inevitably leads to investigations of the interaction of the individual with the institutions of society and to an attempt to discover the motives which lead to the individual's interest in science or art and his need for religion, politics, and sport.

The work began with the need to cure adult hysterics and 'obsessional neurotics, but it soon became clear that there were infantile neuroses which reappeared in early adult years (the first psychodynamic treatment of a child, by a sort of child-guidance technique, was undertaken by Freud in 1909); the application to psychotics in and out of institutions came later.

The barriers which separated medicine proper from insanity and the neurotic from the normal have begun to break down. Clinical medicine, which has never been blind, has acquired a new interest and grasp in listening not merely to the sound of organs but to the voice of the whole personality seen in a social setting. If the contribution of psychological medicine to general medicine could be summed up in a single sentence, one would say that it has given a new dimension to the medical interview. The study of psychodynamics has progressed step by step with the improvement of clinical skill applied to discourse between doctor and patient: as in science generally, so in psychological medicine, progress consists in an ever-developing scrutiny (in this case without the aid of apparatus) of what lies in the field of observation. Nowadays we can get more out of a consultation than could be got before—that is to say, clinical skill has been increased.

Conclusion

It was said that the psychodynamic ideas outlined above have given a new dimension to medical thought; in no branch of medicine is this more true than in psychiatry. That the child is father to the man and that the child models himself on his parents have long been guessed, but how the process worked was not realized. These studies have led to a way of looking at the growth of personality in health and disease which is valuable because it provokes further thought (one of the best criteria for assessing the worth of a theory); psychiatrists, while developing other techniques for the empirical treatment of mental disease, find themselves, wittingly or not, when trying to explain the behaviour of their patients, employing some or most of the ideas here so briefly sketched.

On this occasion it may not be out of place to recall that the key idea to this great advance in medical theory and technique was published just fifty years ago: Freud's *Interpretation of Dreams*. A clinician, without laboratory aids or other such devices, by the closest attention to the material before him, unpromising and the least worthy of scientific care as it was then thought, changed his specialty out of recognition and raised the potential of every doctor's clinical interviews.

"In the first instance, when the illness first came upon me, I seemed to be aware of what was about to happen. I became powerfully impressed with the idea that the Devil was about to seize me, and I felt convinced that the only way to meet him—if efficient way there was—was to remain awake waiting for him all through the night, and combat him in a naked condition. I therefore threw off all my clothing, although it was a bitterly cold February night, and there awaited the Evil One." "The Late Mr. John Ruskin: Mr. Ruskin's Illness Described by Himself." From the *British Medical Journal*, January 27, 1900, p. 225.

FIFTY YEARS OF TROPICAL MEDICINE

BY

J. S. K. BOYD, O.B.E., M.D., D.P.H.

Director, Wellcome Laboratories of Tropical Medicine

The progress which has been made during the past fifty years in the field of tropical medicine is so vast that no adequate account of it can be given within the compass of a short article. Inevitably many matters which are far from unimportant must either be omitted or be given but scant reference.

The discovery of the relationship between malaria and mosquitoes, made at the end of the nineteenth century, gave both impetus and direction to research along similar lines in other tropical diseases. Several hitherto unrecognized pathogenic parasites have been identified, and in many cases the part played by an intermediate host in transmitting the disease to man has been demonstrated, thus allowing new and precise methods of prevention to be applied. In these investigations much fresh ground had to be broken. At first little or nothing was known of medical entomology or parasitology, while microbiology, though a rapidly expanding science, was still in its infancy. Most of the detailed knowledge of these subjects that is now available has been amassed in recent years, during which time both laboratory and field specialization in the different branches may be said to have evolved. Important work has been done by specially appointed bodies such as the Plague Investigation Committee which worked in India under C. J. Martin, the Commission under Sir David Bruce appointed by the Royal Society to investigate sleeping sickness, the Kala-Azar Commission working under the Indian Research Fund Association, the American Yellow Fever Commission, and various teams sponsored by the Indian Research Fund Association, the Rockefeller Foundation, and the Medical Research Council.

In matters of therapy no important new "herbal" remedies have been discovered, although some advances have been made in the extraction and purification of the active principles of those already in use. Investigation along the lines of immunology yielded some valuable vaccines for prophylaxis and antisera for therapy, but the latter have become less important with the advent of specific chemotherapy and of antibiotics.

Vitamins were first identified during this period, and the aetiology of deficiency diseases, such as beriberi and pellagra, was explained.

Some credit for the progress made must be attributed to the stimulus of the two world wars, during which the presence of large numbers of troops in unhealthy tropical surroundings was an incentive to intensive research—some, as for example the work on malaria with human volunteers, of a kind which could not have been carried out in less urgent circumstances. Financial restrictions, the stumbling-block of most research workers, ceased to be of significance, and efforts on an unprecedented scale were made to solve outstanding problems. The results achieved were in some cases of the greatest value, and must be classed among the best of the few good things which emerged from these wars.

