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TROPICAL MEDICINE—PAST, PRESENT, AND FUTURE*

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I would like to give you a bird's-eye view of the outstanding events in tropical medicine in the latter half of the nineteenth century. It is well to remember that most tropical diseases were once almost as common in the cold as in the warm countries. Let me give a few examples. During the last century there had been at least five epidemics of cholera in Europe, causing millions of deaths. Plague flourished for centuries; the great pandemic that occurred in the fourteenth century was known as the Black Death on account of the terrible toll it took of human lives. Malaria was endemic in England even in the nineteenth century, and severe epidemics have been recorded in Denmark, Holland, and North Germany. Leprosy was for long widespread in Europe, where it still lingers in some places. Yellow-fever epidemics were reported from the eastern states of the U.S.A., but have been practically banished in the last 50 years. Even as late as 1933 there was an outbreak of amoebic dysentery in Chicago with 1,400 cases and over 40 deaths.

As a result of these pestilences and other common diseases there was what we may call sanitary awakening, and people began to associate disease with filth and demanded that something be done to counteract it. In England the Public Health Act, 1848, led to the purification of water supplies and improvement of sewerage, and this was followed by a rapid decline in the two main intestinal infections, typhoid and cholera. This campaign against environmental filth was based on the conception of atmospheric impurities emanating from insanitary privies, etc., and preceded any knowledge of disease germs as causative factors. Another stimulus to the study of tropical diseases came from an entirely different direction—the Europeans' interest in their overseas colonies, where they suffered from these diseases as much as or perhaps more than the indigenous population.

Microbes, Vectors, and Immunity

It was during the last three decades of the nineteenth century that the development of bacteriological techniques and their application led to the unravelling of the aetiology of many infectious diseases. In 1871 the anthrax bacillus was thoroughly studied and proved to bear a causative relation to this disease. Then the investigators turned successfully to other diseases. This was the era of Pasteur and Koch, associated with great activities in the bacteriological field in which many causative agents were recognized and

described, including those of leprosy, amoebic and bacillary dysentery, cholera, enteric fever, malaria, undulant fever, and plague. By 1900 the aetiology of most major tropical diseases was known. The discovery of rickettsias and viruses belongs to the twentieth century.

The study of parasitic worms had been initiated by naturalists. One of the parasites, hookworm, is a source of considerable ill-health in the Tropics. Its pathogenicity had been known since 1854. Lööse in 1897, in Egypt, accidentally discovered its mode of entry into the human body. The interest aroused by this discovery led to the investigation of numerous worms parasitic in animal and man. Many have been shown to have extremely complex life histories.

No less important was the discovery of vectors and their role in spreading disease from man to man, knowledge of which has made possible the adoption of radical preventive measures. Manson in 1878 made the important observation that *Filaria bancrofti*, which had been known to live in the blood of man, went through part of its development in the mosquito, which served as intermediate host. This was the first time that an insect was shown to be a disease carrier. Manson also formulated the mosquito-malaria hypothesis, and in 1897 Ross, while working in Secunderabad, discovered malaria oocysts in the stomach wall of the anopheles mosquito. The following year, while working in Calcutta, he demonstrated the life-cycle of the allied parasite of birds, the infection being conveyed from one bird to another by the mosquito in the act of biting. Subsequently Grassi, in Rome, demonstrated a similar cycle of development of human malaria parasites in the *Anopheles maculipennis*. Flies, lice, ticks, mites, and fleas have also been traced as vectors of certain diseases.

One important observation made by Koch (after his discovery of *V. cholerae* in Egypt and India) while studying cholera, which is of great epidemiological importance, was that convalescent cases or contacts with minor symptoms were excreting the vibrios. It was thought that these apparently healthy persons might be responsible for outbreaks or spread of the infection when no other obvious cause could be found, and this was soon proved to be the case with other infections. The occurrence of the chronic carrier is now well established in diseases like diphtheria, dysentery, typhoid fever, etc., in which these symptomless carriers form an important reservoir of infection.

Bacteriological researches towards the end of last century led to many results in the laboratory which

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have been widely applied. Notably there arose the study of immunity and the development of immunotherapy.

No less important than the triumphs of active immunization was the discovery of bacterial agglutination in 1896 and its application to the diagnosis of typhoid and later of brucellosis and other infections.

Chemotherapy

Up to the first decade of the present century tropical medicine had hardly any specific drugs except quinine for malaria and ipecacuanha for amoebic dysentery. But even towards the end of last century Paul Ehrlich was planning to find synthetic remedies, his aim being that these remedies would be toxic to the parasites but harmless to the patients. His first objective was preparation of an antimalarial drug which would be more potent than quinine, and his choice fell on methylene blue because he had observed that it stained the malaria parasite and that it was harmless to the body. Though its effect was inferior to that of quinine, modern chemotherapy may be said to have been born with this experiment. Later, his effort with a benzidine dye, trypan red, against trypanosomiasis was equally unsuccessful, but it led to a series of researches which culminated, after his death, in the discovery of a complex substance named suramin ("germanin"), still a potent drug for the early stage of this disease. After the failure of trypan red Ehrlich had turned his attention to an organic arsenical, atoxyl, and in 1909 discovered salvarsan, a drug with outstanding activity against spirochaetal infections.

