THERAPEUTIC MALARIALIZATION OF GENERAL PARALYTICS IN THE TROPICS.

By A. W. H. SMITH, M.R.C.S., L.R.C.P., D.P.M.,

Acting Medical Superintendent, Central Mental Hospital, Tanjong Rambutan, Federated Malay States.

DURING the last few years, in which pyretotherapy has figured so largely in the treatment of general paralysis of the insane, the question must have arisen in many minds whether general paralysis occurs in communities where malaria is indigenous, and if so, whether satisfactory results would be obtained from further malarialization on artificial lines.

The Central Mental Hospital of the Federated Malay States has over 2,500 patients in residence, and draws its cases from the whole of the Malay Peninsula. Many races are represented besides the native Malay and associated races—Chinese, Japanese, Siamese, Indian, etc.—and malaria is indigenous over the whole territory.

Fifty-six general paralytics were treated at this hospital, the cases being drawn from all nationalities, and the following is a summary of results :

Out of 56 patients inoculated, 1 was " cured " (discharged), 2 were markedly improved (discharged), 1 slightly improved, 6 not improved, 2 died of malaria.

Forty-two failed to contract malaria, and no improvement was noted among any of these such as might be attributed to " apyrexial malarial therapy."

Of those cases that failed to contract, all 42 were reinoculated at least once, 29 were reinoculated thrice intramuscularly, 5 were reinoculated four times intramuscularly, and 10 were reinoculated intravenously after the first intramuscular attempt.

The other 12 cases commenced rigors within from 7 to 18 days of the first intramuscular injection with the exception of one case which was reinoculated after 21 days, the original rise of temperature having proved abortive ; 11 of these cases remitted spontaneously, only 1 requiring quinine, and that the " cured " case.

All cases were males and were selected on strong clinical evidence in the first place, the diagnosis being confirmed later by the serological findings before inoculation.

https://doi.org/10.1192/bjp.79.324.94 Published online by Cambridge University Press

No case was chosen with pathological changes less than—Blood Wassermann, ++ ; blood Kahn, ++ ; cerebro-spinal fluid Wassermann, ++ ; cerebro-spinal fluid globulin, + ; cerebro-spinal fluid cells, 10.

No concurrent anti-luetic drug treatment was employed and, although the histories were defective, it is unlikely that any of these cases had received such before admission.

Case.—K. S. K—, an educated Chinese of the " towkay " class, a commercial man of some means, could speak English and Malay as well as three dialects of Chinese, and possessed an extremely interesting and forceful personality. Shortly after admission he exhibited fatuous exaltation and well-marked slurring articulation, but later, towards the close of his convalescent period, these defects disappeared, revealing a character unusually interesting as compared with the average found in an Asiatic mental hospital.

On examination the pupils were circular, but slightly unequal, the right being the larger, and they reacted equally but very poorly to light, especially consensually.

Accommodation and reaction on accommodation seemed to be normal so far as it was possible to ascertain in a patient of extremely restless habit and poor attention. A patch of integument over the bridge of the nose spreading for half an inch on to the forehead was completely analgesic and apparently anæsthetic. There was no facial asymmetry, but the facies lacked the vigour of expression that might have been expected from the amount of euphoria displayed.

A well-marked " trombone " tremor of the tongue was present and he appeared to have a little difficulty in swallowing. Articulation, as already stated, was definitely dysarthric and slurring in quality. Most superficial reflexes were accentuated and the tendon reflexes diminished, in particular the knee-jerks, while both plantar reflexes were extensor. The gait was extremely unsteady and the patient swayed on standing, even with his eyes open. The blood Wassermann and Kahn tests showed a double +, the cerebro-spinal fluid Wassermann was double +, the globulin markedly increased and the cells numbered 25 per c.mm.

The mental characteristics of this man were most interesting, as deterioration was so rapid. Within a few weeks he lost his knowledge of all languages except his mother tongue, and in the reverse order to that in which they had been acquired. English, the school-taught language, disappeared rapidly ; Malay, the *lingua franca* of these parts, which is picked up in infancy, more slowly ; and lastly, the other Chinese dialects akin to his mother tongue. When he recovered he regained all four in the reverse order again—that is, in the original order in which he had first learnt them. In this polyglot corner of Asia the losing and regaining of tongues forms a very useful guide to the diagnosis and prognosis of the psychoses, and bears ample witness to the truth of the law of reverse degeneration or dissolution (1).

His euphoria was intense and his grandiose delusions superb. Thus he owned half the wealth of the country, and all other towkays had to submit cheques to him before they could be honoured at the bank. He was the first to own an aeroplane in these States and now possessed a fleet of several hundred, some of which were so fast that he could take his family to China for week-ends. His wives, of which he possessed four, as well as four hundred concubines, were all royal princesses of the ancient Imperial family and each had a separate palace in Kuala Lumpur, the capital of the Federated Malay States.

