well received as, in fact, were all the British observations on any subject under discussion.

The profession in Hungary has suffered from the lack of foreign influence during the war years but foreign journals are now being received again and the leeway should soon be made up. All these sessions were punctuated by heavy detonations outside the building where the Danube bridges, destroyed in the final siege, are in process of demolition and replacement, while indoors, a battery of flashlight photographers operated on the speaker from every angle.

The reception accorded to the British representative by all the nations taking part was very pleasing. The Director-General of the Hungarian Army Medical Service was a most courteous and friendly president and host. The President of the Hungarian republic himself expressed his wish to meet the British Army delegate and impressed on him that he would like confrères in England to know how great a believer he, the President, is, in congresses such as this, with all the nations gathered together in amicable discussion.

Budapest devastated in parts only, its famous bridges a tangled mass of wreckage, is rising from its ashes. Its former glories can be glimpsed, its restaurants can still give points to those of any European capital. The Tsigane fiddler supplies the mixture as before. The Corps Diplomatiques help to make a visit memorable, His Majesty’s Minister and Embassy Staff are the most delightful of hosts.

The Congress ended, the delegate leaves for Vienna in a train packed with Hungarian passengers. They accompany him as far as the frontier—but no farther.

PROGRESS IN THE TREATMENT OF SCRUB-TYPHUS

A Statement Prepared in June 1948 at the Institute for Medical Research, Kuala Lumpur

Last month a scientific paper entitled "Chloromycetin in the Treatment of Scrub-Typhus" was read before the Fourth International Congress of Malaria and Tropical Medicine at Washington, D.C.

It embodied the early results of six weeks’ concerted investigation by two groups of workers at the Institute for Medical Research, Kuala Lumpur, of the curative properties of a new drug, Chloromycetin, in the treatment of scrub-typhus. The authors were Dr. Joseph E. Smadel, Dr. Theodore E. Woodward, Lieut. Herbert L. Ley, Colonel Cornelius B. Philip, and Major Robert Traub, comprising a Research Unit of the U.S. Army, and Dr. R. Lewthwaite and Dr. S. R. Savoor of the staff of the Institute.

This event was of deep significance to layman and scientist alike. To the layman resident in the Far East, whether civilian or serving soldier, it indicated that a once grave and often mortal infectious fever had now, in the presence of the drug, become trivial. To the scientist it marked more than a notable advance in the curative field; for the drug, chloromycetin, which is an extract of a mould, appears to provide an excellent means for treating the rickettsial diseases, of which the typhus fevers are the most widely known examples.
A glimpse of this successful collaboration in medical research may be of interest to the general public; and is perhaps its due, since it sustains such investigations by contributions from the public purse.

**THE DISEASE**

Scrub-typhus, known also as Japanese River Fever and the Tsutsugamushi Disease, was first conclusively shown to exist in Malaya in 1924 by the late Dr. William Fletcher, then Director of the Institute for Medical Research. His colleagues at the Institute rapidly amplified his findings. Dutch workers in the N.E.I. added their contribution. The causal organism and the mite vector were identified; the rôle of the rat was elucidated; the disease was reproduced in laboratory animals; a second form of typhus, "shop-typhus," was clearly differentiated from it, and shown to be flea-borne. Its pathology in man was studied, and found to have much in common with typhus fevers the world over; strains of some of these, from America, Australia and Sumatra, were brought to the Institute and compared and contrasted with scrub-typhus.

From the knowledge thus gained it was possible to recommend to the planting community certain preventive measures, mainly concerned with the avoidance of mites and the reduction of rats. Attempts to develop an effective vaccine failed during the pre-war period.

**THE IMPACT OF WAR**

The impact of war, with its stake of national survival, provided the concentrated intensive international acceleration of effort that has led to impressive advances towards the curbing of this disease.

In pre-war days the menace of scrub-typhus was largely to the planting community, throughout which the disease was much dreaded. Though less common than malaria, tuberculosis and dysentery, its critical course in most victims, fifteen out of every hundred of whom died, and many of whom remained long incapacitated, caused it to be regarded as one of the major medical hazards of those whose occupations involved contact with the countryside, especially where rats and lalang abounded.