The advances in therapeutics that followed during the next twenty years were many, and mainly benefited tropical medicine. These were saline treatment of cholera, emetine and a number of arsenical and iodine compounds for amoebic dysentery, antimony for kala-azar and schistosomiasis, tryparsamide for trypanosomiasis, and later "plasmoquine" (pamaquin) and "atebrin" (mepacrine) for malaria. But the story does not end here, for now followed an epoch-making period which has benefited all branches of medicine and revolutionized the treatment of most infectious diseases. It began with sulphonamides, and for the first time we had a drug for bacillary dysentery. But the greatest advances were made under the stimulus of war with chemotherapeutic substances quite different from the type envisaged by Ehrlich—namely, antibiotics. The first of these was penicillin, and this was followed by streptomycin, "chloromycetin" (chloramphenicol), aureomycin, "terramycin" (oxytetracycline), and others. We have also got new antimalarial drugs, more powerful than any previously used. Armed with these, we can to-day tackle most infections, including those caused by rickettsiae and some of the viruses. Last, but not the least, is the discovery of insecticides—namely, D.D.T. and B.H.C. (dicophane and benzene hexachloride)—which have rendered the control of malaria and typhus over large areas a matter of simple and inexpensive organization.

I shall now proceed to give a brief outline of the outstanding developments, but as the subject is vast I shall limit myself mostly to the important diseases that prevail in India.

Malaria

Tissue Phase of Parasite

There have been many developments in our knowledge of malaria, which is the most important disease in tropical climates. An outstanding event was the discovery of the tissue phase of the malaria parasite. After Laveran's discovery of the parasite and Ross's description of its passage through mosquitoes, Schaudinn in 1903 reported that he had observed sporozoites of *P. vivax* actively penetrating red blood cells, in which they then developed into the ring form of trophozoites. His account was accepted universally until towards 1930, when doubts began to arise, as some of the observed facts could not be explained in this way.

James¹ in 1931 postulated that sporozoites on their entry into the human body passed into the tissues, where they underwent further development before reaching the blood stream. This hypothesis received support when, a few years later, tissue-invading forms of malaria parasite were demonstrated in birds in which the complete cycle was worked out.²⁻⁴ A tissue phase of development in the liver was also demonstrated for the malaria parasite of squirrels.^{5, 6} It was expected that the malaria parasite of man and monkey would develop along similar lines, but in spite of intensive research in India, Britain, and America no success was obtained until Shortt and his associates,^{7, 8} in 1948, announced the finding of tissue forms of *P. cynomolgi* in the liver of monkeys; soon after they^{9, 10} succeeded in demonstrating the tissue stages of *P. vivax* and *P. falciparum* in liver biopsy specimens from volunteers who had previously been subjected to heavy sporozoite infection.

This discovery fills an important gap in our knowledge of the human cycle of the malaria parasite, and it is now evident that parasites pass through a pre-erythrocytic stage of development in liver cells before infecting the red cells and producing clinical symptoms. In the case of *P. falciparum* the initial tissue phase probably dies out soon after the infection has developed in the blood corpuscles, but in *P. vivax* some of the merozoites enter fresh liver cells (e.e. phase) and subsequently produce a second generation of merozoites; this may repeat itself indefinitely and infect red cells at any time, thus giving rise to the relapses of vivax malaria.

Metabolism of Malaria Parasites

More interest is now being taken in the study of metabolism and nutritional requirements of malaria parasites, as this may open up a new approach to successful treatment. But the subject is not so easy, since to gain knowledge of the physiological behaviour of the parasites it is necessary to grow them *in vitro*. After the introduction of newer methods for the successful growth of *P. knowlesi* we recently attempted to cultivate the human malaria parasites, but with little success. Some workers are trying to find out if there is any correlation between the chemical constitution and activity of antimalarial compounds on the enzyme system of parasites. Meanwhile, two interesting observations have been made.

First, the effect of starvation on *P. berghei* in albino rats and mice.^{11, 12} When the animals were kept fasting only a few parasites appeared in their blood, but when they were fed again the parasites grew normally. Our results were similar to those of Geiman and McKee¹³ in monkeys infected with *P. knowlesi*. It is of interest to recall that a similar adverse effect of starvation was observed on the growth of human malaria parasites during the Bengal famine in 1943.¹⁴⁻¹⁶ It was found among sick destitutes that so long as their condition was low they were often afebrile, with a few or no parasites in the blood, but the fever and parasitaemia became manifest in many as soon as their general condition improved with nourishing diet in the hospital.

Secondly, Maegraith *et al.*¹⁷ and Bray and Garnham¹⁸ have observed the suppressive activity of milk on *P. berghei* in rats and *P. cynomolgi* in monkeys. Hawking¹⁹ attributes it to the lack of *p*-aminobenzoic acid (P.A.B.A.) in milk. Variable suppressive results were obtained in our animal and human experiments with milk, but failures were also noted.^{20, 21} Addition of P.A.B.A. or certain other growth factors did not seem to increase the intensity of the infection. These investigations are still in the preliminary stage, but they may reveal some weak points in the parasites where attacks may be successfully delivered.