The practice of tropical medicine calls for an intimate knowledge of subjects which play only a minor part in the normal medical curriculum. To meet this need special teaching establishments have been founded, of which we have in Britain the London School of Hygiene and Tropical

Medicine (with which is affiliated the Ross Institute of Tropical Hygiene) and the Liverpool School of Tropical Medicine. In India, the Calcutta School of Tropical Medicine was for many years under the direction of the Indian Medical Service, while more recently, in Australia, a School of Tropical Medicine was established by the University of Sydney. These Institutes are engaged not only in teaching but also in research, both at home and in the Tropics, and have made valuable contributions in every branch of their special subject.

Malaria

Malaria is the most important of tropical diseases, and in consequence has been widely studied in all its different aspects.

Life-cycle of the Parasite

It was long believed that the sporozoite injected by the mosquito into man entered a red cell and multiplied by schizogony until parasites were numerous enough to produce symptoms. A suspicion that this process might be of a more complicated nature was aroused by the observation that benign tertian (*Plasmodium vivax*) infection, when induced by blood inoculation, was cured by quinine, whereas mosquito-bite infections usually relapsed after similar treatment. This suspicion was deepened by the discovery of exoerythrocytic or tissue forms in chicks infected with *P. gallinaceum* and by certain observations made in experimental human infections by Fairley and his colleagues in Australia. Nevertheless, exhaustive examination of tissues obtained by ordinary methods gave uniformly negative results, and it was not until hyperinfection was induced, first in monkeys with *P. cynomolgi* and later in human volunteers with *P. vivax* and *P. falciparum*, by Shortt, Garnham, Fairley, Covell, and Shute, that dividing forms were found in the epithelial cells of the liver, thus demonstrating conclusively the exoerythrocytic development of the sporozoite. This discovery is not merely of academic interest but is closely linked to still unsolved problems of causal prophylaxis and prevention of relapse.

Mosquito Destruction

Early attempts to eradicate malaria by destruction of larvae were, with a few notable exceptions, disappointing. The methods then employed—canalization of streams and the oiling of stagnant water—were relatively inefficient and involved much recurring work which, in sparsely populated localities, was too costly to be practicable. This was well shown in the 1916–18 campaign in Macedonia, when all attempts at destruction of larvae failed to yield a significant reduction of mosquitoes.

At a later date, when more became known about the malaria-carrying properties of different anophelines, better results were obtained by "species control." By studying and taking advantage of the individual, and often peculiar, habits of the carrier species it has on occasion proved possible to devise some simple yet highly effective method for the control of this particular species, which can be applied without having recourse to the expensive "blunderbuss" technique needed for the destruction of all the different mosquitoes in the area. Such special methods are now used successfully in various parts of the world, good examples being the control of *Anopheles melas* and *A. gambiae* in Lagos and of *A. leucosphyrus* in North Borneo.

The most important advances, however, have been made in the materials used for destruction of larvae. The original method—oiling—though effective when thoroughly carried out, was laborious and ill suited to certain types of water.

At a later date dusting with paris green was introduced, and in some cases proved better. Both these larvicides have now been superseded by D.D.T. dissolved in oil, which is more economical (one gallon will treat the same area of water as ten to twenty gallons of plain oil), much more efficient, and more persistent in action. This preparation can be applied either by hand-sprayer or, in inaccessible regions and on a larger scale, by aircraft. Such wholesale application has the disadvantage of killing many other insects besides mosquitoes, and needs careful control.

Until recent years the destruction of adult mosquitoes played a minor part in the prevention of malaria, although, with the advent in the middle 'twenties of atomized sprays containing pyrethrum, the comfort of the resident in the Tropics was greatly increased. During the first part of the second world war pyrethrum-spraying as an anti-malarial measure was used on a large scale in Southern India, and a significant reduction in incidence was claimed. D.D.T. is now employed for this purpose, and has the advantage of being non-volatile, so that when applied in suitable form to the walls and roofs of dwellings it persists as a fine crystalline deposit for a period of months, and poisons any mosquitoes which become contaminated with it. Even this method has its limitations, for, while it kills mosquitoes which alight inside the hut before or after feeding, it is quite harmless to other species which habitually fly in and out without settling except when biting. Into this latter category come certain well-known malaria carriers, a fact which emphasizes the importance of having an exact knowledge of the habits of each species. In some cases "gammexane," another potent new insecticide, has succeeded as a "residual" insecticide where D.D.T. has failed.

By attacking both larvae and adults with these modern weapons it has in certain places been possible to exterminate the entire mosquito population and hence remove all risk of malaria. Islands such as Cyprus, where a campaign along these lines has just been completed, are ideal for all-in measures of this kind, as reinfestation can be prevented by quarantine measures; but even in less fortunately situated localities it has proved possible to effect and maintain a reduction in mosquitoes sufficient to influence malaria incidence.

