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EDITORIALS

Editorials are written by members of the Editorial Board and opinions expressed are those of the writers.

THE JOURNAL, 1942 - 1947
A REVIEW OF THE SCIENTIFIC PAPERS

On January 1, 1948, the Editor of the JOURNAL, Dr. H. Windsor Wade, resumes his editorial duties. The JOURNAL again becomes in fact as well as in name the organ of the International Leprosy Association. The American Leprosy Foundation (Leonard Wood Memorial) will continue to make up the financial deficits which should become smaller as the paid membership increases. The Editor will be assisted by Dr. Huldah Bancroft, recently appointed Associate Professor of Biostatistics at Tulane University and who has been Assistant Editor for the past three years. Doubtless the Editor and the Association will wish to fill the many vacancies in the list of Contributing Editors. Friends of Dr. Wade will be happy to note that his return to the JOURNAL signifies his restoration to health and will join the Acting Editor in wishing him many years of continued activity.

The Japanese raid on Pearl Harbor, the consequent precipitation of the United States into the war and the early involvement of most of the other American Republics widened World War II into a veritable global conflict. It was soon evident that the war would be long and desperate and that human freedom depended upon the defeat of the axis powers. The first duty of medical scientists as of all other citizens of the democracies was to devote their abilities and energies to the attainment of victory. For fundamental medical research the outlook was grim. Such research could be kept alive only by the extraordinary efforts of those who had some surplus of strength and resources.

In leprosy the danger was especially acute. Many of the ablest workers, including the Editor of the JOURNAL, were in the hands of the enemy. Action was urgently necessary. The President and Trustees of the American Leprosy Foundation, acting on the advice of the Advisory Medical Board of the Foundation, determined to do their part to assure that a minimum position would be held from which a fresh start might be made after the war. The following quotation from the Editorial by the Acting Editor in the First Special War Number (Volume X, December, 1942) gives the decision of the Foundation: "Cognizant of the dangers of the situation the American Leprosy Foundation has taken two important steps. The first recognizes Latin America as the most promising current source of scientific workers in leprosy. Fellowships are being offered to physicians of these countries and a descriptive note will be found in the News Items of this issue. The second action maintains a medium for publication of original articles. Special issues of the JOURNAL will be published from time to time as sufficient numbers of manuscripts are received." The Foundation assumed the total cost of publication and the writer agreed to become Acting Editor.

The Acting Editor has looked upon the JOURNAL as a trust to be protected and nurtured until it could be restored to its proper guardians. Fortunately, the task was not his alone. The JOURNAL is indebted to several hundred contributors who have provided the original papers and reviews which are its flesh and bones, and the interesting letters and notes which are its fat. It is indebted also to the able assistants of the Acting Editor who were, successively, Miss Delta Derrom, Mrs. Dorothy D. Miller, Mrs. Ruth Meyer and Dr. Huldah Bancroft. Dr. Lyon N. Richardson, Editor, Western Reserve University Press, saw Volume XI through the press. There must be mentioned also the assistance rendered by the Judson Printing Company and the Central Publishing House, both of Cleveland, Ohio, who, although handicapped by war restrictions on paper and other supplies and by a critical shortage of skilled labor, nevertheless produced highly creditable work. The managers of both these publishing companies regarded the enterprise as something more than a business proposition; they shared the trust. Finally the JOURNAL is indebted to the President and Trustees of Western Reserve University for making available the services of the Acting Editor and of those assistants who were employees of the University, and also for providing office space and appurtenances. The team work of all resulted in the preparation of an index for Volume IX, which was closed without a fourth number, in publication of single annual numbers as volumes for the

years 1942, 1943, 1944, 1945, and 1946, and of the normal volume of four numbers for the current year. In addition, a special supplement to Volume XII entitled "Geographical Distribution and Prevalence of Leprosy" was revised and issued, based upon a draft prepared by Mr. Perry Burgess, President, American Leprosy Foundation, Dr. Norman C. Kiefer, Special Assistant to the President, and their assistants.

As the official medium of the Association it is the function of the JOURNAL to keep its readers apprised of current research through original publications, reprinting of notable articles, and abstracts of current literature. It will be of interest therefore to classify the articles which have been published during this period and to indicate their principal findings. A full review of leprosy research during the war and immediate post-war period is beyond the scope of this Editorial and would require consideration of many articles which appeared in other leprosy journals which were successful in maintaining their activity, notably the *Revista Brasileira de Leprologia, Leprosy Review,* and *Leprosy in India,* as well as in many less specialized publications. Abstracts of most of these articles have appeared in the JOURNAL.

In all, 99 articles were published, 83 original and 16 reprinted. These have been classified according to major field of discussion and year of publication as follows:

		YEAR OF PUBLICATION						
Classification		1942	1943	1944	1945	1946	1947	Total
I	Epidemiological	5	0	3	1	1	8	18
II	Bacteriological	0	1	1	2	1	4	9
III	Immunological	1	2	3	0	0	4	10
IV	Experimental	1	1	0	2	0	2	6
V	Biochemical	1	1	0	1	1	1	5
VI	Pathological	2	0	0	1	0	1	4
VII	Clinical							
	(Descriptive	0	1	1	0	1	2	5
	(Therapeutic	2	2	5	1	4	9	23
	(Classification	0	0	0	0	0	5	5
VIII	Administrative and Social	2	1	0	3	2	4	12
IX	General	0	0	0	0	2	0	2
	Total	14	9	13	11	12	40	99

I. EPIDEMIOLOGICAL

Under this heading are included 18 articles, which may be further broken down as 13 historical and descriptive, and 5 analytical.

Historical and descriptive: Dharmendra (1947.4)* concluded after study of the most ancient Indian medical writings, those of

* Footnote: The references in parentheses refer to volumes of the JOURNAL.

Charak, Sushruta, and Vag Bhatta, that leprosy was well known and well described in India at least 2,500 years ago, that in ancient times the disease was treated with chaulmoogra oil, and that the ancient literature of no other country contains such an authentic and complete description of leprosy.