He received 4 c.c. of benign tertian blood well loaded with sporocytes, and his first rigor commenced fourteen days later, after an initial fever of four days' duration. He raised a marked reaction and sustained fifteen rigors, some of them being quotidian, though other forms of parasites were never found in the blood-smears. On the twenty-fourth day his condition became so weak that it was deemed

advisable to exhibit quinine, and he was put on Sinton's treatment, which effectively stopped all fever and acted as a remarkable tonic.

Already, during the active stages of the treatment, his delusions had progressively diminished, and now he was sadly shorn of much of his former magnificence. Gone were all his aerial fleets and most of his wives, though he still remained a fairly rich man. It took another three weeks before he relinquished all claims to excessive wealth, and he never entirely lost his abnormal self-confidence and somewhat hilarious *bonhomie*. He did, however, leave the institution within the remarkably short time of three months from the date of inoculation, capable of taking his place in the business world again and of conducting his affairs without undue embarrassment to his family; and to date, nearly a year afterwards, has remained fairly successful in spite of the worst trade depression known in the East.

So much for the single cure out of the 56; the other cases were not sufficiently distinctive to warrant comment. It is at once obvious that these results are extraordinarily poor as compared with those usually obtained at mental hospitals in Europe and other temperate climates.

Thus, three only were discharged out of a total of 56 cases treated, a—recovery-rate of 5·4% as against an average of about 25% for Europe.

Meagher (2) gives 25% as the figure collected from 11 mental hospitals in England for the year 1923, and as much as 26% from 22 mental hospitals in 1924. Even taking figures from mental hospitals where therapeutic malarialization was not practised for the year 1927 the recovery-rate is as high as 2% (3). This author (quoting Dr. Clarke of Whittingham) points out (4) that remissions met with in untreated cases denote a transitory improvement mitigating the value of this 2%, whereas the 25% discharged after malarial therapy form a much more permanent type of "cure."

It must here be stated that the same holds true of the other two out of the three cases discharged from the Central Mental Hospital; they were removed by importunate relatives, and hardly came up to the standard usually accepted as fit for discharge, so that the real figure for percentage of recoveries should rather be 1·8.

Owing mainly to difficulty of access to the literature, the writer has not been able to compare results with any that may have been accumulated in other tropical countries, though two cases of "neuro-syphilis" and one of manic-depressive insanity were inoculated with malarial blood at the Ranchi Mental Hospital (5) in 1930—it is stated with no improvement.

The question then arises as to the reason for such poor results attending malarial therapy in a malario-indigenous country. In the first place, regarding the correctness of diagnosis and the degree of efficiency of treatment: the writer has shown, he trusts, that sufficient care was taken to render the diagnosis certain before choosing cases for treatment, while, in the actual treatment itself, a like care was exhibited to ensure efficient inoculation. Thus blood was always taken from donors about half an hour after a rigor and injected without delay, a sample being examined to ascertain its malarial

content. If this sample was not loaded with parasites the recipient was reinoculated at a later date.

Five c.c. of blood were employed on every occasion, and great care taken to ensure that antiseptics should not come into contact with the needle, syringe, or the skin of either donor or recipient. Benign tertian, subtertian, mixed tertian and malignant varieties were employed, and all were taken from "roaring cases of rigorous reaction." In no case had the donor received any quinine. Working with the above precautions in this warm, humid climate the chances of death of the parasite were almost *nil*.

One point which may perhaps account for a small proportion of failures is the disadvantage the worker is under in Malaya, as in other less advanced countries, of not being able to obtain satisfactory histories; indeed, in most cases no history at all is forthcoming. This militates against efficient selection of suitable cases for malarial therapy both with regard to the stage of advancement of their dementia and the possibility of considerable previous malarial infection. The Schilling index, however, proved useful in rejecting some of the more advanced cases; a few with an immature neutrophile leucocytosis of as much as 15% were rejected, with others, by this method.

The assumption, however, that one is drawn to is that artificial malarialization fails because of the large previous infection of those patients who have been subjected to it most of their lives. This is supported by the fact that K. S. K—, the only really successful inoculation, although born in this country, had returned to China frequently, and, coming of a better class than the other patients, would not be likely to have contracted malaria so frequently.

