsenic tonics which are frequently given with the quinine. Of one thing I am certain, and that is that quinine does not exert its maximum effect unless the intestinal tract is in a receptive state for its absorption. Therefore, it is necessary to combine quinine therapy together with a saline aperient such as Epsom salts, which should be given at the commencement of quinine, and subsequently once or twice weekly.

Although intravenous and intramuscular quinine injections may on occasions be useful in combating specially virulent benign tertian infections, yet there is no evidence to show that the course of the disease is necessarily shortened thereby. In malarial cachexia I am convinced that only small doses of quinine are indicated; it is much more

advisable to give suitable arsenical tonics and iron injections than to resort to continuous drenching with quinine.

Subtertian malaria infections may run a very mild course or be extremely severe. The parasite differs from the foregoing, mainly by the rapidity with which it multiplies and by its mode of reproduction by sporulation in the smaller capillaries, which by these means may be completely blocked with masses of parasites and blood-stasis may be produced. It is a curious fact that the trophozoites are extremely susceptible to the action of quinine even in small doses, while the sexual forms, or crescents, are extremely resistant. Thus it comes about that it is comparatively easy to control the more urgent signs and symptoms with relatively small doses of quinine, yet when the patient is recovering and the fever is quiescent, crescents may be found in numbers in the bloodstream and they may persist for several weeks. In fact, it is extremely difficult to extirpate the crescents with quinine. I have records of cases in which crescents persisted in the blood for 28 days after 840 grains of quinine had been absorbed. When there is no persistent vomiting or other contra-indication, quinine should be given by the mouth in subtertian malaria. It is not necessary to give such large doses as in benign tertian. One should commence with grs. XV of the alkaloid in solution and gradually increase to the maximum of gr. XXX daily. But in very severe toxic cases, in which there has been a considerable degree of blood destruction with consequent anæmia great caution has to be observed in " pushing " quinine on account of the liability to *blackwater fever*, a danger to which further allusion will be made. One should, therefore, commence with grs. V daily and gradually increase. In the more severe clinical forms with bilious vomiting, and it may be with delirium, quinine given by the mouth does not suffice to control symptoms, then resort must be had to intramuscular injections. In such circumstances intramuscular injections appear to act like a charm and are certainly indicated. The bihydrochloride salt should be used. The whole rationale of intramuscular quinine has been much discussed. It is unquestionable that whenever or wherever quinine comes into contact with muscle fibre it causes a degree of necrosis, so that the dosage of quinine must be carefully guaged and the site of injection selected. The proper dosage for quinine injection is about 10 grains, and the site the gluteus maximus muscle. I am very averse to multiple quinine injections and I cannot see that they are therapeutically indicated, even when given daily I am very

much opposed and I consider three or four weekly ample. It is hardly necessary to state that quinine injections, especially if given into a limited area and at frequent intervals, are not without danger. They may produce profuse necrosis and even (in the absence of any specific microbic injection) profuse suppuration and tetanus. I have seen cases uncontrolled by blood examination (which they should be) treated by continued injections in the belief that they were controlling fever, when all the time the rigors were brought about, not as had been supposed by a particularly resistant parasite, but by the continued absorption of pus from minute intramuscular abscesses.

Intravenous injections of quinine are indicated in the so-called pernicious forms of subtertian malaria, especially when the sporulating parasites are congregated in the capillaries of the brain, producing coma, or in the coats of the intestines producing choleraic diarrhœa or other forms of abdominal disease. The rapidity with which intravenous quinine acts in these dramatic states is remarkable. The hydrochloride salt should be used, in a dosage of 10 grains in 10 c.c. of distilled water and given into the median basilic vein. There is no indication for more heroic doses than this as larger quantities of quinine are very apt to bring about too great a dissolution of the parasites and dangerous symptoms may ensue. Much safer is it to give smaller injections of quinine—grs. III—each at frequent intervals, so as to avoid this contingency. As it has been shown that intravenous injections of quinine are apt to be followed by a fall of blood pressure it is advisable to combine it with the injection of 5 min. of a 1 : 1,000 solution of adrenalin.

Subtertian infections are more easily cured by quinine than are benign tertian, so that it is not necessary to give such a prolonged course of anti-relapse treatment, and I am convinced that often in this disease the desideratum of *Therapia magna sterilisans* is attained. However, in general the main scheme of quinine therapy should be adhered to.