Treatment

"Many drugs have been employed in the treatment of malarial disease, and many drugs have some influence on it; all sink into insignificance in comparison with quinine. In serious cases, to use any drug to the exclusion of quinine is culpable trifling." Thus wrote Manson in 1900, and for many years these words were unchallenged. In some ways they are still true, for quinine holds its place as a schizonticide, and in the opinion of many is the drug of choice when given intravenously for the treatment of cerebral malaria. On the other hand, it has certain important shortcomings to which attention was directed by the malaria outbreak in Macedonia during the 1914–18 war. Contrary to experience in peacetime conditions in certain of the Colonies, it was found that quinine was unsuccessful as a prophylactic and had little effect in countering the massive infection which prevailed at that time. It failed to produce radical cure, particularly in benign tertian (*vivax*) malaria, as shown by the numerous relapses which subsequently occurred. Finally, it did not destroy gametocytes of *P. falciparum*, which continued to circulate unaffected even by intensive courses of quinine.

In the last twenty-five years a number of new anti-malarial drugs have been synthesized that are of value

mainly because they have among them a wider range of action than quinine and cover some of the gaps in which quinine is ineffective.

"Plasmoquine" (now called pamaquin) is a relatively poor schizonticide but is active against the sexual forms of *P. falciparum* and against the resting forms of *P. vivax*, which maintain infection between relapses. Unfortunately this action is limited by toxicity, so that the small doses of the drug which can be administered with safety are not always sufficient to kill all these forms. Pamaquin is usually given for radical cure either with quinine or following one of the other schizonticides to be described. This combination of drugs reduces the relapse rate in vivax malaria to about 10%, or roughly one-sixth of what it is when a schizonticide alone is used in treatment. Two other closely related compounds, pentaquine and isopentaquine, have a similar action and no outstanding advantage over pamaquin.

"Atebrin" (renamed quinacrine and finally mepacrine) has schizonticidal properties which parallel closely those of quinine. It is relatively tasteless, and rarely causes unpleasant symptoms, although, for cosmetic reasons, objection may be taken to the yellow coloration of the skin which it produces on prolonged administration. Its outstanding action in suppression will be mentioned later.

The compound now known as chloroquine (synonyms, "resochin" and "aralen"), first produced in Germany and resynthesized in U.S.A. after being "captured" in North Africa, has proved of great efficiency both in treatment and in suppression.

Finally, the British product, "paludrine" (proguanil), gave promise of outclassing all other antimalarials. In routine use it has proved to have certain drawbacks, the most serious of which is a tendency to induce the emergence of drug-resistant variants of the parasite. Should these forms become widely distributed, the use of proguanil will be greatly restricted, if not contraindicated. Its schizonticidal properties in falciparum infection are not outstanding, but in vivax relapses in a premunized community a single dose effects a cure. Its most important application is as a prophylactic or suppressant.

With these compounds, selected in accordance with the circumstances of the case, it is now possible to attack effectively every stage of the parasite with the exception of the resting or tissue forms of *P. vivax*, and even these are partially sensitive to the pamaquin series.

Drug Suppression

Probably the most monumental work on malaria in recent years is to be found in the investigations of Fairley and his colleagues which were carried out at Cairns, in Australia, during the 1939-45 war. By means of experiments with controlled infections in human volunteers irrefutable evidence was produced on the problems of causal prophylaxis and suppression. Quinine was shown to be inadequate against massive infecting doses of sporozoites, while mepacrine gave complete suppression. There can be no doubt that the rigorous application of mepacrine suppression had a vital influence on the course of the campaign in the South-West Pacific, as malarial infections, which might have been expected to rival those of the first war in Macedonia, were negligible.

Later experiments along the same lines showed that chloroquine was also a reliable suppressant and proved that proguanil not only suppressed vivax malaria but was a causal prophylactic against falciparum infection. It is disturbing that recent work by Field suggests that the long-continued administration of proguanil for prophylactic

purposes may lead to the emergence of resistant strains, for in certain ways this compound has advantages over the other preparations.

To summarize, it can be claimed that ways and means have been discovered by which, in favourable circumstances, mosquitoes—and hence malaria—can be eradicated; by which infection can be suppressed where eradication is impossible or impracticable; and by which attacks of malaria can be cured where suppression has been faulty or when suppressive drugs are withdrawn. The major problems of malaria are now administrative rather than medical.

Blackwater Fever.

The immediate cause of an attack of blackwater fever still remains to be discovered, though its relationship to recurrent falciparum malaria and quinine administration is amply confirmed. However, when the new suppressive drugs are conscientiously used, as they were in the South-West Pacific campaign, the risk of this disease, whatever its cause, is all but eliminated.