With the outbreak of the Japanese war, and the ebb and flow of jungle warfare that followed, the Armed Forces in their scores of thousands lived and fought in jungle areas, and thus of necessity became exposed to the bite of the larval mites. To a much greater degree than in peacetime, man supplanted the rodent as a temporary host of the mite; and the incidence of the disease correspondingly soared, to reach a total figure of some 25,000 cases amongst the Allied Forces.

From the Assam-Burma theatre of war an appeal for instant aid was made to London; from the South-West Pacific theatre a similar appeal was made to Washington. Research was intensified and followed two main trends: the development of a prophylactic vaccine and of a mite-poison. Success in the former proved elusive; trials of one of the most promising were cut short by the
Clinical and Other Notes

sudden cessation of hostilities. Success in the latter was notable. For an Australian team of entomologists, led by McCulloch, developed the most effective wartime weapon against scrub-typhus. They demonstrated that a chemical substance, di-butyl phthalate, when smeared on the clothes by an approved technique, poisoned mites; and survived considerable laundering. The use of this method in the field reduced the incidence of the disease by 75 per cent. It was later shown that another chemical, benzyl benzoate, was equally effective.

The present work with chloromycetin and scrub-typhus stems directly from the wartime efforts of British and American investigators on penicillin. The antibiotic penicillin, which has proved so important in the treatment of many bacterial infections, is a purified extract of a mould.

The Drug Chloromycetin

Medical research workers in Britain and the U.S.A., especially the research divisions of the large biological business houses, were not slow to explore further this new path of advance in curative medicine. Strains of moulds by their thousands were tested; from one of them came streptomycin. In 1947, Dr. Paul R. Burkholder of Yale University, U.S.A., experimented with a mould collected from soil in Venezuela; and from it isolated an extract that showed anti-bacterial properties. It was referred by him to the Research Laboratories of Parke, Davis & Co., Detroit, Michigan, where the extract was obtained in crystalline form, and named “Chloromycetin.” It was subjected to preliminary trials in test-tube and laboratory animal, its range of action was explored, and methods for its quantitative estimation in blood were devised. An early finding was the protection given by it to chick embryos infected with the causal rickettsial organisms of louse-borne typhus, i.e. the “classical” devastating form of typhus.

The drug was referred to Dr. Joseph E. Smadel, Head of the Department of Virus and Rickettsial Diseases, Army Medical School, Washington, D.C., and one of America’s leading virus experts, for extended laboratory trials, primarily against the viral and rickettsia agents. The investigations of the Army Medical School showed that the protective properties of the drug extended to most of the rickettsial agents including the cause of scrub-typhus and of certain virus infections; and (of prime importance) that its toxicity to animals, including man, was low.

A short visit to Mexico by Dr. Smadel and Lieut. Ley in January 1948 confirmed, in a small series, that the drug was effective in man against louse-borne typhus.

Scrub-typhus next claimed attention, since its importance had been enhanced in the post-war period by two new factors: first, the presence of Allied armies of occupation in the Far East; secondly, the spreading of the disease by the increase in numbers and dispersal of the rat population.

The U.S. Research Team in Malaya

Through official negotiations between the respective Governments, the United States Army Medical School, Washington, sought the views of the Institute for Medical Research as to the feasibility of collaboration between U.S.
and Malayan scientists in trials of chloromycetin in human scrub-typhus in Malaya.

With the challenge of scrub-typhus still not fully answered, and with the success of wartime Anglo-American collaboration still fresh in the memory, there could be in response but one attitude, viz. *carpe diem*; and the project was warmly welcomed.

In March 1948 Dr. Smadel and four colleagues arrived in Malaya by a special U.S. Army plane, complete with two tons of equipment, jeeps, and the world supply of chloromycetin, viz. one pound; a modern argosy that was to prove of profound import to Malaya and countries adjacent to it.

Within twenty-four hours of reaching Kuala Lumpur they had settled into the laboratories set aside for them at the Institute for Medical Research, and the treatment of three early cases of scrub-typhus had begun.

