M 3, A NEW DRUG IN THE TREATMENT OF MALARIA

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THE Italian Biochemical Institute of Milan which have introduced the antimalarial drug to which the trade name of 'M 3' has been given, claims that this preparation not only confers absolute protection against malaria on an individual which may last for about 6 months in the tropics, but that it is also capable of preventing relapses. It is also claimed as a curative in chronic malaria, and it is said that the cure is brought about by the destruction of the gametocytes. A marked diminution in the size of the spleen and improvement of the general condition of the patients are said to follow its administration in such cases. The manufacturers recommend treatment of acute cases with quinine, after which they advise that M 3 should be prescribed.

The fact that this preparation does not possess any prophylactic properties has already been pointed out by Chopra and Basu (1939). In the experimental work which these authors carried out, volunteers who had been given the prescribed course of M 3 were allowed to be bitten by *Anopheles stephensi*, artificially infected in the laboratory. The infection developed in due course.

Our conception of the part played by gametocytes in causing relapse is quite clear and therefore if the drug has any action in preventing relapse it can only do so by destruction of the asexual forms of the parasites.

The manufacturers, at the time they sent this drug to us, assured us that it had stood and would stand any clinical tests. This induced us to assess its value in the treatment of malaria, and investigations were carried out on the following lines in the Carmichael Hospital for Tropical Diseases :—

(1) The action of M 3 on the sexual and asexual stages of plasmodial parasites of man was determined.

(2) Its power of preventing relapse was observed.

(3) Its utility in the treatment of chronic malaria was estimated.

The type of cases experimented upon and the results obtained are recorded below :—

Case 1.—A student, who was admitted into the Carmichael Hospital for Tropical Diseases, and showed malignant tertian rings and crescents in his blood, was put on a course of M 3, one tablet daily. His fever was not checked in the course of four days. On the other hand, it increased to such an extent that he had to be treated immediately with quinine and plasmochin. Just before quinine was administered, laboratory-bred *A. stephensi* were fed on him. The occurrence of infection in the salivary glands in due course clearly indicated that the crescents had not been acted upon by this drug. The patient was thereafter put on a full course of M 3 and, as he was discharged before the course was completed, the matron of the hostel where he was staying was specially instructed to see that the rest of the course was given to him in the morning in her presence. After an interval of a month, he was given another course of M 3, and we are satisfied that the patient took this medicine regularly, according to our instructions.

Soon after the termination of the second course, he had two attacks of fever and each attack was temporarily checked with quinine. As he showed no signs of improvement, and as the spleen was considerably enlarged, he had to be treated with ordinary antimalarial remedies.

Case 2.—The patient was admitted with malaria and malignant tertian rings in fair numbers were detected in blood smears. He was put on M 3, one tablet a day, which was discontinued on the fourth day on account of a high rise of temperature which necessitated treatment with quinine. He was again put on a course of M 3 and the directions given by the makers were strictly followed. Towards the later stage of its administration, he had a relapse which was treated with quinine; M 3, however, was not discontinued. Soon after the fever was stopped gametocytes made their appearance in the peripheral blood and continued to be present in spite of the fact that M 3 was being administered. They were later destroyed by treatment with plasmochin.

Cases 3, 4 *and* 5.—Three volunteers, who had been given a regular course of M 3 as prescribed by the manufacturers, were successfully infected with malignant tertian malaria by the bites of *A. stephensi* one month after this drug was stopped. The fever induced by the mosquito bites was treated with M 3, and when it was found that the drug made no impression in regard to fever and parasites in the peripheral blood it became necessary to treat them with quinine. One of these patients had four relapses and the other six in course of three months. During the period they were under M 3, crescents appeared in the blood of two of them. *A. stephensi* fed on one of them, even after a fortnight of M 3 treatment, became infected.

Case 6.—This patient had suffered from chronic malaria for a long time. Blood examination at the time of his admission showed rings and gametocytes of *Plasmodium malariæ*, though there was no fever and the spleen was considerably enlarged. He was put on a course of M 3, but treatment for ten days had no

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Acknowledgments

We wish to thank Lieut.-Colonel Amir Chand, I.M.S., Professor of Medicine, King Edward Medical College, Lahore, for allowing us to publish his cases, Dr. Pran Nath Chhuttani, M.B., B.S., for doing the blood counts of the recent case and Dr. Vishwa Nath, Assistant to the Professor of Pathology, K. E. Medical College, Lahore, for the post-mortem reports.