Mosquito Eradication

In the past attempts were made to eradicate malaria by destruction of larvae by methods such as canalization of streams, oiling, and application of Paris green. These were relatively inefficient and costly. At a later date came "species control" by which selective measures were taken

to prevent the breeding of only the dangerous species of mosquitoes, being based on an intimate study of the habits of the carrier species. This method has been successfully employed in several places. A biological method is the use of certain kinds of fish—for example, *Gambusia affinis*—which devour mosquito larvae voraciously. Pyrethrum spray to kill mosquitoes was a further improvement. D.D.T. or B.H.C. is now being employed for this purpose, and these substances have the advantage of being non-volatile, so that when sprayed on the walls and ceilings of dwellings they persist as a fine crystalline deposit for a few months and poison mosquitoes that come in contact with them. But the basis of all control is a knowledge of the behaviour of the mosquito. Thus, while D.D.T. kills mosquitoes which alight inside the hut, it is quite harmless to other species which habitually fly in and out without settling except when biting. In some cases B.H.C. has given better results than D.D.T. D.D.T. dissolved in oil can also be used as a larvicide. At present D.D.T. is generally employed in destroying adult mosquitoes, occasionally combined with the other methods mentioned above.²²⁻²⁴

Treatment of Malaria

For three centuries quinine and other cinchona alkaloids were the only drugs available against malaria, and they held their place even up to the first quarter of this century. Since then various synthetic drugs have appeared, including pamaquin, mepacrine, chloroquine, amodiaquine ("camoquin"), proguanil ("paludrine"), and pyrimethamine ("daraprim").

The appearance of a number of antimalarial drugs raised the question of their choice in treatment, as the initial claims based on animal experiments and preliminary clinical trials have not always stood the test of time. The ideal drug acting on the different stages of the malaria parasites has yet to be found, but, even as it is, the action of some drugs varies with different species and strains of parasites, and the appearance of drug-resistant variants is another difficulty. It was therefore necessary to assess the therapeutic and prophylactic value of the drugs under Indian conditions, and this work was taken up by us on patients admitted to hospital and in some hyperendemic malarious villages near Calcutta.²⁵⁻²⁸ In spite of the development of the newer drugs the efficacy of quinine cannot be questioned, and parenteral quinine still remains the drug of choice in pernicious malaria.

Mepacrine is as effective as quinine, but occasionally causes unpleasant symptoms if given in large doses and for prolonged periods. High hopes were at first raised about proguanil, and it was reported to have an action on the pre-erythrocytic phase of parasites, thus acting as a causal prophylactic.²⁹ Later experience,^{25,30,31} however, showed that it has disadvantages, the chief being that it is slow in action and some strains of parasites are resistant to it.³²⁻³⁴ We have also demonstrated this by passing the parasites from one volunteer to another and administering proguanil to each. In view of this, it will be extremely unwise to rely on proguanil alone for the treatment of severe falciparum infection.^{37,38} It was also claimed that proguanil prevents the development of sporozoites in the mosquito, but recently we have been able to produce infective mosquitoes after feeding them on patients on proguanil treatment, and to transmit the disease.³⁹ Chloroquine⁴⁰ and amodiaquine^{41,42} have been found to be very potent drugs which promptly terminate a clinical attack and are effective even in single doses.⁴³ With these two drugs it may be possible to introduce a one-dose regimen of treatment among semi-immune people. However, this may not be enough for severe cases and for radical cure. The action of the new drug pyrimethamine^{44,45} is uncertain in falciparum infection, and therefore cannot be relied upon for the routine treatment of malaria. It has been suggested that cross resistance between proguanil and pyrimethamine⁴⁶ may explain the failure in some cases, though all are not agreed on this point.⁴⁷

Vivax relapses are still a problem, but it is difficult to assess the relapse rate after treatment with a drug unless the trials can be undertaken in suitable non-endemic sites and followed up properly. None of the above drugs, even the most potent of them, when used alone, would radically cure relapsing vivax malaria. But better results are obtained by combining a schizonticidal drug, like quinine or chloroquine, with pamaquin or primaquine, which in itself is a poor schizonticide but active against tissue forms of *P. vivax* that harbour infection between relapses. Its efficacy was amply proved in the Korean war, and we found a very significant reduction of vivax relapses with Indian strains of parasites.⁴⁸

Drug Prophylaxis of Malaria

No drug is yet available which will prevent infection taking place when a susceptible person is bitten by a mosquito, but the existing drugs can prevent the infection from developing into the clinically recognizable disease. Great credit is due to Fairley and his colleagues for their researches during the war, which showed that with small daily doses of mepacrine it was possible to live in a hyperendemic area without getting overt attacks of malaria. Since then drug prophylaxis has been given trials in civilian practice with excellent results. We have carried out mass prophylaxis in malarious villages for five consecutive years during the transmission season without any anti-mosquito measures, with weekly dose of proguanil, chloroquine, amodiaquine, and pyrimethamine, and compared the results with similar groups receiving no treatment at all or at best occasional doses of quinine.^{25,49,50} All the four drugs decidedly reduced the incidence of malaria and improved the health of the people, proving unquestionably effective as suppressive drugs. Proguanil is cheap and useful provided drug-resistant variants do not emerge, but the most potent suppressive drugs were found to be chloroquine and amodiaquine. The latter was as effective when administered at fortnightly intervals.⁵¹ A village farm-worker taking it regularly every fortnight during the malaria transmission period may pursue his work without being laid down with malarial attacks during the period.

With the development of primaquine for the ultimate eradication of established vivax infections, mechanisms are at hand for simple and essentially complete chemotherapeutic control of malaria, which should go far towards minimizing its ravages until such time as insect vector eradication becomes a reality on a wide scale.