Hasseltine (1944) reviewed the history of leprosy in the New England states from the records of the various state boards of health. He noted that, although 70 cases had been discovered in these states, until 1943 no case had occurred in any person who was born and had lived his entire life within these states. In 1943, a young man 24 years of age who was born in Massachusetts of foreign-born parents and who had never been outside of the state, was found to have leprosy. The report of Johansen (1947.4) on leprosy in Texas is a marked contrast. From the records of the National Leprosarium at Carville, Louisiana, he found that 231 patients from Texas had been admitted since 1921, of whom 173 had been born in the United States, for the most part in Texas and Louisiana. The wide distribution of leprosy in Texas is indicated by the fact that the patients were admitted from 45 counties of the state. Approximately 60 per cent of the patients were of Mexican birth or of Mexican parentage and 40 per cent were of European ancestry.

Supplementing an earlier paper by Hasseltine (The JOURNAL, 1940) on Spanish American and World War I veterans who were admitted to the National Leprosarium at Carville, Louisiana, Faget (1944) gave a brief report on the records of the current war. Whereas practically all of the Spanish American War veterans who were admitted came from states in which leprosy is non-endemic, those of World War I and of World War II came from endemic areas in the United States, indicating that the leprosy of World War I, and that of World War II to the time of writing, were not related appreciably to military service. He noted that 7 of the 17 patients of the World War II group had manifestations of leprosy prior to enlistment. The other 10 were apparently in good health when they commenced their military service.

Saunders (1942) described the history of leprosy in the Virgin Islands of the United States. This was followed by the discussion of the results of a prevalence survey on the Islands by Saunders and Guinto (1942). The disease was demonstrated to be about ten times as prevalent in St. Croix as in St. Thomas. The latter is favored economically; its people have a more adequate diet, and it has considerably lower general mortality and morbidity rates than St. Croix. A very unusual finding was that leprosy was about equally as prevalent in males as in females, a condition similar to

that found in West African natives, but in contrast to that in the Philippines and most other areas.

In nearby Puerto Rico, from a study of registered cases, Doull, Martinez Rivera, Saunders, Guinto and Garrido Morales (1942. Rep.) estimated a prevalence rate of only about 11 per 100,000 of the population as compared to an estimate of 100 to 150 for St. Thomas and of 1,000 to 1,400 per 100,000 for St. Croix. In Puerto Rico there was a marked excess of males among registered patients.

Basing his opinion upon the records of health departments and of institutions, Muir (1942) reported on the prevalence of leprosy in the British West Indies and in British Guiana. The number of patients isolated in institutions was as follows: Jamaica 165, Leeward Islands 75, Windward Islands 56, Barbados 76, Trinidad 399, and British Guiana 374. The number of unisolated patients could not be judged accurately because of concealment and the absence of any general systematic survey. Dr. Rose had estimated, from his wide experience, that there were about 1,000 in British Guiana. There were approximately the same number in Trinidad; in Barbados the number was probably not less than 200; in Saint Kitts and Nevis about 80; in Antigua about 50; in Saint Lucia about 50; in Dominica probably not fewer than 50, and in Granada and Saint Vincent not more than 30. In Montserrat, another small island, the disease was said to be almost unknown. In Jamaica there were perhaps 325 unisolated. Thus, in the whole of the British West Indies and British Guiana there were probably fewer than 3,000 persons with leprosy.

Continuing to South America, Floch (1947.2) reported 1,131 living patients on the register in French Guiana and probably not more than 300 unregistered, or 6.5 per cent of a total of 22,000 inhabitants. There was the usual excess of males. Batisti Risi (1947.3) classified the registered cases of the National Leprosy Service of Brazil according to type and geographical region and concluded that high relative humidity appeared to be the climatic factor of greatest importance in the spread of the disease. In areas of higher temperature the disease seemed to be less severe, temperate or cold climates favoring its more acute development. From Brazil also Pessoa Mendez and Gilberto Mangeon (1947.3) reported on the history of the disease in the state of Rio Grande do Sul. The current rate of prevalence was only 32 per 100,000, with a high proportion of contagious cases and an excess of males.

From Europe, Reenstierna (1945. Rep.) reviewed the history of the disease in Sweden. Only a few elderly patients remained. It never was a serious problem as it was in Norway in the 19th Cen-

tury. Contreras Duenas (1947.2) in a similar study for Spain reported an estimated prevalence rate for the mainland and the Balearic Islands of between 16 and 32 per 100,000 inhabitants. For the Canary Islands he judged the rate to be about 96 per 100,000.

Analytical: Chaussinand (1947.4) submitted an essay on Sex in Leprosy. His data were obtained from French Indo-China and relate to prevalence rather than to incidence. (Prevalence is the product of two factors, namely, the incidence rate and the duration of the disease. For a discussion of this subject, see the JOURNAL, 1942, p. 107 *et seq.*) The author expressed his belief that males are more exposed than females because of their mode of life, and also that males have a greater susceptibility to the disease, susceptibility being perhaps related to the functioning of the endocrine system.

Four analyses were published of data collected in Cordova and Talisay, Cebu, P. I., in studies jointly supported by the Bureau of Health of the Philippines and the American Leprosy Foundation. The first paper, by Doull, Guinto, Rodriguez and Bancroft (1942), gave the basic material. This paper was reviewed in an Editorial in the JOURNAL (1944) and need not be discussed here except to emphasize that the risk of contracting leprosy when exposed in the household to the lepromatous type was found to be far higher than is generally appreciated. The second paper, Bancroft, Guinto, Rodriguez and Marquez (1944), dealt with the important and frequently discussed subject of the influence of family relationship on the risk of developing leprosy. Unfortunately the experience was relatively small. The records of 283 families were used, in each of which there had been a primary case of lepromatous leprosy. In these 283 families there were 1,450 individuals with a total life experience following exposure of 17,230 person years. There were 1,840 person years following exposure to a son, 1,012 person years following exposure to a daughter, and 1,634 person years following exposure to husband or wife. Among these persons only one case of leprosy developed and that followed exposure to a son. The balance of the life experience totaled 12,744 person years and yielded some interesting results. The highest attack rate for lepromatous leprosy was 4.31 per thousand, for the group exposed to a father. The rates following exposure to mother, brother, and sister were practically equal, being 3.57, 3.61 and 3.60 per 1,000 respectively. In the third article of this series, Doull, Guinto, Rodriguez and Bancroft (1946. Rep.) reported a clear relationship between age at the time of exposure and the risk of developing lepromatous leprosy. The risk was highest for those exposed before the age of five years and decreased progressively as the age at time of exposure in-

creased. This was true for both males and females. The fourth paper by the same authors (1947.4) demonstrated the value of the historical method in determining the trend of leprosy in an area. In the communities studied there was definite evidence of declining incidence.