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effect on the parasites, either sexual or asexual. Administration of quinine became necessary on account of the high rise of temperature and M 3 was discontinued.

Case 7.—This patient, like case 6, had suffered from chronic malaria for a long time before he was admitted into the Carmichael Hospital for Tropical Diseases. At the time of his admission he had no fever though scanty malignant tertian rings and a few gametocytes were detected in blood smears. The spleen was enlarged. He was put on a course of M 3 and parasites soon disappeared from the blood. About three weeks after the commencement of the course of M 3, rings appeared in the blood associated with a high rise of temperature.

Case 8.—Another patient who gave a history of having suffered from chronic malaria showed a large number of rings and scanty gametocytes of *P. vivax*. As his general condition was unsatisfactory, he was treated first with atebrin after which a full course of M 3, as laid down by the manufacturers, was prescribed. The patient remained in fairly good health for about three weeks after the termination of M 3 treatment when there was a relapse.

The cases referred to above clearly prove the inefficacy of the drug M 3 in treatment of malaria. Its power of destroying gametocytes, as has been claimed, has not been substantiated by the trials we have carried out. Even when acute cases were first treated with quinine, atebrin or plasmochin and thereafter put on M 3 treatment, they were not free from relapse. One of our patients (case 1) who had had two courses of M 3 at an interval of a month had two relapses. Neither improvement in the general condition of the patient nor any reduction in the size of the spleen was observed in chronic cases after a full course of M 3 was administered.

When we come to consider its value in protecting an individual against an attack after he has had a course of M 3, we refer to the experimental observations on the same subject made by Chopra and Basu about which reference has already been made in this paper. Such patients are no better protected than those who have taken no drug at all.

The series of cases on which the drug has been tested is undoubtedly small, but in view of the definite results obtained we did not feel justified in carrying out further trials.

Summary and conclusion

M 3, a drug introduced by the Biochemical Institute of Milan, is said to consist of iron, manganese and extract of spleen. It was tried in a small series of cases, and proved ineffective both in the treatment of attacks of malarial fever, and in preventing relapses even after the patients had been treated with quinine, atebrin or plasmochin. It did not improve the general condition of the patients, nor did it cause any reduction in the size of the spleen when it was given in the manner prescribed by the manufacturers.

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INTRACUTANEOUS INOCULATION OF GUINEA-PIGS FOR THE DIAGNOSIS OF TUBERCULOSIS

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TOPLEY and Wilson (1936) in dealing with the diagnosis of tuberculous infection write :—

'The most delicate test for tubercle bacilli is animal injection, and the most suitable animal is the guinea-pig. The susceptibility of the guinea-pig is extremely high; even minute amounts of infective material will render this animal tuberculous. The material—sputum, pus, milk, etc.—should be injected subcutaneously or intramuscularly into the thigh; the advantage of intramuscular injection is that the local abscess which forms does not ulcerate through the skin. It is wise to inject at least two animals, in case one dies of secondary infection—an occurrence which is very common after the inoculation of urine or fæces. One animal should be killed 3 to 4 weeks later and, if no signs of tuberculosis are apparent, the other should be kept for 6 to 8 weeks after inoculation before being killed'.

The great drawback to the extended use of animal inoculation tests (particularly valuable for the demonstration of small numbers of tubercle bacilli in a pathological specimen) is the long delay before a definite diagnosis can be made. After a subcutaneous, intramuscular and intraperitoneal injection of suspected tuberculous material an interval of two months may be necessary before a diagnosis can be made. Although a tuberculin test may be used for the diagnosis of tuberculosis in a guinea-pig during life, the result must be confirmed by post-mortem examination.

Intracutaneous inoculation.—This method of inoculation of the suspected material has definite advantages over the subcutaneous and other methods. There is an appreciable shortening of the time in which a positive diagnosis can be made and the subsequent manipulation consists of the demonstration of acid-fast bacilli in smears taken from the ulcer which develops at the site of the intracutaneous injection.

After an intracutaneous injection of the tuberculous material a small nodule develops at the site of the inoculation in 3 to 4 days. The nodule breaks down to form a punched-out ulcer in 7 to 14 days. Tubercle bacilli can be found in smears made by scraping the base of the ulcer. With the development of the ulcer there is an enlargement of the regional