Now we come to the difficult question of blackwater fever. Does quinine produce this catastrophe, or does it pre-dispose towards it, or does it not ? I confess I find it more difficult than ever to answer this question. To my mind it is unquestionable that blackwater fever is an accident which occurs only in subtertian infections, not in the other two forms of malaria. In many cases I have noted that the exhibition of massive doses of quinine (by this I mean 20-50 grains) does certainly seem to precipitate the attack, and I have learned to be specially suspicious of those cases of subter-

tian malaria who are obviously ill, whose spleens are greatly enlarged, but in whose blood relatively few parasites are to be found. It may be that quinine is but one of the factors that predispose towards the blackwater state—there may be others, such as cold, alcohol or the toxins of some other disease—or it may be that quinine in certain individuals brings about a state in the red corpuscles of greater susceptibility to læmolysis. At any rate it must be borne in mind that the rôle of quinine in the production of blackwater fever is very widely held. The outcome of this is that one should treat suspicious cases of subtertian infection with great circumspection, combining graduated quinine dosage with alkalies and with a liberal supply of glucose.

There is not very much to be said about the use of quinine in quartan malaria. Large doses should be used and the maximum dose of 30 grains should be persisted in longer than in benign tertian, as quartan parasites are much more resistant to the action of quinine than the other two, so that parasites can be demonstrated in the blood for ten or more days after the initiation of quinine therapy. The question of anti-relapse treatment is also important as quartan is by far the most persistant infection and relapses may occur over as long a period as five years. The tendency of quartan infections to be associated with nephritis should also be noted, and it has been shown that the appearance of albumin in the urine in this infection is an indication for pushing the quinine dosage, not the reverse.

It is necessary now to give a short account of recent attempts to improve the standard treatment of malaria by newer compounds. In attempting to synthesize quinine in the laboratory Schulemann, Schönhofer and Wingler produced some seven years ago a derivative of quinoline—(alkyl-amino-6-methoxy-quinoline) which is now known as *plasmoquine*. The probable action of this compound on malaria in man was gauged by its comparative action upon the *plasmodium* of birds (canaries artificially infected). Roehl and Horlein were better enabled to do so as it had already been shown by Sargent and Giemsa that quinine acted similarly upon the plasmodium in the birds' blood as it did upon the human malaria parasites. Plasmoquine in doses of 0·06 g. (gr. I) daily caused a rapid disappearance of benign tertian parasites from the blood of man, but had a less effect upon the ring forms of the subtertian parasite. Most remarkable, however, is its marked selective action upon the sexual forms of these parasites. The benign sporonts disappear almost immediately, whilst the

otherwise refractory crescents disappear in about four days after a total of 0·24 g. of the drug, so that in plasmoquine undoubtedly a new malaria specific has been discovered. But there are cogent defects in the drug. The large doses originally advocated, 0·25 g. and 0·12 g., daily were obviously far too large and were often accompanied by alarming toxic symptoms, such as a livid blue cyanosis of the lips and nails, which is due to the conversion of hæmoglobin into methemoglobin by plasmoquine. Moreover, its inability to control subtertian fever and to extirpate the ring forms of the parasite associated with this fever were disappointing. It was then demonstrated by Schulemann and Memmi that, not only was the therapeutic action of plasmoquine greatly enhanced, but its toxic manifestations were greatly diminished, or rather neutralised, by the addition of a small amount of quinine. Hence the composition of *plasmoquine compound*. Each modern tablet of plasmoquine compound contains 0·01 g. (one-sixth grain) plasmoquine with 0·125 g. (2 grains) quinine sulphate. The scheme of dosage is to give the drug in full doses of six tablets daily for one week (*i.e.*, plasmoquine gr. I and quinine 12 grains daily) with three days' interval between each weekly course for five separate weeks, and as anti-relapse treatment.

The question next arises—can one estimate the present position of plasmoquine in malaria therapy? Personally, I believe that plasmoquine compound is a useful adjuvant to quinine treatment and in many circumstances is an efficient substitute. Firstly it is easy to take, and it is comparatively tasteless. Many people can tolerate it who are intolerant of quinine in ordinary therapeutic doses. It is, in my opinion, more efficacious in controlling benign tertian malaria than is pure quinine; it frequently cures an infection which appears resistant to pure quinine. It banishes the crescents from the blood in subtertian malaria; it is readily taken and readily absorbed by children in smaller doses and it is readily borne by pregnant women in whom it controls the fever and does not predispose to absorption, as does pure quinine. I have had several cases of intractable malaria in pregnant women who have gone to full term on plasmoquine therapy without any further attacks.

Manifestly the plasmoquine has attained a distinct place in our armamentarium against malaria.

Whatever may prove to be the limitations of plasmoquine in its present form, it has opened up new avenues for exploration, so that it is quite possible that less toxic and more highly specific antimalarial compounds may be obtained.