The validity of this hypothesis depends very much upon the question whether an attack of malaria confers immunity against subsequent attacks. Manson Bahr (6) affirms that it has been shown that the natives of malarious districts do acquire immunity to this disease, and that they acquire it from repeated and persistent infection in childhood. It is a matter of common observation in malarious countries that many natives who have suffered from ague in childhood or early life can expose themselves to infection with a remarkable degree of impunity, while many immigrants to the country who suffer severely during their first year or so are later free from the disease. Many authorities, including Schuffner (7), conclude that differing degrees of immunity to malaria may be found, and he mentions *immunitas sterilisans* and relative immunities. This certainly appears to be the case in artificially produced malaria, second and third inoculations being notoriously difficult to render effective if the patient has responded at all to the first inoculation, while Rudolf (8) states that the degree of immunity varies directly with the number of inoculations.

There are many other indigenous fevers, in Malaya at least, that might

be supposed to affect the course of general paralysis, most of them being themselves spirochætal, such as Weil's disease, 7-day fever, yaws and Sodoku or rat-bite fever, which latter has been used successfully in pyretotherapy (9).

But is general paralysis, in consequence of all this, less prevalent in the East than in the West? As far back as 1923 the average percentage of admissions to all hospitals in the Netherlands East Indies was as follows:

Europeans	9·1
Malays and Chinese	2·9

while the figure given at that time for Prussia was 9·5.

Fletcher (10) states that "Though syphilis is widespread in most tropical countries, the parenchymatous affections of the central nervous system, *viz.*, tabes and G.P.I., are comparatively rare, at any rate among the native population."

Castellani (11) expresses a similar opinion. Kirk (12) as recently as 1931 writes: "Parasyphilitic diseases, as locomotor ataxia and general paralysis of the insane, are very rarely met with in the tropics."

But our experience at the Central Mental Hospital so far as general paralysis is concerned has been quite different. As against the European figures of 4·2% to 5·7% (average percentage on direct admissions to mental hospitals), this hospital gives an average figure of 4·9% during the last 15 years, while the later records of the Singapore Mental Hospital, which, however, draws its cases much more largely from among seafaring men and from overseas shows 8% for the year 1931.

Tabes is, undoubtedly, extraordinarily rare in Asia; de Lange reckons it among the rarest of diseases in Java; Montel has only seen one case at Saigon among 100,000 patients in 15 years, and the records of the Central Mental Hospital do not show a single case in 25 years.

Another factor to be reckoned with among the peoples of Asia in considering their reactions and immunity to the toxins of disease is that of idiosyncrasy. This phenomenon, comparatively rare at home, is more than common here; it is in fact a racial characteristic, and its manifestations are remarkable in the extreme, especially among the Chinese. Thus the well-known tolerance for opium, due possibly to centuries of selective breeding, goes hand in hand with the equally remarkable intolerance of iodine, ipecacuanha and belladonna, while opium addicts are so intolerant of mercury in any form that a dose of 5 gr. of grey powder has been known to cause necrosis of the lower jaw.

Recognizing, therefore, some degree at least of metabolic differentiation in the physiology of the Oriental, one is led to be cautious in drawing conclusions, but it seems to the writer permissible to conclude that the percentage of general paralytics in the Malay States would be even larger were it not for the minimizing influence of malaria, and, as will be shown later, so many other antigenous affections and diseases.

But there is yet another factor that has to be considered in contemplating the effects of frequent febrile diseases on the course of syphilis contracted by a native population lower in culture and hygiene than the average found in Europe, and that is the one of selective survival. Most general paralytics in the East have maintained their syphilis in spite of all these natural inoculations, and are therefore less amenable to any form of treatment ; either their natural resistance to syphilis is unusually low, or their particular strain of spirochæte is of an unusual virulence.

Consideration of the dermotropic and neurotropic lesions of syphilis as found in Asiatics confirms these conclusions. Organic lesions apart from the central nervous system, such as luetic alterations of the cardio-vascular system are not common, while syphilides of the skin are extraordinarily frequent in the East. This is in keeping with the Oriental's strong predisposition to ulceration and inflammation of the skin at all times. When it is remembered how large a part the skin plays in the formation of antibodies, especially in a climate where pigment and sunlight abound, it is not difficult to understand why the cases that come for treatment are only those that have persisted in spite of all *materia medica naturæ*.

Harrison (13), quoting Brown and Pearce's experiments, states that the severity of any phase in syphilitic manifestations is influenced by the intensity of reaction in the previous phases. He maintains that an attack of syphilis produces a resistance which is proportional to the amount of tissue reaction that occurs, and with special reference to syphilides, he concludes that this factor may contribute to the holding in check of general paralysis among uncivilized communities.

