

The Malaria Treatment of General Paralysis.

By Prof. WARRINGTON YORKE, M.D.

UNTIL recently the outlook for patients suffering from the disease known as general paralysis of the insane was practically hopeless. For many years, however, it has been known that the symptoms sometimes exhibited remarkable remissions, the delusions and other mental disturbances subsided or even disappeared for a time, whilst the physical condition underwent a similar improvement. It had been further observed that these remissions were often associated with some intercurrent disease, and attempts were made to induce them artificially by such measures as the production of abscesses or injection of bacterial toxins. The improvement was, however, only transient; sooner or later the mental symptoms reappeared, the patients returned to the asylum, and the disease pursued its relentless course to a fatal termination. In 1919 Wagner v. Jauregg of Vienna, as the result of many years' observation of general paralysis, concluded that possibly it was the rise of temperature, which accompanied the intercurrent disease, abscess formation, or toxin inoculation, that was in some way responsible for the improvement produced in the nervous condition. With the view of testing this hypothesis, he cast round for an infection which could safely be administered to the patients and could, after it had run the necessary course, be readily controlled by the administration of drugs. Two diseases occurred to him, namely, malaria and relapsing fever; and after preliminary trials it was found that the former was the more satisfactory. Wagner v. Jauregg therefore proceeded to infect a long series of general paralytics with malaria, and during the years 1920-21 published results of a most promising nature.

It was the publication of these papers that induced Dr. Clark, the Medical Superintendent of the County Mental Hospital at Whittingham, to test the treatment at his institution; and in July 1922 a number of general paralytics were infected by inoculation of blood from patients who had contracted malaria in the tropics and had come to the hospital of the Liverpool School of Tropical Medicine for treatment. These general paralytics in due course developed typical malaria, and from them other paralytics were inoculated, and so on, the malaria strain being preserved by regular passage from one paralytic to another. Later, the work was commenced at the other mental hospitals in the neighbourhoods, namely, Rainhill, Winwick, Belfast, and Chester.

For various reasons it was decided in a number of instances to modify the mode of infecting the patient, and, instead of producing the disease by the inoculation of malaria blood, to do so by Nature's method; *i.e.* by the bite of infective mosquitoes. The mosquitoes used were two commonly found in Great Britain, namely, *Anopheles maculipennis* and *Anopheles bifurcatus*, and for a constant supply of the former we are greatly indebted to Mr. Rees Wright, of the Department of Zoology, University College, Bangor, who during the winter collected the hibernating females in farm buildings in Carnarvonshire.

Up to April 1924, at the various institutions mentioned and at the Royal Infirmary in Liverpool, 139

cases of general paralysis had been infected with malaria, 98 by the method of direct inoculation of infective blood withdrawn from malaria patients, and 41 by the bites of infective *Anopheles*. A sufficient time has now elapsed to enable a judgment to be formed regarding the effect of the malaria treatment in respect of 84 of these patients. Summarising the opinion of the medical experts at the mental hospitals, we find that of the 84 patients, fourteen (16.6 per cent.) have died, most of them immediately, or shortly after the completion of the course of malaria treatment; although all these cases had been treated with quinine before death, and parasites had disappeared from the blood, nevertheless it is impossible to affirm that in none of them was death accelerated by the malaria. No noticeable change in mental or physical condition has been observed in twenty (23.8 per cent.); with regard to these cases, however, it is to be borne in mind, as the mental hospital doctors have frequently pointed out, that in the ordinary course of events many of them would now be dead. In ten (11.9 per cent.) there is definite physical improvement but no change in the mental condition. In seventeen (20.2 per cent.) there is great physical and distinct mental improvement. Finally, in twenty-three (27.4 per cent.) the mental and physical improvement has been so great that the patients have been, or are about to be, discharged from the mental hospitals.

It is to be noted that in a number of the cases the improvement has been maintained for many months—in some for so long as a year—and that quite a number are back at their old occupations. As time goes on, it may be found possible to discharge still others of these 84 cases, for, as Wagner v. Jauregg writes: "The maximum of the improvement does not manifest itself at once at the end of the period of fever, but does later. On the contrary, the improvement continues often for a long period, so that in many cases the result seemed to be an incomplete one where later, however, a complete remission came to pass."

Whether the improvement is temporary or permanent, time alone can decide, but the results already achieved can only be regarded as remarkable, when it is realised that no patient suffering from general paralysis had previously been discharged from the mental hospitals in question.

A number of hypotheses have been advanced to explain the mechanism whereby the one disease produces a beneficial action on the other disease; but as none of these hypotheses are based on any substantial foundation, nothing is to be gained by discussing them here.

As might be expected, work of this nature has enabled us to observe malaria in exceptionally favourable circumstances, and as a consequence much has been learned regarding this disease, and many hitherto unsolved problems have been answered. From this point of view the natural infections, *i.e.* those produced by the bites of infective Anopheline mosquitoes, have been especially valuable. They have enabled us to prove beyond all doubt that the three common malaria parasites are all true species and not merely different

stages of the same parasite, as has been so long maintained by Laveran and numerous other observers of the French school. The incubation period of simple tertian malaria—that is, the period which elapses between the bite of an infective mosquito and the development of symptoms and the appearance of parasites in the peripheral blood—has been shown to vary between 9 and 22 days; and much has been learned regarding the clinical course of the disease.