II. BACTERIOLOGICAL

Of the 99 papers, 9 dealt with bacteriology. Davison (1943) drew attention to errors of diagnosis from failure to recognize that diphtheroids in nasal secretions or in pus may be slightly acid-fast. Hasseltine (1944) emphasized consideration of the lesion from which the specimen is obtained, technique of obtaining specimen, staining reaction, and morphological data including arrangements of the organisms one to another and their relation to tissue cells that may be present. Hallberg (1946) described a new method for staining leprosy bacilli.

Six papers were contributed by Hanks (1945 and 1947.1.). The earlier papers were from the Leonard Wood Memorial Laboratory at Culion, P. I., and those of 1947 from the recently established Leonard Wood Memorial Laboratory at Harvard University. They represent the initial stages of an approach to the subject by the method of tissue culture. The following results were reported: The impression gained from the direct smear method that leprosy bacilli grow *in vitro* in small bits of lepromatous tissue was shown to be erroneous by a method which completely disintegrates the tissue and permits the estimation of the actual number of bacilli present. Nodules were demonstrated to contain frequently more than a million leprosy bacilli per cubic centimeter. Tissue cultures from lepromata were maintained in a viable condition for from 14 to 34 days, during which time the infected macrophages died early and deposited their bacilli within the necrotic mass of the original explant. The only cells that persisted through the life of the culture were fibroblasts, which ordinarily contain no bacilli or only a few. Cultivation and maintenance of the fibroblasts from nodular or tuberculoid lesions for periods of two to seven months did not result in multiplication of leprosy bacilli within these cells. Fibroblasts from human lepromata could be maintained *in vitro* for seven to fourteen weeks but the proportion of cells containing bacilli and the content per cell decreased continuously. Leprosy bacilli seen in the plasma surrounding explants from lepromatous tissue were shown to be derived from cell transport or other mechanical means and not to arise by free multiplication in the plasma.

III. IMMUNOLOGICAL

Ten papers fall into this general category.

Lepromin test: Fernandez (1943) reported that it is possible to sensitize presumably non-leprous persons to lepromin by intradermal injection of either an oily or an aqueous suspension of *M. leprae,* killed by heat; that sensitization to lepromin can be produced also by intradermal injection of suspensions of *M. tuberculosis,* killed by heat; that the early lepromin reaction is attributable to previous sensitization which may be induced by *M. leprae* or by *M. tuberculosis,* and that sensitization to lepromin is not induced by previous intradermal injection of purified lepromin protein nor by injection of a suspension of *E. typhosus,* killed by heat.

Fernandez and Mercau (1947.4) made a comparative study of lepromin in oil and in water base. Suspensions of *M. leprae* in mineral oil, olive oil, and ethyl esters of chaulmoogra oil, killed by heat, were injected intradermally in concentrations of 1:2500 for the chaulmoogra suspensions and of 1:5000 for the suspension in other oils, to establish their antigenic activity. A suspension of *E. typhosus* in oil was used as control. The three types of lepromin thus prepared caused intense local reaction in twenty-four to forty-eight hours in all cases of leprosy, even in the lepromatous form. Later the oil provoked the formation of a vaselinoma, to which was added in persons allergic to lepromin "the specific nodular reaction which *M. leprae* provokes." The suspension of *E. typhosus* also provoked an early positive reaction, but this was less marked than the lepromin reaction. Controls injected with only the three oil vehicles showed that these substances had little or no irritating effect. Some patients with lepromatous leprosy gave a positive reaction to ordinary lepromin a few months after injection with lepromin suspended in oil. It was concluded that the early reactions to oily lepromin are not specific. Evidently the antigenic properties of *M. leprae* are accentuated by an oily medium. This is attributable to greater and more prolonged contact of the bacilli with the dermis when oil preparations are injected because these do not diffuse as readily as aqueous suspensions.

Olmos Castro and Arcuri (1947.2) found a very high percentage of agreement between early and late readings of lepromin tests in contacts and concluded that using bacterial or whole antigen the early reading therefore was sufficient.

Testing tuberculosis patients with lepromin in a non-endemic area Convit, Azulay, Bermudez, and Salgado (1944) noted that 70 per cent were positive on the early (Fernandez) and 46 per cent on the late (Mitsuda) reading. The authors considered that the high proportion of Fernandez positives might have been attributable to

the fact that all the patients were tuberculin positive. If so, the Mitsuda is less affected by cosensitization with *M. tuberculosis* than is the Fernandez reaction. Among syphilitic patients in Cleveland, Ohio, mostly Negro adults, Azulay and Convit (1947.3) found that 74 per cent reacted to full strength lepromin, 66 per cent of the males and 86 per cent of the females. Only 33 per cent of the total reacted to a 1:10 dilution of the same lepromin.

Antiserum: Henderson (1944) reported that injection of acid-fast bacilli obtained from spleens of human leprosy patients into normal rabbits did not lead to the development of an antiserum which would react with the serum of leprosy patients in such a way as to indicate the presence of specific leprosy bacillus antigen in leprous serum. Reenstierna (1947.1. Rep.) reported on electrophoretic tests of so-called anti-leprosy sera. His sera were prepared by repeated injections into sheep of increasing doses of toluol-treated cultures of Kedrowskij's Russian strain and Reenstierna's Swedish strain. Reenstierna's results demonstrated a difference in electrophoretic composition between anti-leprosy and normal sera greater than that between all other immune sera which he had tested and their corresponding normal ones.