Kala-azar

Since the eighteen-sixties kala-azar has been known as a very deadly disease, endemic in Bengal and Assam and assuming periodical epidemic proportions. The actual cause of the disease was unknown till the beginning of this century, when in 1903 its mystery was unravelled by the discovery of the causative organism independently by Leishman and Donovan. In 1904 Rogers cultivated the parasites and described the flagellate form. But the transmission of kala-azar remained an unsolved problem for a long time. Knowles *et al.*⁵² first brought forward evidence to incriminate the sandfly as the probable vector, but it took 25 years of research to establish that the sandfly could transmit visceral leishmaniasis to susceptible animals and to human beings.⁵³⁻⁵⁵

But long before this the remedy had been found in a salt of antimony. In 1913 Vianna had tried intravenous injections of tartar emetic and successfully treated South American muco-cutaneous leishmaniasis. In 1915 Rogers obtained very encouraging results in Indian kala-azar. The most important advance was the introduction of pentavalent aromatic antimony compounds, in the development of which the contribution of Brahmachari⁵⁶ is so well known. It raised the cure rate to 95% in Indian kala-azar, which had a mortality as high as 90%. This is a truly remarkable achievement. A number of these compounds are available

for intravenous and intramuscular injections.⁸⁷⁻⁹² The next advance came in the form of aromatic diamidines,⁶³⁻⁶⁷ which gave very good results, but which owing to some unpleasant sequelae, especially with stilbamidine,⁶⁸ are used for antimony-resistant cases and those complicated with pulmonary tuberculosis.⁶⁹ The treatment of cancrum oris, the most deadly complication, has been found to be satisfactory with penicillin plus specific treatment.⁷⁰

In the diagnosis of kala-azar, besides demonstration of parasites, the aldehyde test and Chopra's antimony test are well known, but for early diagnosis the complement-fixation test, using an antigen prepared from certain acid-fast bacilli,⁷¹ has proved to be of great value, although positive reaction may occasionally be obtained in tuberculosis and leprosy.

Kala-azar, which in the early 'eighties was depopulating Assam, can now be easily diagnosed and cured in the vast majority of cases. But a proportion of cases prove resistant to treatment, and these and the dermal cases serve as a reservoir of infection to the community. In spite of mass treatment campaigns for over 30 years in Assam, the disease still persists.⁷² It is, however, probable that if anti-sandfly measures are adopted simultaneously better control may result.

Dysenteries

Bacillary dysentery can now be promptly cured by sulphonamides, and the use of antiserum has been abandoned except perhaps in some severe shiga infections. Streptomycin and the newer broad-spectrum antibiotics offer no advantage over sulphonamides but may be needed occasionally, as in a case of post-dysenteric arthritis, in which we gave streptomycin with excellent results after sulphadiazine had failed.⁷³

Amoebic dysentery, acute or chronic, is probably the commonest intestinal disorder of the Tropics. From an analysis of 9,015 unselected cases admitted during ten years to the hospital of the Calcutta School of Tropical Medicine⁷⁴ we found that 26.2% were harbouring some protozoa in the intestine, and 8.8% had *E. histolytica* infection. Of the patients who harboured amoebae, 51% came with abdominal symptoms—some typical, some quite vague; while the other 49% were admitted for various other diseases. The latter were apparently carriers of infection or in a quiescent phase. Symptomless cyst-passers are quite common and B. M. Das Gupta⁷⁵ found *E. histolytica* in 10.87% of an unselected population in Calcutta. The pulmonary form of amoebiasis,⁷⁶⁻⁷⁸ either primary or secondary to liver abscess, is apt to be mistaken for tuberculosis but clears up with emetine injections. Similarly, amoebic granuloma or amoeboma^{79,80} is apt to be mistaken for carcinoma, and in one of our cases the two were actually associated.⁸¹

Since the introduction of emetine, acute amoebic dysentery has been readily amenable to treatment, but results in chronic cases are often poor. This difficulty has been at least partially overcome by the introduction of compounds of emetine, arsenic, and iodine. The number of amoebicidal drugs is increasing every day, and we have now aureomycin, oxytetracycline (terramycin), and a few others added to the list. The importance of eradicating secondary infection in chronic amoebiasis was recognized at the Calcutta School of Tropical Medicine many years ago, and bacterial vaccines were advocated.⁸² The concept was revived by Hargreaves,⁸³ who advocated penicillin and sulphonamide for the purpose, but now an initial course of aureomycin or oxytetracycline would serve the purpose. We have tried all these remedies,^{74,84-88} and it may be pointed out that the existence of so many drugs for a single disease suggests that the ideal amoebicide is yet to be found. At present there is a good deal of enthusiasm over the newer antibiotics, but they suffer from the same defects as the older drugs—namely, the initial results are good, but the relapse rate is high. In fact, none of these drugs, given singly, prevents a relapse. For some time past it has be-

come customary to use a combination of drugs, which is often more effective than any one alone.

One of the notable advances at the present time is the very successful use of emetine and chloroquine in amoebic hepatitis and liver abscess.⁸⁷⁻⁹¹ Operation is now seldom required except in advanced cases, when aspiration repeated as necessary is usually sufficient, antibiotics being also used to combat secondary bacterial infection. Formerly these patients, with open drainage tubes and slowly dying of secondary sepsis, were familiar but depressing sights in our surgical wards.

