concentrating neurohumor of Fundulus. These studies on the so-called nervous control of the melanophores of fishes point with great certainty to neurohumors as the agents really concerned and suggest the probability that there are two classes of such agents, one of which consists of materials, like pituitrin, soluble in water and hence transportable by the blood, hydroneurohumors, and the other soluble in oil and hence transmissible through the fatty or lipoid constituent of the tissues, liponeurohumors.

Although the instances here discussed are taken from only a single group of effectors, chromatophores, and their nervous connections, it is possible that reactions of this kind extend throughout the whole of the nervous organization of animals and that the relation of receptor cells to neurones, of one neurone to another, as well as of neurones to effectors, may be based upon the same principle that appears to apply to chromatophores. This in fact is the neurohumoral hypothesis, a view which in its essence has been expressed already by a number of workers and which under the general caption of the chemical interrelation of nervous elements has permeated the thinking of not a few of the neurologists of to-day.

THE UNSOLVED PROBLEMS OF LEPROSY[1]

By Professor FREDERICK P. GAY

DEPARTMENT OF BACTERIOLOGY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY

THE earliest medical records from Egypt and India are said to include descriptions of clinical leprosy.[2] Although the somewhat indeterminate description of cutaneous ills summarized in the term "zaraath" in the Old Testament may well have included several separate entities there is every reason to believe that it was incidentally descriptive of the disease now known as leprosy. The horror, fear and pity which leprosy in its exaggerated forms have always excited led to early attempts at segregation of its sufferers in many places. At all events the modern clinical description of leprosy dates from the work of Danielsenn and Boeck in 1847. It seems certain that Hansen in 1868, and even before he had anilin dyes to use, actually described with fidelity the massive aggregates or globi of the leprosy bacillus which we now recognize as a constant feature in the cutaneous form of the disease. In spite of these two relatively early evidences of objective certainty, the history of leprosy as a process remains in many of its significant phases as baffling to-day as it was a century ago. It may well take all the short time placed at my disposal to list with anything like sequential probability what the outstanding and unsolved problems of leprosy are, but this, at least, I shall attempt to do, with the further hope that I may emphasize two of the main junction points in the historical pathway which this brief survey covers.

It is still uncertain precisely what effect the segregation of lepers has had in suppressing the disease. Such isolation can never be completely carried out, particularly under the conditions of living in those countries where it is most prevalent, and a belief in its effectiveness is based largely on the disappearance of leprosy from Continental Europe in the Middle Ages, although certain other factors, such as other decimating epidemics, changes in dietary and even of climate, may well be involved. At all events the disease still remains in precisely those localities of the world where it was first described, in Africa, in the Orient and in the West Indies. Until we know more fully the precise epidemiology of leprosy no process of segregation could be expected to be efficient.

There is no question as to the great prevalence of leprosy in the early years of life, and the modern trend of thought goes farther in believing that infection takes place, at least in the majority of instances, in these very same early years, irrespective of the precise time of its clinical detection. We would not go so far as does Manaling, who, in view of the slow development of the disease and its frequent spontaneous cure in children before the complete evolution of the disease, would deny the possibility of its inception in adult life. In fact, there are recent well-controlled instances of accidental and experimental infection which render it probable that natural adult infection normally, although perhaps rarely, occurs.[3]

Far too little attempt, it would seem to us, has been made to ascertain the possibility of eliminating leprosy by immediate segregation at birth. Most of the references on the effect of removing the offspring of leper parents are misquoted and deal rather with separation at varying periods after birth than at the moment of delivery. The extraordinarily important results reported by Hasseltine in Honolulu have not, so far as we are able to determine from the literature, or on direct inquiry from those most concerned, been followed up. It will be recalled that Hasseltine found

[1] Address delivered before Section N—Medical Sciences, American Association for the Advancement of Science, Pittsburgh, December 31, 1934.

[2] Rogers and Muir.

[3] deLangen, Marchoux.

a single case of leprosy over a period of fifteen years in 219 children who had been removed from their leper parents at birth. In further investigation of these results, and in their prompt general application if they are confirmed, lies in our mind the first important pathway toward the eradication of the disease.