Miscellaneous: Doull and Bryan (1942) reported that leprosy patients in Puerto Rico have, as a rule, substantial quantities of diphtheria antitoxin in their blood; toxoid treatment therefore did not appear indicated. Eccles and Ross (1943) found that, when examined with Mazzini flocculation slide test, sera of presumably non-syphilitic leprous patients exhibit a tendency toward falsely positive results, but to a lesser degree than with the Kolmer simplified complement fixation test and the Kahn standard test. Mom and Basombrio (1944) found that leprous infection modifies the diffusion factor R found in normal skin. Modifications are due to the presence of *M. leprae* and are more pronounced the greater the number of bacilli in the skin. In cases of lepromatous leprosy the diffusion activity completely disappears from the skin.

IV. EXPERIMENTAL

Six papers fall in this class. Cochrane, Menon, and Pandit (1945) reported on later observations on monkeys (The JOURNAL, 1939:377-381) inoculated with human leprosy material after splenectomy. In the earlier work seven animals had been inoculated, in only one of which was there any evidence of possible dissemination of the infection. Of 16 monkeys inoculated in the later series three died within a few days after inoculation and four were inoculated too recently to be considered. The nine remaining were divided into three series: (a) inoculated with leprosy material on

several occasions; (b) inoculated with leprosy material and fed on *Colocasia antiquorum,* and (c) inoculated with blockage of the reticulo-endothelial system by India Ink. The apparent success in one animal of the earlier experiment was not repeated. It is suggested that the reason for failure may be that resistance developed as most of the animals became strongly positive to the lepromin reaction. It is noted that two of three animals receiving India Ink did not develop a positive lepromin test. After six years of investigation, in which a total of 38 monkeys were inoculated, Cochrane and Ramanujain (1945) concluded that definite conclusions could not be drawn. One Rhesus monkey was splenectomized and inoculated in November, 1940 and reinoculated on December 1, 1941 and March 20, 1943. Between October, 1942 and February, 1945 erythematous patches appeared between the eyebrows and on the inside of the thigh, extending down the leg. These patches were more prominent when daily injections of lepromin were being given. On August 2, 1945, a biopsy specimen, taken from the lesion on the forehead, revealed round cell infiltration with giant cell formation in one field. The hypothesis of the authors is that active tissue defense can be developed only in the corium of the skin and that in tuberculoid leprosy the formation of epitheloid foci results in anchoring the bacilli and in preventing their dissemination throughout the reticulo-endothelial system. Lepromatous leprosy on the other hand, is a manifestation of ineffective tissue defense resulting in wide-spread dissemination and multiplication of the bacilli.

Hanks (1947.1.a) showed that inoculation of rats with either inked explants of rat leproma or with suspensions of rat leprosy bacilli in India ink resulted in lesions indistinguishable from those produced without ink except in color. The same author (1947.1.b) found no evidence of growth of human leprosy bacilli during the short interval between the inoculation of bacilli into chick embryos and the hatching of the chicks.

Two contributions are of collateral interest but deal with experiments not directly related to human leprosy. Failure of diphtheria toxoid as a therapeutic agent was recorded for murine leprosy by Carpenter, Ackerman, and Ashenburg (1942) and for human and bovine tuberculosis in guinea pigs by Feldman and Moses (1943).

V. BIOCHEMICAL

Five papers dealt with biochemical subjects. Ross (Sister Hilary, 1943) examined sera from 150 patients for euglobulin, total proteins, albumin, and globulin. The tyrosin index for euglobulin was above normal in 147 cases. The greatest variation occurred

in active, advanced leprosy. The albumin-globulin ratio was below normal in 123 cases. The tyrosin index was above normal in 24 instances in which the total proteins and the albumin-globulin ratio were normal. The suggested explanation is hepatic dysfunction from liver damage.

Bimbad (1945) studied the blood glutathione and concluded that the glutathione content is of aid in determining the state of the oxidation-reduction processes in the patient. In the tuberculoid and maculo-neural forms of leprosy the total amount of glutathione did not differ from normal, but the amount of the oxidized form decreased with the corresponding increase of the reduced form. The qualitative and quantitative values were normal in the regressive stage of slight and moderately advanced lepromatous leprosy; in the active phases of lepromatous leprosy all the glutathione values were decreased, and in the reactive phase (lepra fever) there was a marked decrease of reduced glutathione and in the total value, although the amount of the oxidized form tended to remain within normal limits.

Pogge and Ross (1946) studied the fasting blood sugar during acute reaction (lepra fever) in 24 patients in which the reaction was characterized by erythema nodosum, chills and fever. In addition 13 cases were studied in which the reaction was localized in tender painful nerve trunks, and two cases of leprous lymphadenopathy. In all but the mildest cases there was a definite increase in the fasting blood sugar. Some evidence was presented that parenteral insulin treatment was of value.

An approach was made by Ross (1947.3) to the important subject of the blood levels and excretion rates of the sulfones in leprosy. Sister Ross found that promin administered intravenously in daily doses of 5 Gm. over a period of from one to six years established average 24-hour residual blood concentrations of from 1.0 to 1.6 mgm per cent. Appreciable amounts of promin were found in the blood after a nine day rest period. There seemed to be no correlation between blood promin levels and clinical progress. The administration of 1.0 Gm. of diasone daily resulted in blood levels being maintained of from 0.0 to 3.6 mgm per cent. Urinary diasone levels indicated a rather definite threshold for diasone since continued treatment appeared to raise the urinary rather than the blood level. The maximum concentration in the urine was 100 mgm per cent.

As regards promizole, the daily administration of 6 to 7 Gm. maintained a blood level of from a trace to 1.9 mgm per cent. The concentration in the urine was as high as 800 mgm per cent.

Mills (1942) reported, as of possible interest in leprosy, on the

thiamin excretion rates of individuals of Panamanian foods. The rates were at or below normal. The author stated that slow-growing tropical meats are deficient as sources of thiamin as compared to meats grown in cooler climates and that there is a heightened requirement for certain of the B fractions in tropical heat.