Cholera

Since the discovery of *Vibrio cholerae*, its aetiological role has been established. But for the production of the disease other factors, such as gastric secretion and personal susceptibility, as well as the property of the vibrio, are also important. Undiluted gastric juice of normal acidity has been found to kill the vibrios immediately.⁹²

Much study has been made concerning the epidemiology and spread of cholera,^{93,94} but it is still uncertain how the cholera vibrios persist in the interepidemic period. Some observers believe that the carrier state does not persist and that in the absence of animal reservoir the infection can survive only by case-to-case transference throughout the year. But this is not often apparent, and it has recently been suggested that there is a possible link between the spread of cholera and some aquatic fauna.⁹⁵

The cholera vibrios were the subject of much investigation, and Gardner and Venkatraman⁹⁶ made the important observation that the O antigens are the specific ones, and gave a systematic classification of the vibrios. The most important advance was the introduction of hypertonic saline and alkali treatment by Rogers.⁹⁷ The efficacy of this treatment cannot be questioned, and is testified by its universal adoption. But with the growth of biochemistry the question of the ideal transfusion fluid for physiological replacement cropped up and it was in an attempt to tackle this problem that we undertook an investigation into the fluid and electrolyte changes in cholera.⁹⁸ Plasma volume per kilogram of body weight was found to be below the line of normal regression in all the cases, showing a reduction of 32% of the mean value in the fatal group, in contrast to 20.6% in the survival group. Change in the interstitial fluid in the survival group was less marked, but in the fatal group the mean value was reduced by as much as 39%. With recovery all the body-fluid changes were corrected, and it seems in some cases they were overcorrected owing to excessive saline infusion.

More recently it has been possible to follow accurately the changes in sodium and potassium concentration with the help of a flame-photometer. We found very little change in the plasma sodium and chloride level, suggesting that the loss of fluid in cholera is probably isotonic in nature. But there is usually an initial high level of plasma potassium,⁹⁹ which may come down even to subnormal level with treatment, and this may cause prolongation of convalescence. In such cases, if there is free flow of urine, judicious use of potassium salt may be helpful. In uraemic cases there is invariably a very high rise of plasma potassium along with nitrogenous retention, which requires careful handling as it is probably an important contributory factor to their fatal termination. Treatment on the lines suggested by Bull¹⁰⁰ for anuria to maintain fluid and ionic balance may be helpful. In cases in which uraemia terminated favourably the plasma potassium declined rapidly along with the urea concentration in the blood.

No specific chemotherapeutic drug has yet been found effective for cholera. The improvements claimed with sulphonamides could not be confirmed.¹⁰¹ More recently we have used chloramphenicol^{102,103} and oxytetracycline¹⁰⁴ with rapid clearance of vibrios from the stools, but with no effect on the clinical course and mortality. Aureomycin¹⁰⁵ also did not improve the results. So correction of fluid and electrolyte balance still remains the mainstay in treatment.

Typhus Fever

This is a very old disease, but only during this century has it been shown to be caused by rickettsial organisms. Apart from the classical epidemic typhus, other infections occurring in various parts of the world have now been recognized as rickettsial infections. Megaw¹⁰⁰ described in 1917 the first case of tick typhus in India; he himself had been the victim. Scrub typhus is fairly common, but the diagnosis is often missed, being mistaken for "enteric" or other fevers. In Calcutta we have encountered mostly scrub typhus and only a few cases of murine or flea-borne typhus.^{107-110 118} Different types of typhus fever have also been described from other parts of India.¹¹¹⁻¹²⁰ A few cases of Q fever have also been recently reported. Scrub typhus, the most important form of tropical typhus, is caused by the bite of the larvae of mites, the reservoir of infection being mite and certain rodents. During the second world war, when scrub typhus became a serious problem, many unsuccessful attempts were made to incriminate the mite species responsible for causation of the disease in South-east Asian countries. In 1949, Krishnan *et al.*¹¹⁰ not only successfully developed a technique for breeding large numbers of all mites prevalent in an infected area in the laboratory, but also used them in transmission experiments. They were also able to show experimentally that *Trombicula deliensis* was responsible for the transmission of the disease in Bengal, and that congenital transmission from infected mites to their progeny occurred at least for four generations.

In the matter of diagnosis the Weil-Felix reaction may be equivocal or negative in a certain percentage of cases, when animal inoculation is helpful. Cox's discovery¹²¹ that rickettsiae could be grown in the yolk-sac of fertile hen's egg led to the preparation of antigen for complement fixation and rickettsial agglutination for some types of typhus fever.

In treatment chloramphenicol and aureomycin have given excellent results.¹²² In prophylaxis the efficacy of D.D.T. and other insecticides and of mite repellents such as dimethylphthalate was abundantly proved in the war. Vaccine is useful in some types of the infection. Conquest of this once world-wide disease is one of the most gratifying results of modern research work.

Typhoid Fever

Chloramphenicol may now be regarded as a specific form of therapy in typhoid fever,¹²³ but a loading dose as originally advised is not necessary and may even be harmful.¹²⁴ Its indiscriminate use should be discouraged, as it may cause, though rarely, aplastic anaemia, and treatment should usually be started after a definite diagnosis has been made, preferably after the first week, when immune reactions begin. Chloramphenicol does not lessen the need for bed rest and dietetic regime until healing of bowel ulceration has occurred. Typhoid patients are no longer put on semi-starvation diet. In our hospital practice we aim at giving at least 2,000 calories and 1 g. protein per kg. body weight with individual variations.^{125 126} Prophylactic inoculation with T.A.B. vaccine is now an established practice. This does not provide absolute immunity, but inoculated persons who acquire the disease suffer rather less severely than the uninoculated.

Leprosy

While leprosy has practically disappeared from the temperate countries where it was once common, it has remained persistently endemic in the Tropics and sub-tropics with varying incidence and severity.

Khanolkar¹²⁷ has made an interesting contribution to our knowledge of the early phase of leprosy. He sets out the evidence showing that the leprosy bacillus enters the body through the skin and has a predilection for subcutaneous nerve tissues, particularly early in life. Leprosy is neural in

its inception, and *Mycobacterium leprae* first appears in clinical lesions in the small nerve plexuses in the skin, travelling up the finest nerve twigs in an ascending infection. He shows that the development of leprosy depends on the bacilli being able to burst out from the subcutaneous nerve and nerve plexuses of the skin into the dermis. The subsequent extension of the disease is determined by the response of the tissue to its mycobacterial invader. If the tissue response is weak, lepromatous leprosy ensues; if it is vigorous the tuberculoid type is likely to develop.