Two days later all three patients had normal temperatures, toxicity had vanished, and convalescence was well on the way. When contrasted with the known severity of the disease in untreated cases, viz. the fifteen days (or more) of fever, the severe toxicity, and the liability to grave complications affecting lung and nervous system, it was immediately evident thus early in the investigation that the success in the laboratory was being fully reproduced in man; that in chloromycetin the physician now had at his disposal a powerful curative agent against scrub-typhus.

Favoured by an explosive outbreak of the disease on an estate near Kuala Lumpur, some 40 proven cases have now been treated with the drug, without a failure, by the physician of the U.S. Unit, Dr. Theodore E. Woodward, Associate Professor of Medicine, University of Maryland, U.S.A. Since in untreated cases death may occur from the twelfth day of fever onwards, the importance of early diagnosis is clear. Yet some amongst the 40 were first treated as late as the eighth day, and one notable case on the ninth day.

The drug is given by mouth, in tablet form. In the first few patients treatment continued for several days, but it soon became clear that one day's administration sufficed in most cases.

Laboratory mice are an all-important adjunct to scrub-typhus research. The considerable stock prepared for this work was rapidly exhausted as the tempo increased. Cabled requests to the Director of the Commonwealth Serum Laboratories, Melbourne, to the Director of the Wellcome Research Laboratories, London, and to U.S. Army sources in Manila for 500 mice from each met with a ready response; 1,500 arrived by air transit.

Arising from the above success, as is invariably the case in medical research, new leads have appeared, and are being followed. Not only medical findings, but entomological findings of importance have emerged; for, *pari passu* with the clinical investigations, intensive field investigations of the natural transmission of the disease have been made by the entomologists of the U.S. Army research unit (Colonel C. B. Philip and Major R. Traub) and by the entomologists of the British Colonial Office research unit now at the Institute (Dr. J. R. Audy, Mr. J. L. Harrison and Mr. K. L. Cockings).
Correspondence

It was particularly gratifying to the investigators that Sir Howard Florey, who had shared with Sir Alexander Fleming and Dr. E. Chain the Nobel Prize for Medicine in 1945 for their discovery and development of penicillin, accepted an invitation to visit the Institute in order to observe and discuss this spectacular unfolding of research in the field of the antibiotic drugs in which he had pioneered. More recently, Dr. J. L. O'Connor, a research worker at the Commonwealth Serum Laboratories, Melbourne, was sent by his Government to observe the progress of the investigation.

The Supply Position

The drug hitherto available has been a pilot lot; large-scale production is not yet in being. In fact, the supply position of chloromycetin is similar to that of penicillin in 1941, i.e. a new drug, proven qualitatively, but scarce. A time-lag in production is inevitable, though fortunately the methods now in use for penicillin and streptomycin will in principle be applicable.

Needless to add, Malaya is already negotiating with Parke, Davis & Company in this matter.

This short review suffices to record a major medical event. It indicates that the visit of the British scientists with penicillin to the United States of America in 1941 has been repaid in full measure to Malaya by this mission of the U.S. Army research unit with chloromycetin. It exemplifies that Commonwealth of Medical Research which transcends frontiers, and in so doing hastens to fruition services to humanity that would otherwise languish through isolation.

Correspondence

Sir,

The writing of the official medical history of the 1939-45 war proceeds. The raw materials out of which it must be built are the reports and the like which Headquarters of formations and units were required to send back to the War Office during the war years. These proffer in great abundance factual information which must, of course, guide the historian’s pen. But these reports were addressed to the War Office and not to posterity; they tell of what was encountered and of what was done, but seldom do they reveal the reasons for action or disclose its results. They give no expression of the thoughts or feelings of those concerned.

This history, when written, must be more than a mere chronicle, it must distil wisdom out of the experience of a generation so that those who follow can, if they so wish, profit. Blood is well shed if it is to be used in such transfusion.

There must be many who served with the R.A.M.C. who can help very materially if they will but unlock the door of memory or hunt out the diaries of those days and tell of what they know. This is more particularly the case in those campaigns that ended in tactical defeat—France 1939/40, Norway, Greece and Crete—for there was much burning of papers, and all that remains