VI. PATHOLOGICAL

Omitting an article by Fite and Gemar (1947.4.Rep.) on retrogressive changes under promin treatment which is discussed later, there were four contributions classified as primarily dealing with pathology. Kean and Childress (1942) presented in some detail the gross pathology of leprosy observed in 103 autopsies performed at the Board of Health Laboratory at the Gorgas Hospital, Ancon, Canal Zone. The findings emphasized were the following: leprosy affected the nasopharynx or upper and outer portion of the upper respiratory tract, whereas tuberculosis affected the larynx and trachea or lower portion of the upper respiratory system; a high incidence of cirrhosis of the liver; a high incidence of gallstones; and a high incidence of nephritis especially glomerulonephritis. The final causes of death were, in the order of numerical importance: tuberculosis, syphilis, leprosy, and heart disease.

Three papers dealt with histopathological features. Saunders and Giffin (1942) described their findings in biopsy material from thirty macular cases in the Virgin Islands. Twenty-three showed well-defined tuberculoid changes and seven only banal inflammation. All cases studied were free of acid-fast micro-organisms.

Stein and Dorofejew (1945) discussed the clinical characteristics and pathological anatomy of leprous iritis. Of 264 patients with lepromatous or mixed leprosy, 10.9 per cent were blind in both eyes and an additional 10.6 per cent were blind in one eye. By the systematic use of the Hartnach lens they observed miliary nodules of the iris in 57 patients or 21.5 per cent. This type of iritis nearly always provoked an inflammatory reaction. In 8 patients the cornea and the adjacent sclera were involved. In 28 there was a diffuse parenchymatous form of iritis without evidence of nodule formation. The authors studied histologically 27 fragments of iris obtained in iridectomy performed for therapeutic reasons. In 8 of these a sero-plastic iritis was present and in 16 the same form of iritis with miliary lepromata. Masses of *M. leprae* were found even in the plastic form without evidence of miliary nodules. The inference drawn is that the plastic form is a leprotic process and not merely a non-specific iritis. (It is impossible to do justice to this article in a brief review. A paper by Prendergast, J. J., *Minn. Med. Jour.*, **23** *1940, 98-101,* abstracted in the JOURNAL, 1945, 162,

should be consulted by those interested in the subject of ocular leprosy. *A/Ed.*)

In an attempt to throw light on the pathogenesis of neural leprosy, Ermakova (1947.1) examined the nerve elements of the tongue root. In a study of seven specimens from seven cases of lepromatous leprosy, nothing of significance was found grossly except perhaps that the circumvallate papillae differed from the surrounding mucosa in that they had a pale yellow tint. For histological examination the method of impregnation of Gross-Bilshowvsky-Lavrentyev was used, supplemented by Ziehl-Neelsen staining. Leprosy bacilli were found in the goblet gustatory cells of the papillae, lying longitudinally along the goblet axis, and in isolated instances, virtually flooding the goblet cells. Under the epithelium of the *Papillae vallatae* receptors of the Meissner type were observed. Bacilli there were few but could be seen singly in the perineural sheath of the fibre as it approaches the terminal corpuscle, or along the axon and closely attached to it. In the *Papillas vallatae* there were found numerous pulp and pulpless nerve fibres spreading fanwise from the base of the papillae towards the periphery; somewhat deeper there were small nerve branches and bundles and ganglia of the autonomous nervous system. Bacillary bundles were found along the entire surface of the fanwise-spreading nerve fibres in the grooves of the perineural sheaths. Deeper, in the nerve bundles and small branches, there were accumulations of bacilli along the peri- and endo-neural sheaths. Varicose changes more or less marked were found in certain of the axons. In some cases this swelling was exceptionally large and was full of bacilli. Such were encountered especially "in the bundles at the bases of the papillae, where the diameter of the varicosity exceeded by five to eight times the diameter of the nerve fibre, and the number of microbes was so great that one could speak of a bacillary depot along the route of the axon."

The bacillary invasion was not limited to nerve bundles in the region of *Papillae vallatae;* the microbes penetrated deeper in the nerve branches which pass through connective tissue on the border of the muscular layer, but the further towards the center the fewer bacilli were encountered and the less reaction on the part of nerve fibers and surrounding tissues. These observations suggested strongly to the authors that the bacilli spread along nerve conductors of the *Papillae vallatae* in a centripetal direction. The authors raise many important questions. How for example do the bacilli penetrate into the *Papillae vallatae?* Is the gustatory goblet to be considered as a possible portal of entry? They state with certainty that the slits in the perineural sheaths play an important role in the

spread of the bacilli. "What forces attract the bacilli to these routes?" "How can their spread in the centripetal direction only be explained?" etc., etc.

VII. *CLINICAL*

There were 33 clinical contributions. Five were descriptive, 23 dealt with therapy and 5 with classification. Peixoto (1943) reported a case complicated by syphilis, Davidson (1944) a case complicated by Hodgkins disease, and Faget (1946) commented on *Alopecia leprosa* which he found in 10 of 360 patients at Carville. A useful review of leprosy of the eye and its appendages by Chatterji (1947.3.Rep.) was reprinted. Wolcott (1947.4) discussed the frequency, clinical and histopathological features, and possible significance of *Erythema nodosum* as observed at the National Leprosarium at Carville, La. His report indicates that it is more likely to occur in treated cases and that it has become more frequent since the advent of sulfone therapy. The suggestion is made that attacks of erythema nodosum may be evidence of increasing resistance. (This suggestion has been made previously; see Pecorado, V. E., *Rev. Bras. Leprol.*, **10**, *1942, 67-83. A/Ed.*) Fuadin proved satisfactory for control of fever and discomfort caused by this complication.

Surgical treatment: An article by Fennel (1944. Rep.) reported apparently successful surgical removal of the primary lesion in two patients. In one there was no evidence of dissemination of the disease 11 years later. The other report related to the historic case described by Goodhue and McCoy in 1916. This patient was identified by Fennel in January 1939 and examined. No evidence of leprosy was found then nor on reexamination by him in 1944. Thus there was no evidence of dissemination 28 years after excision.