The old theory as to the dermotropic and neurotropic manifestations of syphilis being due to two varieties of the *Spirochæta pallida* appears to have fallen out of favour. Collier and Adie (14) support the more modern and now more generally accepted view that the cause of the variation lies in the victim rather than the virus. Eddison (15), pointing out that general paralysis tends to occur in the type of patient with a scanty history of earlier syphilitic lesions, maintains that involvement of the reticulo-endothelium by the syphilitic virus constitutes one of the factors which determine whether a given syphilitic patient will develop paralytic dementia ; but Bruetsch (16) affirms that the immediate tissue reaction of the body to the malarial plasmodium consists in a stimulation of the reticulo-endothelial apparatus, leading to a new formation of macrophagic tissue in various organs. Bruetsch further states that in therapeutic malaria the individual cells of the reticulo-endothelial system found in the blood-stream, the histiocytes, are mainly derivatives of the specific endothelium of the spleen, marrow, etc., and, to a minor degree, the common capillary endothelium is engaged in the formation of intravascular phagocytes. In general he concludes that " Therapeutic malaria produces an activation of

the mesodermal tissue, in which the stimulation of the histiocytes and the activation of the undifferentiated mesenchymal cells are outstanding features."

May we not, then, in malarialized syphilides, and in cases of general paralysis + malaria + dermatitis, visualize large quantities of blood surcharged with histiocytes being drawn into the congested dermis, there to be opsonized by "quanta" of tropical sunlight?

Power (17) says that "At all events the appearance of a rash is of good omen as regards the subsequent development of paresis, and this fact is worthy of very serious consideration from a possible therapeutic standpoint. Might not a primary spirochætal disease, such as yaws, exert a beneficial influence on general paralysis?" Apparently we fail in our pyretotherapy in the East, because Nature, so prodigal and yet so ruthless in the birthplace of mankind, has, relenting, anticipated us with her own remedies.

Finally, one other consideration of great importance—the lateness of most cases seen by the practitioner in the tropics, whether in the general, hospital or institutional field. The mental hospital in Asia fortunately does not suffer in the least degree from the stigma attached to such places in the mind of the people of Europe, but it does experience humanity's other great failing—procrastination—to a much greater extent, so that when we consider that the native patients, for the most part, apply for medical assistance only on account of serious and far advanced stages of disease, their number acquires an entirely different significance.

For the present, until a larger series of cases can be examined or correlated, the writer is forced to the following deductions:

Conclusions.

(1) General paralysis of the insane is as prevalent among the population of the Malayan peninsula as among that of Europe.

(2) This prevalence is, moreover, even less than it would otherwise be on account of—

(i) The retarding effect of concurrent protozoal infections.

(ii) The tendency of the Oriental's metabolism towards dermotropic rather than neurotropic lesions in all spirochætal diseases.

(3) General paralysis of the insane responds very much less to anti-malarial treatment in Asia, because these neurotropic cases represent the most developed of the cases of lues, *i.e.*, cases which have persistently resisted the action of exogenous and endogenous antibodies.

(4) It is extremely difficult to obtain effective malarial inoculation in Asiatics of the coolie class who have been brought up in a country where malaria is indigenous, and who may be presumed to have acquired some degree of immunity.

References.—(1) *Vide* Jones, Ernest, *Psychology of Everyday Life*, p. 56.—(2) Meagher, Surg. Rear-Adml. E. T., "General Paralysis and its Treatment by Induced Malaria," quoted in *Journ. Ment. Sci.*, October, 1929, p. 715.—(3) *Idem, ibid.*—(4) *Whittingham Mental Hospital Annual Report*, 1924.—(5) *Ranchi Europ. Ment. Hosp. Ann. Report*, 1930.—(6) Manson-Bahr, *Tropical Diseases*, p. 9.—(7) Schuffner, "Dementia Paralytica in the Tropics," *Trans. of Vth Biennial Congress, Far East. Assoc. Trop. Med., Singapore*, 1923, p. 866.—(8) Rudolf, *Therapeutic Malaria.*—(9) *Idem., ibid.*—(10) Fletcher, *Practice of Medicine in Tropics.*—(11) Castellani, *Trop. Med.*, p. 101. (12) Kirk, J., *Practitioner*, April, 1931, cxxxvi, No. 4, p. 463.—(13) Harrison, L. W., "Treatment of Syphilis," *Lancet*, April 5, 1930, p. 736.—(14) Collier and Adie, *Price's Text-Book of the Practice of Medicine*, p. 1441.—(15) Eddison, H. Wilfred, "Problems of Pyretotherapy in Paralytic Dementia," *Journ. Ment. Sci.*, January, 1930, p. 69.—(16) Bruetsch, Walter L., "The Histopathology of Therapeutic (Tertian) Malaria," *Amer. Journ. Psychiat.*, July, 1932, p. 61.—(17) Power, T. D., "The Ætiology of General Paralysis of the Insane," *Journ. Ment. Sci.*, July, 1930, p. 528.