In striking contrast to the cases of malaria which occurred in such enormous numbers during the War, and those with which one has to deal in the ordinary practice of tropical medicine, the general paralytics were readily cured of their induced malaria by a three-days course of quinine, and relapses were remarkably rare. Why this should be so is a question of no mere academic interest, but one of great practical importance and one to which my colleague, Dr. Scott Macfie, and I devoted much thought and work. As the result of a most careful analysis of all the facts available, the conclusion was reached that the remarkable susceptibility to treatment exhibited by the cases of induced malaria is bound up with the fact that in these cases one is concerned with the early treatment of the disease, or, in other words, with the treatment of primary infections.

In our opinion the train of events in the treatment of malaria is as follows: quinine given to a patient whose blood contains numerous malaria parasites invariably destroys—probably indirectly, *i.e.* after it has been changed in some manner by the human body—large numbers, but not all, of the parasites, and by this means sets free a considerable quantity of soluble antigen. The antigen provokes, by stimulation of the host's tissues, the formation of immune-body. The immune-body, if sufficient in amount, destroys the remaining parasites, thus resulting in sterilisation of the infection and in the cure of the patient. When, for any reason, the host is unable to produce immune-body in sufficient amount, the infection is not sterilised and a relapse occurs. We surmise that certain individuals are unable to produce a sufficiency of immune-body to sterilise the malaria infection, possibly

owing to inadequate treatment at the time of the first attack, possibly owing to ill-health at the time of infection and treatment, or possibly owing to a personal idiosyncrasy. Whatever be the cause, these are the patients who develop into chronic relapse cases of malaria; such patients can no longer be cured by quinine, not because the parasites they harbour are quinine resistant, but because, owing to a defective formation of immune-body at the time of the initial attack and treatment, the parasites have not been completely destroyed and have gradually acquired an immune-body resistance. If this view be correct, it indicates the paramount importance of adequate quinine treatment at the time of the initial attack of malaria; a course of treatment which suffices to sterilise the primary malaria infection fails to prevent the occurrence of relapses when administered to a case of some standing, and this explains the complete lack of success which followed the most drastic efforts to sterilise the infection in the patients invalided with malaria to Great Britain during the War.

Whether the daily taking of quinine will protect from malaria those living in the Tropics, and subject to the bites of infected mosquitoes, is naturally a question of the greatest importance. Notwithstanding the enormous literature bearing on the subject, no precise information has hitherto been obtained, mainly owing to the great practical difficulties which surround any attempt to make observations from which it would be possible to draw conclusions free from very obvious fallacies. The present investigation has, however, provided the answer to this important question. Our observations showed that the administration of quinine before a person is bitten by an infected mosquito is useless, and that the drug has little if any action on the sporozoites injected by the mosquito. In order to prevent the malaria from developing, the administration of the drug must be continued for at least ten days after the feed of the infective mosquitoes; the daily dose of quinine given has but little influence apart from the fact that, with very large doses (30 grains), the period for which the drug has to be given to prevent development of the infection is a little shortened.

Obituary.

DR. W. B. HEMSLEY, F.R.S.

WILLIAM BOTTING HEMSLEY, whose death, in his eighty-first year, took place at Broadstairs on October 7, was born at East Hoathly, Sussex, on December 29, 1843. A member of a family which had a long and honourable connexion with horticulture, Hemsley's knowledge of plants began with his knowledge of the alphabet. Being a somewhat delicate child he had to be educated privately, and before his education had been completed, in order to lead, so far as possible, an out-of-door life, he began his training as a gardener in his father's establishment. Already his taste for botanical pursuits was so marked that, as soon as his training had been completed, he entered Kew as a young gardener in 1860, when in his seventeenth year.

Before the period of two years to which the service of a young gardener at Kew is normally limited, Hemsley's remarkable botanical aptitude had so

impressed both the Curator and the Director that he was transferred from the garden to the herbarium. Here young Hemsley's capacity attracted the attention of Mr. G. Bentham, who was then at work on his great "Flora Australiensis," in the preface to the first volume of which reference is made to Hemsley's services. While a temporary technical assistant in the herbarium, Hemsley gave all his spare time to general botanical studies; in 1863 he gained a first prize in botany, awarded by the Royal Society of Arts. In 1865 a vacancy occurred in the permanent herbarium staff, and Hemsley was selected to fill it. But Hemsley's physique could not stand the strain to which the enthusiasm and assiduity with which he performed the duties of Herbarium Clerk subjected it. In 1867 a complete breakdown in health compelled Hemsley, to the regret of his superior officers, to relinquish his clerkship and retire to Sussex. Here, in spite of his illness, Hemsley devoted himself to mastering Latin,