Leishmaniasis

Kala-azar

At the beginning of the century kala-azar was known as an ill-defined and very deadly disease which had become prevalent in Assam in the preceding fifteen to twenty years. It has subsequently been recognized in other parts of the world—China, Central Asia, the Mediterranean littoral, and parts of Africa and South America. The human disease has been found to be associated with a canine reservoir of infection in certain countries, and the epidemiology in Southern Sudan suggests that another reservoir may exist in small rodents.

The discovery of the causative parasite, *Leishmania donovani*, made independently by Leishman and Donovan in 1903, led to a prolonged search for the vector, a problem which was not finally solved until 1942. Although direct transmission long remained suspect (for leishmania parasites are found in the faeces and nasal discharge of victims of the disease) the evidence incriminating an insect vector—which ultimately narrowed down, so far as Assam is concerned, to one species of sandfly (*Phlebotomus argentipes*)—was overwhelming. A complete cycle of development was found in this insect when it was fed on kala-azar cases, yet numerous attempts to transmit the disease by its bite to susceptible animals (hamsters and mice) and man were for many years unavailing. Success came later in a surprising way when it was discovered by Shortt and his colleagues that a minor modification in the feeding of the infected sandfly—a diet of fruit juice (raisins) instead of blood after the first blood-feed from the kala-azar patient—made it possible for the insect to transmit the disease to experimental animals and human volunteers.

Antimony has been found to have a powerful action on the leishmania parasite. First administered as tartar emetic, it is now given with better results in the form of quinquevalent compounds, of which the most effective are "neostibosan," "urea stibamine," and quinquevalent sodium antimony gluconate ("solustibosan," "pentostam"). With these drugs a high percentage of cures can be obtained, the last-mentioned in particular being successful even in the very refractory type of the disease which occurs in Sudan.

Good results have been given by certain of the diamidines, particularly stilbamidine, but this preparation has fallen into disfavour because of its tendency to cause late cranial nerve lesions.

Oriental Sore

Parasites first described in Russia in 1898 as the cause of oriental sore were subsequently identified as Leishman-Donovan bodies, and their relationship to the disease was confirmed by experimental transmission. As in the case of kala-azar, the parasites have been shown to be carried by the sandfly and, where local treatment fails, antimonial preparations given intravenously effect a cure. Here, too, some evidence has been adduced to incriminate a rodent reservoir of infection.

Trypanosomiasis

Nothing was known of the aetiology of sleeping sickness in 1900, and the best suggestion that Manson could make at that time was that it might be associated with infection with *Filaria perstans*. The discovery of the trypanosome in the blood and cerebrospinal fluid, and its incrimination as the cause of sleeping sickness, was made in the early years of the century, and was followed by the gradual unravelling of the details of its development in and transmission by the tsetse fly.

The campaign to control the more chronic and widespread sleeping sickness of West Africa (which is also found elsewhere throughout the tsetse belt) has been unremitting. The provision of centres for mass treatment has played an important part, both in giving relief to sufferers and in reducing the reservoir of infection. In the earlier years of the century tartar emetic was used with considerable success, but this has been replaced with more potent synthetic preparations, of which suramin ("antrypol," "Bayer 205") and, more recently, pentamidine are the most favoured. Unfortunately, these compounds do not pass the blood-brain barrier and hence have proved of little value in the treatment of advanced cases in which the trypanosomes have reached the nervous system. For such late cases arsenical compounds, of which tryparsamide is regarded as the most effective, have been used. Tryparsamide, in turn, has a serious fault. On prolonged administration it tends to give rise to drug-resistant strains of the trypanosome against which it is inactive. These strains retain their resistance in cyclical transmission through the tsetse fly. No satisfactory preparation which will attack the trypanosomes in both blood and central nervous system, and which will not produce resistant strains, has yet been found.

In addition to mass treatment, the extermination of the vector has developed as an essential part of prophylaxis. A study of the oecology of *Glossina palpalis* and *G. tachinoides*, which transmit *Trypanosoma gambiense*, has shown that these flies breed only within a few yards of water and cannot survive in the absence of suitable shade and humidity. In consequence they can be controlled by cutting down all trees within a few yards of streams near villages and by making wider protective clearings at fords and other spots where man habitually approaches the water. An alternative method of "selective clearance" has been tried in Gold Coast territory. It was observed that the requisite "microclimate" for breeding could be provided only by certain species of trees which have a patchy distribution. By training native gangs in the recognition of the types of tree in question and by setting them to cut these out over an entire system of river and tributaries a dramatic reduction in tsetse flies and sleeping sickness has been effected in certain areas.

In Nigeria the removal of entire villages from highly endemic areas which cannot be economically cleared of flies to a specially prepared fly-free tract of country has been carried out with success under the "Anchor

Corridor" scheme. The new homes are in the form of hygienic model villages and settlements, with a suitably organized scheme of local government and educational facilities designed to improve the general standard of living. This experiment has important implications other than its success in eradicating sleeping sickness, and is being watched with much interest.

