than 10 c.cm., and from our experience in one case in which by an error double the dose was given we doubt if an increase is advisable, for in that case the patient developed a severe rigor with an alarming collapse; nevertheless, the haemorrhage which had menaced his life and had failed to be controlled by other haemostatics ceased instantly. We have found that occasionally the 10 c.cm. will check the haemorrhage for some time, and then slight recurrence occurs. In such cases the dose may be repeated, a further 10 c.cm. being given in four to six hours. In a large number of cases treated with this drug we have only had two in which the haemoptysis was not sufficiently controlled and other methods were necessary.

Other Methods

In cases of gastric and duodenal haemorrhage results have also been satisfactory, though perhaps not quite so certain as in haemoptysis. Other methods of obtaining stasis which have been suggested, such as the introduction of adrenaline into the bronchial tree, have not impressed us with their efficacy. Adrenaline may be introduced by the nasal catheter, crico-thyroid route, or by the bronchoscope. We have used the first two methods, but in any case the solution is so diluted with blood that effect can scarcely be expected; moreover, the bleeding point is usually so distant in the bronchial tree that it is unlikely that any direct result could be produced. Quite different are the severe and somewhat alarming haemorrhages which occasionally take place in the removal of polyps or a section of malignant growth via the bronchoscope; in this case adrenaline can be applied direct in large quantity over the bleeding area.

In the event of failure of other methods, the induction of an artificial pneumothorax is often successful in staying the haemorrhage. The cause of the haemoptysis must, however, first be considered. If the lesion is an early tuberculous one it will probably be successful, but in these cases the bleeding is usually not so severe as to cause alarm; if the lesion is in an advanced bilateral case artificial pneumothorax may be done as a temporary measure, even if it may be deemed inadvisable to keep it up permanently. In this type of case difficulty may arise in deciding as to the side from which the haemorrhage is coming. If an X-ray is available then the side showing a cavity is the most likely to be the offender, if not, one has little guide, as the ordinary methods of physical examination are not available. Often, however, the patient knows which is the worst side, and in many instances is able to indicate the side from which the bleeding is coming from subjective sensations. But as a contralateral artificial pneumothorax may be successful in stopping the haemorrhage, the position is not quite so difficult as it might appear. If the lesion is a lung abscess or a bronchiectasis, one must weigh up very carefully the urgency of the haemoptysis with the risk, especially in the former case, of producing a pyo-pneumothorax. Occasionally repeated haemoptyses call for some preventive measure. Such are frequently cases of dry bronchiectasis and chronic fibrosis, and an artificial pneumothorax or phrenic avulsion may be a useful procedure.

Conclusions

In a pulmonary haemorrhage the bronchi must be kept free. This can only be attained by leaving the patients their cough reflex. Some method of haemostasis is desirable, and in the failure of the ordinary methods Congo red has proved in our experience to have a very definite use.

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OBSERVATIONS ON THERAPEUTIC MALARIA

WITH SPECIAL REFERENCE TO A CASE
OF HAEMOGLOBINURIA

BY

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Malaria is still the most popular of all forms of treatment for general paralysis in spite of the numerous attempts which have been made to supersede it by other forms of pyrexial therapy. Its popularity with clinicians is derived not so much from the high measure of complete recoveries achieved as from its relative immunity to serious accidents. In thus combining a moderate degree of success with comparative safety, it has proved itself superior to, and generally more acceptable than, any of its rival methods of treatment.

The truth of this claim has been amply borne out by our experience of some 300 cases of therapeutic malaria during the last ten years at Rainhill Mental Hospital. With a judicious selection of cases the number of untoward complications has been almost negligible, and the great majority of patients have succeeded in completing a course of ten rigors, with associated rise of temperature, at no greater cost to the patient than a mild prostration and some degree of anaemia. With adequate after-treatment both of these temporary set-backs have been successfully combated. In about 10 per cent. of the cases a mild degree of jaundice has been observed, associated with the anaemia appearing towards the end of the malarial course, but in all instances clearing up completely after the administration of quinine.

Both the benign tertian and quartan forms of malaria have been employed at different times, but of the two the former has proved the more satisfactory. In our experience the quartan is less reliable, and not so readily controlled with quinine. Despite this, relapses are of very rare occurrence. As will be noted from the accompanying temperature chart the rigors sometimes occur at much more frequent intervals than is characteristic of this strain of malaria. This phenomenon is by no means an uncommon experience with therapeutic malaria, particularly after many generations of the parasite have passed through the human host, and in our opinion is attributable to the fact that propagation is carried on solely by the asexual cycle for so many generations. Blood films examined from such sources show that the parasites mature at different periods, and in the same sample of blood parasites at all stages of development are to be seen. This offers some explanation of the irregular pyrexia, but, in addition, there is some evidence for thinking that there may be a personal factor also concerned.

Case Record

A case which provides an outstanding exception to this general experience has recently been encountered at Rainhill, and because of its unusual features it is deemed worthy of a detailed consideration.