Sloan (1944) contributed a useful illustrated article on the technique and value of tracheotomy in leprosy.

Diphtheria toxoid: Schujman (1942), Faget and Johansen (1942), and Mosier (1945. Rep.) all found that diphtheria toxoid failed to give benefit.

Blood plasma: Faget and Pogge (1943) described their failure with pooled blood plasma in treatment.

Calcium gluconate: Pogge (1944) reported beneficial results with intravenous calcium gluconate in cases of painful neuritis.

Streptomycin: Faget and Erickson (1947.2) made a preliminary report on treatment with streptomycin injected intramuscularly.

Ten selected patients were placed on a four months' course of intensive treatment in June 1946. At the end of that period, since the results were not conclusive, the treatment was prolonged with reduced doses for another four months. Streptomycin was administered in doses of 0.25 gram every three hours or a total of 2 grams in 24 hours. Each gram lot was dissolved in 6 cc of saline solution making the volume of each injection 1.5 cubic centimeters. Toxic manifestations were encountered, the most serious complications being tinnitus and impaired hearing, and an exfoliative dermatitis. More common and rather severe manifestations were vertigo, fever, and skin eruptions. Less serious conditions were eosinophilia, fall in blood pressure, headache, malaise, nausea and vomiting. Beneficial effects could not be demonstrated conclusively but encouraging changes seem to have occurred in some cases. The writers were of opinion, however, that unless streptomycin can be further purified to render it less toxic or the effective dose can be reduced or different methods of administration developed, such as streptomycin suspension in oil or wax, streptomycin will not become a treatment of choice in leprosy. Five patients were treated with a combination of streptomycin and sulphones and the degree of response to treatment seemed slightly better than with streptomycin alone. The numbers treated were too small to give statistical evidence of this.

Penicillin: Two groups of workers reported on the unsuccessful use of penicillin in treatment. Faget and Pogge (1944) treated seven patients suffering from lepromatous leprosy with doses of 50,000 and 100,000 units daily for a period of several weeks and found penicillin ineffective. The authors conclude that except for the healing of non-leprous ulcers, penicillin in doses even larger than those found adequate in treatment of syphilis, is ineffective in treatment of leprosy. Mom and Bernal (1946. a) reported on a clinical trial of penicillin in eight cases, seven of which were of the lepromatous type and of long duration. Daily doses were used of from 25,000 to 60,000 units over periods of 21 to 53 days for a total of 1,050,000 to 2,550,000 units. The drug was used by three different techniques; first, intramuscular injections every three hours; second, intravenous drip 8 to 10 hours a day; and third, one intramuscular injection a day in suspension of a mixture of peanut oil and beeswax. These authors likewise reached the conclusion that penicillin appears to have an influence either on *M. leprae* or on the course of the human disease. It does have considerable value in treatment of patients with secondary infections caused by Streptococcus or Staphylococcus. In such cases the single daily intramuscular injection in oil suspension is sufficient to give good results.

Chaulmoogra oil: Only one author submitted an article on chaulmoogra. Schujman (1947.2) presented the facts regarded as most interesting concerning patients treated with chaulmoogra over a period of 17 years. He stated that disagreement regarding therapeutic value of chaulmoogra is due essentially to lack of uniformity in selection of cases. Only the lepromatous type should be considered. With derivatives of chaulmoogra oil he considered that he had achieved persistent clinical and bacteriological negativation of lepromatous cases. Treatment must be early, be sufficient and be continued. Failures he regards as due to irregular and insufficient treatment.

The sulfones: The sulfone drugs which have been used in leprosy are promin, diasone, promizole, and sulphetrone. The active principle of each of these seems to be diamino-diphenyl sulfone, the basic chemical from which they are derived. The drugs of this class vary greatly in solubility and in toxicity.

The first report was made by Faget, Pogge, Johansen, Dinan, Prejean, and Eccles and was reprinted in the JOURNAL (1943. Rep.) They reported that promin seemed to possess some chemotherapeutic property against leprosy, as evidenced by apparent inhibition of the progress of the disease. This opinion was reaffirmed by Faget, Pogge, Johansen, Fite, Prejean and Gemar (1946) who reported on treatment of 177 patients who had received 268,836 grams of promin intravenously in daily doses averaging from 2 to 5 Gm. per day. Omitting 40 discontinuing for various reasons there were 137 patients who had received regular treatment. In 75 per cent of these the disease was "predominantly lepromatous," in 22 per cent frankly mixed and in 3 per cent neural. At the time of writing 7 patients had been classified as arrested by the Parole Board. An additional 12 patients had had six or more consecutive monthly negative skin and nasal smears. With a rest period it was necessary to give iron and liver therapy in 20 per cent of cases. Kidney complications were not observed except in patients with preexisting renal insufficiency. Manifestations of skin sensitivity were usually mild. The regressive changes in the lesions under promin therapy were described by Fite and Gemar (1947.4. Rep.): "Under promin treatment, the improvement in leprosy is not accompanied by characteristic cellular changes. Those which do occur are predominantly atrophic in character, with extremely slow and gradual lessening of numbers of organisms in the lesions to the point of final disappearance in 10 of 32 cases examined. These changes do not differ materially from similar changes occurring in spontaneous remission without treatment of any sort,

or during interim periods of inactivity or regression between phases of acute activity.

"The important finding is that promin appears to eliminate bacillary infection of the blood vessels and blood stream, thereby preventing the formation of new lesions. The atrophy of focal lesions is also more apparent in areas with a more generous blood supply. The results indicate strongly that the best results may be expected in those cases in which treatment is begun in a comparatively early stage of the disease.

"A more powerful bactericidal agent than promin appears necessary for the chemical destruction of bacilli within tissue cells, and especially those within globi."