Drug prophylaxis in trypanosomiasis has been tried in recent years, particularly in Belgian Congo, and pentamidine has proved to be the most successful compound for this purpose, though suramin has also been used with good results. It is claimed that a single dose of pentamidine will give protection for six months, a claim which at first sight appears extravagant but which is being substantiated by a growing mass of figures. If finally confirmed, this constitutes a most important advance.

The control of Rhodesian sleeping sickness has proved more difficult because of the scattered breeding-places and different habits of the vectors, *G. morsitans*, *G. swinnertoni*, and other less important species. By increasing the human population per square mile beyond a certain density and reducing or eliminating the big game (on which the flies feed), conditions are produced in which the flies cannot survive; but such a method has a restricted application. Discriminative clearing of trees and other biological methods of control have been successfully used, and spraying D.D.T. from aircraft, though very expensive, has also given good results in fly destruction.

No easy road to the solution of the trypanosomiasis problem has been discovered. By the application of the methods which have been outlined, a notable degree of control has nevertheless been established, and further progress may be confidently anticipated.

In South America, *T. cruzi* has been shown to be the cause of *Chaga's disease*, an acute febrile condition which if not fatal becomes chronic, with cardiac complications. It is carried by certain flying bugs of the genus *Triatoma*, and is found in various wild mammals. In the conditions which exist in the villages where the disease occurs little can be done to prevent it. No satisfactory cure is yet known.

Dysentery

Differentiation of amoebic and bacillary dysentery was vague fifty years ago. The former was recognized, but, although Shiga had identified the organism which has been named after him, the significance of his discovery was not appreciated for some time. Many other types of dysentery bacilli have subsequently been found, and it is probable that the majority are now known. The differential diagnosis of amoebic and bacillary dysentery and the isolation and identification of the different types of dysentery bacilli are now matters of laboratory routine.

Despite much research a great deal has still to be learnt about the aetiology of amoebic dysentery, for which the amoeba does not appear to be solely responsible. The symptomless cyst-passer or carrier, who can be found in appreciable numbers in countries, such as Britain, where overt amoebiasis is very rare, remains an enigma. Theories which postulate non-pathogenic races of amoebae or suggest the synergic action of certain species of bacteria with the amoeba, have been actively explored but still lack factual confirmation.

A notable advance in the treatment of amoebic infection—whether as dysenteric ulceration of the bowel or as tropical abscess in the liver—was the identification of emetine as the active principle of ipecacuanha. With this alkaloid in one form or another it became possible to cure

most cases of amoebiasis, though in old-standing infections with much secondary bacterial invasion (as seen in patients invalided from the Burma campaign) adjuvant treatment with penicillin and a slowly absorbed sulphonamide, sulphasuxidine, has been found of much advantage. Certain other compounds, such as the oxyquinolines ("yatren" and chiniofon), carbarsone (an organic arsenical), and "diodoquin," have been shown to be useful in some cases, while the recently discovered antibiotic "aureomycin" is also claimed to be effective. Despite all efforts to break new ground it has to be confessed that emetine is still unrivalled.

Once bacillary and amoebic dysentery were clearly differentiated it became evident that the former was both more common and epidemiologically more important than the latter, a fact well demonstrated by the crippling epidemics in Gallipoli and Macedonia during the 1914-18 war. The approved treatment at that time—saline purgatives—was of doubtful value, and antitoxin for Shiga infection had no more than a temporary effect. With the advent of sulphonamide treatment (sulphaguanidine was the first preparation used, being tried in the Middle East Force late in 1940) the picture changed dramatically. Almost without exception immediate improvement followed the administration of this compound, and when adequate supplies became available bacillary dysentery, though it still had a high nuisance value, ceased to be a disease of major importance. Subsequent trials showed that all the sulphonamide drugs were effective to a greater or lesser degree. Sulphaguanidine has, however, remained the preparation of choice with British practitioners, as it rarely produces any unpleasant side-effects and is safe to use in tropical climates because, unlike certain others of the series, it has no tendency to crystallize out in the urinary tubules.

With the exception of antitoxin, which has still a place in acute Shiga infections coming for treatment late in the disease, all other methods of treatment formerly in vogue have been given up in favour of sulphonamides. The use of these drugs in bacillary dysentery is one of the major advances in tropical medicine, the advantages of which can be fully appreciated only by those who had experience of dysentery in the days before they were available.

Plague

The development of the plague bacillus in the rat flea and the role of this insect in transmitting plague between animal and man was first suspected and finally confirmed in the early years of this century. On the basis of this discovery, destruction of rats became a standard method of preventing plague. This has been successful where carried out with thoroughness, but in the insanitary conditions which prevail in native villages the results have often been disappointing. Of recent years flea destruction with D.D.T. powder blown into rat-holes or thickly applied to captured and subsequently released rats has been attempted with apparently good results.