One of the most striking features of leprosy is its differentiation into types which may be so extreme as to justify a restricted diagnosis of the disease as "neural," "cutaneous" or finally "tuberculoid." All combinations of these extreme forms exist and they are all apparently preceded by the identical primary lesion. The several forms furthermore markedly predominate in certain countries; for example, although all types exist in the United States, on the other hand the cutaneous form is almost exclusively seen in the Philippines, and the neural form bulks large in India.

These clinical forms of the disease are extremely divergent in their individual pathology, and these differences are marked particularly by the almost complete absence from the neural form of the enormous numbers of acid-fast bacilli which are constantly present in the moderately advanced cutaneous disease. Diagnosis, indeed, in the neural form is often difficult, owing to the absence of the characteristic bacteria which facilitate recognition of the cutaneous form. One may well speculate as to this diversity of clinical types, which involves not only geographical distribution, conceivably owing to differences in climate, and which is also accompanied by marked differences in spontaneous cure, the neural form being on the whole milder and more frequently recoverable. This leads us directly to a consideration of the etiological agent of the disease itself.

We have already referred to the enormous aggregates of acid-fast bacteria that are found in typical cutaneous cases of leprosy, but non-acid-fast and even branching forms and forms like the Much granules in tuberculosis have also been casually observed. These latter forms might seem more significant if they were diligently sought for and it is not inconceivable that their relation to the neural form is an important one.

A series of observers since Neisser, nearly fifty years ago (1886), aggregating well over 60 authors or groups of authors to date and involving many more separate publications, are readily to be found in literature. Each of these authors in turn has believed that he alone has isolated the true organism of leprosy and feels that each of his predecessors has at best been only partially successful in attaining the desired result. A recent critical survey of this baffling question has led us to a belief somewhat different from the usual accepted one, namely, that a number of these observers have in reality grown the specific microorganism, rather than the generally accepted view that no one or only one particular investigator has as yet been successful. We should be embarrassed to attempt to name all these isolations which we should regard as etiologically correct. One is inclined at first glance to rule out the numerous observations which impute etiological significance to Gram-positive non-acid-fast diphtheroids if it were not for two main lines of argument. It is true that such organisms are readily found in the normal skin. On the other hand, it is certain that acid-fast contaminants might also be present.

In at least 18 instances in the 68 separate descriptions of isolated organisms that we have found and studied, diphtheroids have been described, and some of these by investigators whose previous work would inspire technical confidence. Both chromogenic and non-chromogenic acid-fast organisms have been obtained in 32 instances, and in view of the recent work on chromogenic variants of the tubercle bacillus now clearly established, there is no inherent reason why any of these isolations should not represent the true etiological agent. We must confess here to an early prejudice. Studies on organisms of the Actinomycetales group by our regretted pupil, Edith Claypole, showed in no uncertain fashion that in her unusual collection of pathogenic members of this genus, as studied over a period of years, individual pure strains not only varied from acid-fast bacilli to non-acid-fast Gram-positive organisms, but further to branching non-acid-fast forms. Furthermore, all these varieties were observed in many single strains when studied at intervals over a long period; and cross immunity reactions were shown to occur between the divergent morphological forms. With this in mind we are receptive to the claims of those 11 investigators who have isolated what they have described as a "streptothrix" in cultures from leprosy as well as those 18 others who found diphtheroids. Some of these cultures were variably acid-fast and even branching. A few authors have described both acid-fast bacilli, non-acid-fast diphtheroids and acid-fast streptothrix in successive isolations.

May we make our position perfectly clear in this matter by quoting a few specific references? We have personally no reasonable doubt that the non-chromogenic acid-fast bacillus isolated by Soule and McKinley, and which retains these characteristics, is the one that is present in characteristic fashion in cutaneous leprosy. But we feel also that it is quite likely that the diphtheroid isolated by Walker, at times, may represent another growth phase of the acid-fast organism which he also found. Salle's recent claim at transformation of a primary acid-fast isolation into a diphtheroid on subculture would,

if corroborated, prove this suggestion of various growth phases, which, to repeat, is not confined to the organism of leprosy.