Muir (1944) reported on a trial of diasone in Trinidad. Unlike promin, he found it well tolerated by mouth in daily doses up to 2 Gm. His early results were promising. Early experience with diasone was favorable also at the National Leprosarium at Carville, La., and was reported elsewhere (Faget and Pogge, *New Orleans Med. and Surg. Jour.—Oct., 1945*). A report on eight months trial of diasone at Rosario, Argentina, was contributed by Fernandez and Carbone (1946). Encouraging improvement was noted but in no case had the bacilli completely disappeared from the lesions.

The third of the sulfones to be tried was promizole. Faget, Pogge, and Johansen (1947. 4. Rep.) thus described preliminary results with this drug: "No claim is made in regard to the ultimate value of promizole given orally in doses of 6 Gm. daily in the treatment of leprosy. Attention is called to the fact that promizole is well tolerated by patients with leprosy and that clinical improvement occasionally can be demonstrated more quickly with promizole than with similar sulfones, such as promin and diasone. It is felt that the therapeutic results thus far obtained are sufficiently encouraging to warrant further clinical study, which will be necessary before a final evaluation of promizole in the treatment of leprosy can be given." In a report giving later observations on patients treated with promizole, Johansen (1947.4) was inclined to discontinue its use. Its therapeutic advantages over other sulfones were not outstanding, the dosage large and distasteful, and the drug expensive to manufacture.

Wharton (1947.3) treated six lepromatous patients, all lepromin-negative, with a fourth sulfone derivative called "sulphetrone." The daily dose of 0.5 Gm. increasing to 3.0 Gm. was given by mouth. Only mild toxic symptoms were observed, but the period of observation was only six months.

Reviews of sulfone therapy were contributed by Faget (1947.1) and by Muir (1947.3 Rep.). Both authorities agreed that the sul-

fone drugs although slow in action produced clinical improvement and in some instances arrest of the disease.

Treatment of ulcers: Definite progress was recorded in the treatment of leprous ulcers. Mom and Bernal (1946.b) reported on the use of tyrothricin which is a mixture of two polypeptids, gramicidin and tyrocidin. A two per cent alcoholic solution of tyrothricin was used. This was diluted with distilled water before use. For application on ulcers, a large DeVilbiss atomizer was used. Treatment was successful in 14 of 15 patients with lepromatous ulcers on the lower limbs. A maximum of 75 days and a minimum of 19 days was necessary to obtain cicatrization of ulcers. Successful use of crude streptomycin broth in the local treatment of ulcers was reported by Fite, Erickson, Gemar, and Johansen (1947.2).

Classification: Four papers on classification were the outcome of the Second Pan American Congress at Rio de Janeiro. For orientation, the paper of Pardo Castello and Tiant was reprinted in the JOURNAL (1947.2. Rep.). In this paper, originally published in 1943 in the *Journal of the American Medical Association,* an attempt was made to correlate the lepromatous, tuberculoid, and non-specific types with the clinical, immunologic, bacteriologic and public health aspects of leprosy. Portugal (1947.2) described his efforts to classify 70 cases from different districts of Brazil referred to him by leprologists. His major difficulty was with the uncharacteristic type. He concluded that this type is heterogeneous as far as evolution is concerned and that there are three potentialities: (a) evolution towards the tuberculoid; (b) evolution towards the lepromatous, and (c) remaining uncharacteristic. Uncharacteristic cases may regress without undergoing mutation. The uncharacteristic type presents a dilemma but cases should be classified provisionally as such until new resources for diagnosis become available.

The pathogenic bases of the South American classification were discussed by de Souza Lima, M., Barba Rubio, de Souza Lima, L, and Rath de Souza (1947.2). The hypothesis of these authors is that the tissues respond to invasion by *M. leprae* in two ways: In one there is absolute absence of reaction on the part of the reticuloendothelial system (uncharacteristic form); in the other there is an intense reaction on the part of that system with complete or incomplete phagocytosis (lepromatous and tuberculoid forms). When complete phagocytosis with lysis takes place a tuberculoid granuloma results, with destruction of the *M. leprae,* constituting the clinical polar form of tuberculoid leprosy. When on the other hand the histiocytic elements (macrophages) do not digest *M. leprae,* but

simply phagocytose them, the typical foamy cell of Virchow is produced. Multiplication of the bacilli may be so rapid as to destroy the cells resulting in the formation of globi. Clinically, this produces the lepromatous type.

The authors recognize that such a cut and dried picture is a rare biological phenomenon and that the same patient may present a variety of tissue changes. Also they have observed cases in which there are clinically uncharacteristic lesions of an erythematous or hypochromic nature in which histologically there was noted a difference from the typical uncharacteristic form in that a slight histiocytic reaction was present. The uncharacteristic group may therefore be divided into two sub-groups, namely, the pure uncharacteristic group and the typical uncharacteristic group. If in the latter the epitheloid cells increase and dominate the picture and complete phagocytosis takes place the case becomes tuberculoid. If, on the contrary, the increase in the activity of the reticuloendothelial cells is incomplete, the change is towards the lepromatous type.

Chaussinand (1947.3) commented that he did not regard the South American classification as a step in the right direction. He objected in particular to the replacement of the classical "neural type" by two new types, the tuberculoid and the uncharacteristic. He regarded as insufficient both the histological and clinical grounds advanced in support of the new classification. Reverting to the Cairo classification he proposed a slight modification: *Nc*, neural leprosy with cutaneous lesions; *Np*, neural leprosy with polyneuritic lesions; *Ncp* or *Npc*, neural leprosy with cutaneous and polyneuritic lesions, the positions of the letters *p* and *c* depending on which is more pronounced. The Arabic figures 1, 2, and 3 would continue to represent degree of seventy. Lepromatous leprosy would be classified only according to severity and mixed forms by NL, etc.

Rodriguez (1947.3) contributed a comprehensive review of the whole subject. He pointed out that leprosy is at present classified on the basis of two main types, one characterized by a specific granulomatous reaction and the other by a non-specific tissue response. Depending on the degree of resistance the second may be further divided into three forms or stages: interstitial proliferation, round-celled infiltration, and tuberculoid granuloma. These forms of the second group exhibit increasing degrees of "clinical stability." A proper collective designation for this second group, as appropriate as the term lepromatous is for the first, remains to be proposed. In the Cairo classification the term is "neural"; in the South American, "tuberculoid." Rodriguez suggested the possibility of viewing lep-

rosy as having one main type, the others being mere stages of the disease. The stages as proposed by him are: I. Interstitial (maculo-anesthetic (neuro-leprid) stage (Mitsuda variable); II. Perivascular round cell (uncharacteristic) stage; III. Tuberculoid stage (Mitsuda positive); IV. Lepromatous (foamy cell) type (Mitsuda negative).