Considerable attention has been devoted to sylvatic plague, which is enzootic in various small rodents over wide areas in different parts of the world and is a persistent source of danger.

Vaccines for immunization against plague, which have been developed from the original Haffkine vaccine, have been widely used with encouraging results. Two doses at an interval of ten days are needed to give good immunity, but such a policy is difficult to pursue in epidemic conditions, and it is more usual to adopt the unsatisfactory practice of giving a single large dose. Recently this difficulty has been overcome by the use of a living vaccine of

non-virulent bacilli, given in the Dutch East Indies and in Madagascar with apparent success. This vaccine has the advantage of being administered in one dose and of causing little reaction, and the disadvantage of deteriorating so rapidly that it can be used only within a limited range of the laboratory where it is prepared. Attempts are now being made to produce a stable dried vaccine which will contain a high percentage of viable organisms when reconstituted.

In the treatment of plague, streptomycin has given promising results, and, to a less extent, so have certain of the sulphonamides. Antiserum and sulphonamides together are good, but unfortunately both streptomycin and serum are too expensive for routine use on a large scale.

Cholera

The cholera vibrio was discovered by Koch in Egypt in 1883, and the spread of the disease by contaminated water and food has long been recognized. Modern methods of sanitation and, in particular, chlorination of water have greatly limited the incidence of cholera. Nevertheless it is still present in endemic form in Central China and Lower Bengal, and from time to time, especially in periods of war and civil unrest, escapes from these boundaries and spreads far afield—witness the outbreak in Egypt in 1947. Prophylactic inoculation with vaccines made from vibrios of the right antigenic type has been shown to give some degree of immunity, but prevention primarily rests on good hygiene. In treatment the replacement of body fluid, preferably with hypertonic saline, was advised by Rogers, and is a life-saving measure when it can be carried out. No specific chemotherapeutic agent has been discovered, and claims made on behalf of the sulphonamides have not been substantiated.

Leprosy

Significant though not dramatic advances have been made in the treatment of leprosy in the course of the last fifty years. Chaulmoogra oil, previously used in the crude state, has been refined and is now given in the form of its ethyl esters or as sodium hydnocarpate. When treatment is started early in the disease beneficial action is usually well marked, though permanent cure is not often achieved.

In the last few years sulphone treatment has been introduced and has proved more effective than anything hitherto tried. The parent compound, diamino-diphenyl sulphone, is active but somewhat toxic and must be given only under careful control. The less toxic but more expensive derivatives "sulphetrone," "promanide" (U.S.A., "promin"), and "diasone" are generally preferred. These drugs are given in comparatively large doses over long periods of time, and during their administration the patient's general health must be carefully maintained. Clinical improvement, especially in the lepromatous form, may be striking, but the patient may not become bacteriologically negative for months or years.

At one time lepers, when recognized as such, were segregated for life. In many countries where reasonable hygienic conditions exist it is now the practice to allow those who have become non-infective to return, under supervision, to their homes and families. This has done much to stop concealment, and more cases are reporting in the early and more curable stages of the disease. Recognition of the fact that leprosy infection is often contracted by the children of leprotic parents has also shaped sociological policy in relation to this disease.

Yellow Fever

In 1900 Reed and his co-workers showed that yellow fever is conveyed by *Aedes aegypti* and that the infective agent, which is present in the patient's blood only during the first three days of the disease and which can be passed through a Berkefeld filter, undergoes some form of development in the mosquito before the latter is capable of transmitting the disease. *A. aegypti* is a "domestic" mosquito which is comparatively easy to control. By active campaigns and constant vigilance it has been eradicated or reduced to negligible numbers in ports and other urban areas where epidemic yellow fever was wont to occur, with the result that this disease is now of considerable rarity. The last recorded outbreak of importance was in the Nuba Mountain area of Anglo-Egyptian Sudan in 1940.

In South America sporadic cases to which the name of jungle yellow fever was given were found to occur from time to time in forest areas, and with the development of immunity tests it became possible to study this problem more closely both in South America and in Central Africa, where a similar state of affairs was later discovered. Yellow fever was found to be enzootic in certain species of monkeys and to be carried by mosquitoes other than *A. aegypti*. This monkey virus, which is identical with the urban epidemic virus, is transmitted to human beings living in or near the forest. There seems little doubt that jungle yellow fever constitutes the reservoir of infection and is capable of lighting up the disease in epidemic form when introduced by some traveller into a city in which *A. aegypti* is prevalent.

With the development of methods of cultivating the virus in the chick embryo large-scale vaccine production became possible. A stable attenuated strain of virus (the 17D strain) has been used throughout the world for this purpose. The immunity produced by inoculation with this vaccine is of a high order and lasts at least four years.