It has now been clearly shown that all cases of leprosy are not infectious; only those patients in whom bacilli can be demonstrated in the skin and nose by routine methods are regarded as infectious cases. Since the disease is transmitted by prolonged and intimate contact of open cases, control measures must aim not only at treatment of the patients but at adequate segregation of the infective cases. The importance of isolation will be evident from an observation in Bombay that more than one-half of a group of contacts showed clinical suspicion of disease and more than a quarter were bacteriologically positive.¹²⁸

Fifty years ago leprosy was regarded as incurable. The first drug used was chaulmoogra or hydnocarpus oil, an ancient Indian remedy that is still in use with some modifications. The sulphone drugs,^{129 130} introduced in 1943, have brought in a new era in the treatment of leprosy, and thiosemicarbazones are of great value.

Plague

In the past a number of epidemics and pandemics of plague have taken a heavy toll of life, but in recent years there has been marked progress in its prevention and treatment. Previously, anti-plague serum was the only therapeutic weapon available, but now even septicaemic and pneumonic cases can be saved with streptomycin and sulphadiazine.¹³¹⁻¹³⁴ For prevention, besides improvement in general housing conditions, the use of insecticides and rodenticides and inoculation is effective.¹³⁷

Helminthic Diseases

An important recent discovery in filariasis is the synthetic piperazine compound diethylcarbamazine acid citrate ("hetrazan"),¹³⁸ which causes rapid disappearance of microfilariae, though its effect on the adult worm is still inconclusive. But one great advantage is that it can render human carriers free from microfilariae and therefore non-infective to mosquitoes for a long period following a course of treatment which lasts about three weeks. Based on these observations, mass treatment is now being instituted in some countries to render mosquito transmission impossible. This, like the drug prophylaxis of malaria, is possibly an interim measure till extensive insecticide spray can be undertaken. In India, active measures are being taken in Orissa to combat filariasis by spraying with D.D.T. to kill the mosquitoes, by bush clearing, and by prophylactic administration of hetrazan.

The frequency of ankylostomiasis, ascariasis, and other helminthic diseases in the Indian villages calls our attention to the lack of sanitation and hygiene in these areas, and it is only by improving these conditions that we may hope to eradicate these infections completely. Potent drugs now available for their treatment include some indigenous preparations like *Butea frondosa*, *Embelia ribes*, kamala,^{139 140} and cashew-nut-shell oil¹⁴¹ (discovered recently), but there can be no lasting benefit to the community unless adequate preventive measures are taken simultaneously with the mass treatment of the victims.

Undernutrition

I think I have said enough to give a picture of tropical medicine taking shape with the birth of bacteriology and having a robust growth with the discovery of modes of transmission, reservoirs of infection, and means of eradica-

tion. But in the Tropics there are many other diseases besides those caused by infection, and of these the disorders caused by lack of nutrition rank high.

Experience shows that when the daily calorie intake by adults falls below 2,000 a good deal of weight is lost, mostly in the early stages, but later the body adjusts itself to the changed conditions and there is no longer any loss of weight. Health is not impaired, but there is difficulty at sustained effort. At an intake of 1,500 calories psychological changes manifest themselves in the form of irritability, apathy, and impaired mental concentration. With further reduction in calories a protein-deficiency anaemia appears; later comes nutritional oedema, the onset of which is accelerated by physical exercise. As the shortage continues, nutritional diarrhoea (para-sprue) occurs owing to impaired absorptive power of the intestine, and signs of vitamin deficiency commonly appear. In the absence of such conditioning factor there may be no obvious sign of vitamin deficiency.

In the treatment of starvation great success has attended feeding with skimmed milk and glucose with vitamins. For advanced cases Krishnan *et al.*¹⁴² successfully used protein hydrolysate, made from papain digest of meat during the Bengal famine. A sudden increase of carbohydrate intake, especially of polished rice, may precipitate an acute state of vitamin depletion. During convalescence patients recover best on a mixed diet of high calorie value with light exercise. Supplementary vitamins and proteins have no apparent effect on the pace of recovery.

Vitamin Deficiencies

The main causes of many of these diseases are now known, but it appears that the deficiencies are often multiple, especially where vitamin-B complex is concerned. During the war, in the Far East, where polished rice was issued to prisoners and the diet was generally very poor, there was widespread evidence of vitamin-B-complex deficiency.¹⁴³ The onset was often precipitated by diarrhoea and dysentery, and by hard manual work. Apart from polished rice, faulty cooking and dietary habits among rice-eating people may bring about attacks of beriberi, and according to Mahadevan and Raman¹⁴⁴ millet-eating people are not exempt from the disease.

Pellagra has been reported from many places. The reason for its prevalence in maize-eating people is that maize is deficient in nicotinic acid. There are strong reasons for believing that maize contains an anti-vitamin antagonistic to nicotinic acid. Rice can be equally poor in this vitamin, as in the case of milled rice, but the tryptophan it contains can be converted into nicotinic acid in the body. It is probable that in some circumstances this does not happen, thus accounting for occasional cases of pellagra among rice-eating people. We do not yet know why pellagra occurs suddenly in a group of people, disappears, and then recurs after a time.