VIII. ADMINISTRATIVE AND SOCIAL

Burgess (1943) in "A World Within a World" developed the idea of the inter-change of products between leprosaria in the different parts of the world. An article by Mr. Hugh McKean (1945) published posthumously, described the prewar out-patient divisions of the Chiengmai Asylum in Siam. At the time of writing 25 centers were in operation. The only costs in each clinic were for medicines, supplied free to the patients, and the salary of an injector, a former patient who held a second class medical certificate. (In a dispatch to the Baltimore Sun, November 16, 1947, it was stated that 13 of these clinics, which were closed during the war, have been reopened. *A/Ed.*) A reprinted article (1942) described recent improvements at the National Leprosarium in Carville, Louisiana. A report of the Leprosy Advisory Committee of the Director of Health (1945) discussed the problem of home isolation in the Philippines, recommending against adoption of the measure at the present time.

Wade (1947.1. Rep.) wrote to the Editor of the Carville Star regarding the problem of leprosy in the United States and especially regarding the education of American physicians and public. McCoy (1947.2) wrote on the public health management of leprosy in the United States advocating fitting the measures to the individual case. Rogers (1942) contributed a review of progress in the control of leprosy in various parts of the British Empire. Muir (1945) discussed the stiuation in Trinidad. Weaver (1947. 2 and 3) contributed an enlightening summary of the work of the Federation of Societies for Assistance to Lepers in Brazil and of the part played by private cooperation. Chala (1946) described progress towards the control of leprosy in Colombia. A very interesting feature is that the teaching of hygienic rules for avoiding infection and the principal facts about leprosy is compulsory in all public and private schools in Colombia. Suarez (1946) described the organization of the National Leprosy Service of Bolivia. The prevalence of the disease on the Andean Plateau is low; it is high in the temperate regions of the Central Valley but reaches the maximum in the eastern plains, where the foci are old. There are three small leprosaria in Bolivia and four dispensaries. A modern colony of

the rural type was under construction in Los Negros in the central part of Bolivia. Based upon registered cases, the prevalence rate for the whole country was 8.8 per 100,000 but the variation between provinces was from 0.1 to 45.0 per 100,000.

IX. GENERAL

Two articles of general interest were reprinted in Spanish (1946): The Constitution of the World Health Organization and an Editorial on that Organization taken from the *American Journal of Public Health*. It is hoped that some relationship may be established between the International Leprosy Association and the World Health Organization to the end that the World Health Organization will stimulate research and control measures in every country in which leprosy is a problem.

X. COMMENT

The war years then were productive, much more so than was anticipated. The JOURNAL played a complementary role. Research contributions made each War Number possible and each Number to some extent stimulated research. The permanent value of the War Numbers depends entirely upon the significance of their content to the solution of the problems of leprosy. In these matters judgment is notoriously fallacious and prediction dangerous.

Certain comments, however, may be ventured. The dramatic pronouncement of the period was the therapeutic effect of the sulfones. Unfortunately none of these drugs produces such quick and unmistakable results as to make controlled experiments unnecessary. In a previous issue (1947.1) the Acting Editor has presented the case for controlled studies. There is a real danger that plans for such tests may be sabotaged, on the one hand by demand for treatment by every patient and on the other by the insidious belief that the response of treated patients furnishes a sufficient guide. The deceptive course of the disease and the uncertain position of chaulmoogra after years of administration should convince anyone of the necessity for adequate controls.

The contributions to the immunology of the disease have left many uncertainties in their wake. This is probably inevitable. Lacking both a culture medium for his antigen and an experimental animal for the production of antibodies there is little light for the path of the immunologist. As regards the lepromin test, the results certainly require clarification. There are conflicting statements concerning the correlation between lepromin and tuberculin reactions. There seems to be only one well-established fact, namely, that in normal persons in both endemic and non-endemic areas

and in tuberculoid patients, the reaction may be positive or negative, whereas in lepromatous leprosy the reaction is nearly always negative.

Studies on histopathology have been few but stimulating. Extension of such studies seems very desirable. The newer techniques applied in early leprosy to biopsy material and to tissues from patients dying from other causes might yield evidence concerning the portal of entry and the path of infection within the body.

The classical bacteriologist and the experimental pathologist have apparently abandoned leprosy for greener fields. There are, however, measures either still untried or imperfectly applied which might reward the patient investigator.

There is likewise much that could be learned from intensive epidemiological studies. One feature which is virtually unexplored is possible association with some dietary deficiency. An exhaustive investigation of the contact histories of children showing early lesions would also be of great interest and perhaps of considerable significance. The possibility of transmission by some house-inhabiting insect or insects has been by no means eliminated. Disparity in incidence as between males and females is observed early in life in the Philippines; this may be attributable to some environmental factor capable of detection.

With the termination of hostilities it was hoped that men and funds would be available for active expansion of leprosy research. After two years little progress has been made. There is a world-wide shortage of scientific workers. The number of scientists in the whole world devoting their full time to leprosy research is very small — scarcely, it is thought, a baker's dozen. Many countries have increased greatly their appropriations for custodial and medical care of leprosy patients but few are contributing anything towards research. This combination of scarcity of men and lack of money threatens to stay the hand of progress.

As at the outbreak of war, so again vigorous efforts are necessary. The need for large expenditures for the training of research workers and for providing essential facilities must be brought convincingly to the attention of governments, foundations, and private philanthropists. The International Leprosy Association might play a very effective role in such a movement. The need for the JOURNAL is more apparent today than every before. Under the direction of Dr. Wade it can be counted upon to do its part.

JAMES A. DOULL