Air transport has greatly increased the risk of the spread of yellow fever to countries in which it has not previously occurred (particularly India and the Far East). Vaccination of all travellers before they are permitted to pass through endemic areas has eliminated this danger so far as the human carrier is concerned, and thorough disinsection of aeroplanes has been used to destroy infected mosquitoes which may be casual passengers. The success of these measures, particularly in the disturbed conditions which prevailed during the second world war, reflects favourably on their efficiency.

Dengue and Sandfly (Phlebotomus) Fever

There is little to be said of these two diseases except that the identification of the insect vectors—species of *Aedes* and *Phlebotomus papatasi* respectively—has made it possible to control their spread. The new insecticides are very useful in eliminating sandflies, which were very difficult to cope with by the older methods.

Scrub Typhus

Certain of the rickettsial fevers are found only in tropical countries, being restricted by the geographical distribution of the vector. Of these the most important is scrub typhus, a disease proved to be conveyed by the bite of the larva of the mite *Trombiculus deliensis*, the reservoir of infection being in certain rodents. This infection has long been known as tsutsugamushi disease in Japan, but was only recently recognized in Malaya. During the 1939–45 war it assumed great importance in the South-East Asia and Burma campaigns, where some thousands of casualties with

a high mortality rate caused grave concern. Prophylaxis was attempted by means of mite-repellents and vaccine. Of the former, dibutylphthalate applied by hand to the clothing was ultimately used with great success by Australian troops, and the incidence of scrub typhus was thereby reduced to insignificant figures. A vaccine prepared from the lungs of infected cotton-rats was developed and was ready for trial when Japan collapsed, and the risk of scrub typhus infection became negligible. Thus a bold experiment did not reach its conclusion, and no information, positive or negative, was gained from it.

In the last two years it has been found that the new antibiotics chloramphenicol and aureomycin have a specific action in scrub typhus, reducing the temperature to normal within two days and bringing about a dramatic improvement in other symptoms.

This important disease has therefore been clearly defined, its cause, reservoir host, and vector have been discovered, successful methods for its prevention have been devised, and a cure for the established disease has been found—a record of gratifying completeness.

Helminthic Diseases

Although the life-cycle of the fluke which causes *schistosomiasis* was accurately forecast many years previously, factual proof of the theory was not forthcoming until Japanese workers in 1913 traced the different stages of *Schistosoma japonicum* through a snail and back to the human host. A year later Leiper made similar observations on the Egyptian schistosomes.

This discovery indicated the steps necessary for the prevention of the disease—the avoidance of water contaminated with infective cercariae and, as a long-term policy, the destruction of the snails which act as intermediate host. The former is comparatively easy for the well-to-do, but impossible for the peasant who spends much of his time working on artificially irrigated land.

The eradication of the intermediate host has so far proved an almost insoluble problem. It involves extensive weed clearance and the treatment of streams, canals, and pools with a molluscicide, copper sulphate being the most effective yet discovered. Reasonably good results have been obtained in areas where the problem is a localized one, as in the Fayoum oasis in Egypt, but it is impossible to treat successfully a vast tract such as the Delta of the Nile, where irrigation canals and infected snails are ubiquitous.

In the treatment of *schistosomiasis* trivalent antimonial preparations have been found to give fairly good results. A long course is necessary and side-effects are unpleasant. Nevertheless, mass treatment centres, at which tartar emetic is administered as a routine, have been widely established in certain heavily infected areas and have been of considerable value in improving the general level of health. A synthesized thiazanthone compound, "miracil D" ("nilodin"), has recently been under trial, with promising results. It is given by mouth.

The *schistosomiasis* problem remains a formidable one, and constitutes an ominous threat in countries such as Iraq, where extensive new irrigation schemes are planned. Active measures are being taken to combat the disease in those countries where it is prevalent, but no striking degree of success can yet be claimed.

Until a few years ago no drug was known to have any action against *Wuchereria bancrofti*, the nematode which causes *elephantiasis* and allied complaints. Recently Culbertson and his co-workers have shown that certain antimony preparations kill the adult worms. This action

is masked by the fact that the microfilariae are unaffected by the treatment and live out their normal life span, slowly and gradually disappearing over a period of nine months to a year. At a still later date a synthetic piperazine compound, "hetrazan" ("banocide") was found to cause rapid disappearance of microfilariae. It remains to be seen whether or not it kills the adult *W. bancrofti*. Its action on *Loa loa*, the worm which causes Calabar swellings, appears to be definitely proved. "Hetrazan" has, however, failed to kill the adult forms of *Onchocerca volvulus*, although it destroys the microfilariae.