Among prisoners of war in the Far East were seen many cases with grossly abnormal neurological signs such as retrobulbar neuritis, nerve deafness, spastic paraplegia, and rarely paralysis of vocal cords. As they occurred often in association with or after attacks of beriberi or pellagra they were thought to be of nutritional origin, but the results of treatment with good food and vitamins were disappointing. One very distressing condition was burning feet, which was worse at night, causing insomnia. It seems to be not uncommon in India, especially in the south.¹⁴⁵

It often happens that in the midst of multiple deficiencies the signs and symptoms due to one particular vitamin predominate. We do not know why. In fact, the more one studies these deficiency diseases the more one is convinced that a lack of vitamin, though of fundamental importance, is not the whole story, and that a variety of stresses and strains determine the body's requirements of these essentials. The same observation was made 200 years ago by James Lind, who first clearly proved that scurvy among ship's crews could be relieved by the juice of citrus fruits; he

emphasized that its aetiology was inseparably connected with the sailor's life at sea, including cold, damp, infection, and fatigue—factors now called "stress."

Protein Deficiencies

In the dietary treatment of many diseases emphasis is now put not only on calories but also on protein, because the latter is needed for repair. In addition, lack of protein in itself may bring about disease. In prolonged fevers it is essential to cover the protein losses with nutritious food so far as possible.

Kwashiorkor¹⁴⁶⁻¹⁴⁸ is a disease of young children among the very poor class of people who are on a high carbohydrate diet lacking in essential amino-acids. Its chief features are growth retardation, dyspigmentation of hair and skin, oedema, low serum albumin, negative nitrogen balance, and fatty infiltration of the liver. The general opinion is that it is mainly due to lack of protein, especially at the time of weaning. Proteins (particularly animal protein) are remarkably curative in the early stages.

Anaemia among the general population and in pregnant women remains an important problem in India. Addisonian pernicious anaemia is very rare there, but nutritional macrocytic anaemia simulating pernicious anaemia is, on the other hand, very common, and is often accompanied by megaloblastic bone marrow. It usually responds well to crude liver extract, folic acid, and vitamin B₁₂. Folic acid deficiency is apparently the main pathogenic factor, but deficiency of vitamin B₁₂ also seems to be present.¹⁴⁹ In addition it is frequently associated with iron deficiency, producing a picture known as dimorphic anaemia.

Nutritional deficiencies have recently attracted much attention as a possible cause of organic disease of the liver. In kwashiorkor, pellagra, chronic alcoholism, and many other conditions there is a slowly developing diffuse cirrhosis of the liver, preceded by fatty infiltration, which takes place in the absence of lipotropic substances such as choline and methionine. Until recently a diet chiefly carbohydrate in composition was recommended in hepatic disease, as throwing least strain on the damaged organ. Animal experiments tend to show that this view is probably wrong and that protein in liberal amount, especially as skimmed milk (a rich source of methionine), should be given along with carbohydrates.

Nutritional oedema has received much attention since the war. Our own observations¹⁵⁰ on nearly 100 cases during the last two years showed that these poor patients lived on a diet grossly inadequate, both in quality and in quantity, in calories and proteins. Previous gastro-intestinal disorder might be an important contributing factor. The severe cases had generalized oedema, low urinary output, steatorrhoea, anaemia, and appreciable diminution of plasma proteins and albumin fractions. In the course of the illness there seemed to be considerable disturbance in the body-fluid compartments,¹⁵¹ the plasma volume being reduced and the thiocyanate space much increased; the latter persisted for some time even after the disappearance of clinical oedema.

Diseases Caused by Food Adulteration

Argemone Oil Poisoning

Of the diseases caused by food-poisoning, epidemic dropsy stands foremost; it is caused by ingestion of edible oils which have been contaminated with argemone oil. The latter is a toxic agent derived from the seeds of *Argemone mexicana*, which grows as a weed. These seeds are very similar to the dark-coloured mustard seeds, and may be mixed up with the latter by design or accident in the manufacture of mustard oil. Contamination of sesame oil and groundnut oil has also been reported. The disease is encountered periodically in Bengal, but occurs also elsewhere in India. Recently there was an outbreak in Bombay (Nadiad district). It may be conveyed otherwise than through oil, as not long ago there was an outbreak in South Africa which was traced to wheat and argemone seeds getting mixed up by accident.

The toxic property of argemone oil was known as long ago as 1878, when accidental poisoning from the use of this oil in food was reported in a number of cases.¹⁵² In 1926 S. L. Sarkar¹⁵³ reported symptoms of epidemic dropsy, in some cases resulting from the use of mustard oil adulterated with *katakar* or argemone oil, and in 1937 Lal and Roy,¹⁵⁴ and later Chopra *et al.*¹⁵⁵ reproduced the early stages of the disease in some instances by feeding human volunteers with the toxic oil. Later, experimental studies on animals were started by us which led to some important observations. An epidemic dropsy-like condition with similar histological appearance and vascular pattern was produced in monkeys fed or injected with argemone oil,¹⁵⁶ and rice diet appeared to favour the accumulation of extracellular fluid.¹⁵⁷ The oil was found to be toxic even in very low concentrations, 1% or 0.5%, after prolonged ingestion.¹⁵⁸