The final and crucial proof of the correct etiological agent of leprosy still remains to be fulfilled. One spontaneous disease in animals, rat leprosy, apparently offers almost complete analogy to the human syndrome, including difficulty in culture of the microorganism in the lesion. In spite of this fact no one has, we believe, produced experimental leprosy in animals with material of human origin with anything like fidelity. No particular surprise need be occasioned by this failure. Many strictly human diseases have not been reproduced in animals, and some have succeeded only on the inoculation of anthropoid apes which have not been sufficiently tested in the case of leprosy. The time element would seem to us important in this connection. We know that human leprosy often requires years after the presumed, or, in a few instances, the known time of infection, before characteristic lesions with bacteria in them are found; so far as we know no experimental animals have been observed longer than a few weeks.

Another field for serious inquiry, in fact, the ultimately most important one in the study of leprosy, is that of specific therapy. There is a firm, and we believe an increasing conviction, that chaulmoogra oil derivatives are to a variable degree effective at least in ameliorating the symptoms and lesions of leprosy. The effectiveness so far depends not only on the preparation used but on the method of inoculation, and human trial must remain the ultimate criterion on which this or any other form of therapy is based. But it would seem as if a fairly obvious experimental method for the testing of the comparative value of anti-leprosy medicaments has only recently been tried; Anderson and his collaborators have compared several derivatives of chaulmoogra oil on rats spontaneously suffering from their own variety of leprosy and have been able to come to a certain decision in reference to the best of these preparations. Surely further attempts in this direction are indicated.

SCIENTIFIC EVENTS

THE FOURTH INTERNATIONAL CONGRESS OF AGRICULTURAL INDUSTRIES

THE fourth International Congress of Agricultural Industries, which is one of the many to be held in connection with the Brussels Universal Exposition of 1935, is being organized by the International Commission of Agricultural Industries.

It will be remembered that the third congress was held in March of last year, at Paris, and although intervals of three years between the congresses will ordinarily be observed, it was decided to hold the next one the following year in order to set up a more effective organization of the congresses and to take advantage of the Brussels exposition.

The congress will be organized in the four divisions: (1) General scientific studies; (2) Agronomic studies; (3) Industrial studies, and (4) Economic studies. There will be some twenty-six sections comprised in these four general divisions. In order to assure that subjects of timely interest are discussed, special reporters upon ten such topics will be appointed and the reports prepared by them printed and distributed in advance in order to assure fruitful discussion of these questions of "priority."

Communications are invited from all who may desire to take part in the program. The texts of communications in triplicate, together with brief abstracts, should be mailed before April 15. The membership fee is 100 French francs and for the families of members, 50 francs. Applications for membership and for further information should be addressed to the International Commission of Agricultural Industries, 156 Boulevard Magenta, Paris (X^e), France.

THE PAN AMERICAN INSTITUTE OF GEOGRAPHY AND HISTORY

A GEOGRAPHICAL and historical congress to organize an international bureau for the compilation of data on exploration was proposed by several South American countries as long ago as 1903. In 1928 at the sixth International Conference of American States plans were perfected for the organization of a Pan American Institute of Geography and History. Sr. Pedro C. Sanchez was appointed director of that institute, and in September, 1929, a meeting to conclude plans of organization was held in Mexico City. At that meeting Dr. Lawrence Martin, of the Division of Maps of the Library of Congress; Dr. George B. Winton, professor of history at Vanderbilt University, and Dr. William Bowie, chief of the Division of Geodesy, U. S. Coast and Geodetic Survey, represented this nation.

The first formal assembly of the institute was held at Rio de Janeiro in December, 1932. At that assembly the United States was represented by Hon. Edwin V. Morgan, Ambassador to Brazil, and Dr. Wallace W. Atwood, geographer, president of Clark University, Worcester, Massachusetts. At the final plenary session the City of Washington was selected as the place for the next meeting in 1935, and Dr. Atwood was chosen executive president for three years.

Several of those who are particularly interested in