There is still controversy regarding the importance of the moderate or insignificant degrees of *ankylostomiasis* which are common in the natives of many parts of the Tropics. Experimental mass treatment campaigns have been carried out in certain communities, and it is claimed that the results have been beneficial. To maintain the ankylostome-free state is wellnigh impossible in the absence of proper sanitation.

Vitamin-deficiency Diseases

Certain vitamin-deficiency diseases, such as beriberi and pellagra, are usually regarded as tropical diseases because they commonly arise from the dietetic habits of the natives of hot countries. At the beginning of the century vitamins were unknown, and, although Japanese workers claimed to have shown that beriberi was due to a deficiency in dietary nitrogen, this view was not accepted, and Manson expressed the belief that it was a germ disease, the germ residing outside the body, perhaps in the soil, where it distilled a toxin which, when absorbed into the body, produced neuritis. The association of beriberi with the consumption of milled rice was later observed and confirmed, and from this sprang several theories, of which the two principal were (1) that a toxin was produced or was present in overmilled rice which was counteracted by its "antidote" in the discarded millings, and (2) that an essential factor, subsequently identified as vitamin B₁ (aneurin, thiamin), was discarded in the polishings. The latter theory (vitamin B₁ deficiency) is now widely held, yet has not been convincingly confirmed by experiment. The administration of aneurin does not of itself cure beriberi. It acts best when supplemented with a diet rich in first-class protein, particularly if given with yeast, which contains all the known B complex vitamins and possibly some unknown ones as well.

Pellagra occurs mainly, but not solely, in communities in which the staple article of diet is maize. First vitamin B₂ (riboflavin) and then vitamin B₃ (nicotinic acid) were claimed to be the missing elements in the diet responsible for this disease. Neither has proved to be wholly successful in treatment, and here also it has been shown that a generous diet rich in protein is necessary. Considerable evidence has been produced in support of the theory that maize contains a pellagrigenic factor which by its toxic action produces the symptoms of this disease.

Sprue

The exact cause of sprue remains unknown in spite of much investigation, and methods of prevention are therefore empirical. Experience in India during the 1939-45 war has shown that long residence in unfavourable surroundings is not an essential part of the aetiology, and also that the disease can occur in men eating full rations and living in a relatively innocuous climate—observations

which run counter to previously held theories. There is evidence that the disordered absorption of fats from the bowel is due to defective phosphorylation, and it has been suggested that the latter results from a breakdown of the enzymic systems concerned in the process, which in turn might arise from an altered biosynthesis caused by a change in intestinal flora. This hypothesis has not yet been confirmed by experimental methods.

In treatment the value of a diet rich in protein and low in fat and carbohydrate has been proved, while crude liver extract has improved the blood symptoms and cleared up the mouth and tongue lesions. Folic acid has, on the whole, been disappointing.

Other Diseases

Some of the more important tropical diseases to which no reference has been made, though all have been the subject of much investigation, are the tropical anaemias, enteric and undulant fevers (which are not confined to the Tropics), louse-borne and tick-borne relapsing fever, yaws, tropical skin diseases, and tropical ulcer (a most revolting condition when seen in epidemic form). In most of these the aetiology has been disclosed, and more or less effective methods of treatment are known.

Conclusion

From this brief review it will be seen that the dweller in the Tropics in 1950 faces a very different prospect from his predecessor in 1900. The temporary resident who takes strict precautions can hope to escape infection or, if he should contract a tropical disease, may expect to be cured without suffering from any grave or permanent ill-effects.

Unfortunately, the same cannot always be said of the native population, mainly because of their poverty and "backwardness." An improvement in the general standard of health can be expected only if there is a parallel improvement in economic conditions and in education—better agriculture, better food, better housing, intelligent hygiene, and the many other things which form part of evolving civilization. It is perhaps fair to say that, in tropical medicine, knowledge of the methods of prevention and cure of disease has outstripped its practical application. Even so, the research worker can console himself with the reflection that there is infinitely more still to be discovered than is already known.

"... For a long time Ross could get no further. He failed to trace the future progress of the flagellum in the mosquito. In the paper which we publish to-day we may have the explanation of his failure. Possibly he was working with the wrong species of mosquito, for now he tells us that at last, in a species of insect which hitherto he had not an opportunity of working with, he has found in certain cells in the stomach wall peculiar pigmented bodies which may turn out to be the maturing form of the extracorporeal or mosquito phase of the malaria parasite. If he has not quite proved that the malaria flagellum or flagellated spore enters a mosquito cell, he has now almost certainly proved, as attested by Mr. Bland Sutton, Dr. Thin, and Dr. Patrick Manson, that a product—melanin—characteristic of the malaria parasite is to be found in certain cells in the walls of the stomach of a certain species of mosquito after it has fed on crescent-containing malaria blood." From a leading article in the *British Medical Journal* of December 18, 1897 (p. 1805), commenting on a paper published in that issue by Surgeon-Major Ronald Ross, I.M.S.