Work has subsequently been started with argemone alkaloids, of which a much greater yield of the different fractions could be obtained by a newly developed method of direct extraction from the seeds than from the oil.¹⁵⁹ S. N. Sarkar¹⁶⁰ has isolated the alkaloids sanguinarine and dihydrosanguinarine. He regarded the former, constituting only 5% of the total alkaloids, as the toxic agent; dihydrosanguinarine, comprising 87%, appeared to be non-toxic, but was readily oxidizable *in vitro* to sanguinarine, and 8% of the alkaloids still remains unaccounted for. Our biochemical investigations in this condition showed increase of plasma chloride and blood pyruvic acid with a lowering of plasma albumin and absence of thiamine deficiency. The plasma volume and extracellular fluid volume were always increased and the total red blood cell mass was contracted.¹⁶¹ Based on these results, a high-protein/salt-poor diet with a moderate amount of fat and carbohydrate has been advocated.¹⁶²

A disease such as this which can cause high mortality, seriously affect the heart¹⁶³ and eyesight, and cause abortion of pregnant women, deserves serious notice, especially when its aetiology is known. Strong public-health measures should be taken to stop the contamination of the cooking oils by argemone oil. The heavy percentage of the latter in many samples of mustard oil points to deliberate contamination. A simple sensitive test has been devised by us to detect the adulteration.¹⁶⁵

Mineral-oil Poisoning

Mineral oil is another menace to public health. It is a petroleum product, easily available, cheap, colourless, tasteless, and almost odourless, and therefore is an attractive adulterant for edible oil. We therefore undertook an investigation of this oil and found it toxic and often lethal to the animals tested.¹⁶⁶ Histological studies of animals showed vascular changes of the same nature as in argemone poisoning.

In England and the U.S.A. during the late war, when fats were short, mineral oils were used in making cakes, in salad oil, and for cooking chipped potatoes, but the practice has since been prohibited. Several workers¹⁶⁷ have shown that continued ingestion of such oils interferes seriously with absorption of fat-soluble vitamins and of calcium and phosphorus. It has also been observed that some of the oil may on absorption be carried and deposited in distant organs such as lymph nodes and liver¹⁶⁸; the fate of such deposits is not known. The question of carcinogenesis has been raised but not settled.¹⁶⁹ But what we know already about mineral oil is enough to condemn it for regular human consumption.

Conclusion

I have attempted no more than a brief and fragmentary survey of the progress of tropical medicine. There has been, especially during the last half-century, brilliant and co-ordinated work by individuals and teams of workers directed to the investigation, prevention, and cure of disease. Too high praise cannot be given to the pioneers, who often worked in adverse circumstances, sometimes at

the expense of health and even life. But our problems are still many. As old problems are solved new ones arise. Viruses have assumed a great importance in recent years, and cancer is becoming increasingly prominent.

Before I end, however, I should like just to consider what the term "tropical disease" really means. There are not many diseases peculiar only to tropical climates, although admittedly conditions in the Tropics are more favourable to their growth and spread. Such devastating diseases as cholera, smallpox, plague, malaria, and leprosy that now prevail here were, as I have already pointed out, once very common in Western countries. If taken in the sense of latitudes, labels such as "tropical diseases" and "tropical medicine" are largely misnomers; what is worse, they perpetuate a false idea that tropical countries, try as they may, are doomed always to suffer from these diseases. "Tropical" diseases disappeared from the West mainly for three reasons: first, better and abundant food as a result of better cultivation at home and the importation of food from overseas; secondly, the removal of poverty as a result of the industrial revolution and the acquisition of colonies; and, thirdly, the institution of public-health measures, which led to better housing and hygiene, improved sewerage, and a safe water supply. If we consider "tropical disease" in this light much of it is reduced almost to "poverty disease." In short, many of our so-called tropical diseases are the symptoms of backward countries and not primarily of tropical climates. Remove food deficiencies in the tropical countries and introduce all the sanitary measures now enjoyed in the West and many of the tropical diseases will be banished. Our knowledge of these diseases, their prevention, and their cure has advanced to a remarkable degree; in fact, it has outstripped its practical application. With a parallel improvement in social and economic conditions, there is little doubt that our efforts to eradicate them will be crowned with success.

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APLASTIC ANAEMIA DUE TO TRINITROTOLUENE INTOXICATION

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Trinitrotoluene (T.N.T.) is the most generally used of all chemical war explosives. Used alone, or mixed with other compounds, it forms the bursting charge in shells, mines, and bombs. The filling of these weapons of war is still largely done by hand, with the use of tools made of wood or non-ferrous metal. A main pre-occupation of the medical officer in an explosives filling factory is the protection of the workers from absorption of T.N.T. Unfortunately, this material finds ready entrance to the body, whether in the form of fume or dust, mainly by inhalation, but also by ingestion and through the skin. When the dose is small and the body healthy, T.N.T. is rapidly detoxified in the liver, the metabolic products are excreted mainly by the kidneys, and no appreciable harm is done. When, however, the dose is larger, or for some reason the detoxifying mechanism in the body is unable to cope completely with the invasion, then T.N.T. or, more probably, the early and even more poisonous products of its metabolism (Channon *et al.*, 1944) accumulate and circulate in the blood stream, inflicting damage upon susceptible tissues.

The clinical manifestations of T.N.T. intoxication are six in number: cyanosis, dermatitis, anilism, toxic jaundice, toxic anaemia, and toxic purpura, roughly in this order of frequency. Each may appear separately from the rest, or in varying combination, simultaneously, or in processional order. The only exception is T.N.T. dermatitis, which rarely, if ever, is present in conjunction with the more serious developments. This paper puts on record all the cases of toxic anaemia and toxic purpura due to T.N.T. which occurred in the United Kingdom, and were noted, during the 1939-45 war.

Toxic anaemia was first made notifiable in January, 1942. Some 15 cases, all ending fatally, were recorded