G. H., a male, 46 years of age, was recently admitted to the hospital in a restless, excited, and grandiose state. He had typical delusions of grandeur, and clinically presented a classical case of general paralysis. Though he had few neurological signs, the clinical diagnosis was amply confirmed by serological tests. Thus the Sigma reaction in blood and cerebro-spinal fluid was strongly positive, there was increased protein in the cerebro-spinal fluid, and the large gold-sol curve read 5555554100. The mental symptoms had only been in evidence for just over a fortnight prior to his admission, and as he was in good physical condition there was no hesitation in prescribing for him a course of malaria. Before

inoculation with 5 c.cm. of malarial blood (2/2/34) his acute mental symptoms had considerably subsided, and he had regained to some extent his insight, a circumstance which rendered his subsequent management and nursing very easy. Eleven days after his inoculation (13/2/34) he had his first rigor, and this was repeated at roughly twenty-four-hour intervals for ten days, with an associated temperature averaging 104° F. On two occasions during the course blood films showed the presence of malarial parasites of the quartan variety with a relative increase in the mononuclear leucocytes. After the tenth rigor (23/2/34) quinine was given orally in mixture form (quinine sulphate, 10 grains t.d.s.). Twenty-four hours later (24/2/34), after he had received five doses of quinine, he had a very severe rigor, with a temperature of 105° , the highest recorded. This unexpected and unusual event gave rise to considerable misgivings, but quinine was continued. Two days later (26/2/34) his temperature rose again to 99.6° without any rigor, and the same day a definite icteric tinge appeared on his skin, whilst a little later his urine was observed to be unusually dark in colour. The following day (27/2/34) the jaundice had deepened, and the urine was diminished in quantity and of a deep red colour.

At this stage a sample of blood taken for examination revealed a marked degree of haemolysis, the serum being of a reddish hue instead of the usual straw colour. An examination of a blood film showed severe anaemic changes with anisocytosis, polychromatophilia, and punctate granular cells. There were numerous normoblasts and a few megaloblasts. Among the white blood cells there were myeloblasts and myelocytes in all stages. The urine contained a large amount of haemoglobin, and spectroscopic examination of both urine and blood serum showed the bands characteristic of oxyhaemoglobin. Another abnormal constituent of the urine, which was alkaline and of high specific gravity, was albumin, present in considerable amount, but there was no deposit of red blood cells or casts. The test for occult blood was strongly positive.

Progress.—This association of malaria, quinine, and haemoglobinuria strongly suggested a diagnosis of blackwater fever, and prompt and vigorous measures were taken to meet this very serious situation. Quinine was stopped (28/2/34), copious drinks were given, and large massive doses of alkalis administered, whilst a careful watch was set upon the quantity and colour of the urine passed. Remarkable to relate, despite this severe haemolysis the patient, who was very clear mentally, had scarcely any subjective symptoms. He made no complaints at all beyond his feeling of weakness, but stated at a later period that for a short time he had seemed a little deaf.

His condition responded exceedingly well to treatment. He passed large quantities of urine, which gradually cleared and became free from haemoglobin and albumin in four days (3/3/34). His blood picture improved *pari passu*, a distinct improvement in the blood films being observed very quickly (2/3/34). The progress of the blood condition may be gauged from the following reports.

2/3/34.—Blood film shows an occasional normoblast; anisocytosis still very marked. Haemoglobin 80 per cent.

3/3/34.—Blood count: red blood cells, 2,800,000 per c.mm.; white blood cells, 7,500 per c.mm.; colour index, 1.4. Leucocytes consist chiefly of myelocytes in various stages of development.

5/3/34.—Blood film shows an occasional normoblast, also many myelocytes. Red blood cells show less marked anisocytosis but severe achromia.

7/3/34.—Halometer reading of red blood cells, 7.32 μ . Blood count: red blood cells, 2,800,000 per c.mm.; haemoglobin, 60 per

cent.; colour index, 1.07. Well-marked anisocytosis still, but no normoblasts seen. Considerable improvement on previous films.

16/3/34.—Blood count: red blood cells, 4,100,000 per c.mm.; haemoglobin, 70 per cent.; colour index, 0.85. Numerous reticulocytes seen in film. Halometer reading approximately 7.32 μ .

5/4/34.—Blood count: red blood cells, 4,600,000 per c.mm.; haemoglobin, 85 per cent.; colour index, 0.9. Only an occasional reticulocyte seen. Halometer reading 7.48 μ .

As will be seen from the report of the last blood examination, the man's blood picture approximated closely to normal. Clinically, his general bodily condition showed corresponding improvement, but at the time of writing (April, 1934) he still has a mild degree of tachycardia—a residuum, no doubt, of the profound degree of anaemia. His mental condition is very satisfactory, and he will shortly be discharged from hospital as fit to resume outside life and pursue his former occupation.

Discussion

The quartan strain of malaria employed in this case had already passed through two female patients, who throughout the course of treatment of the usual length had not manifested any unusual or alarming symptoms.

Further, another male patient, inoculated simultaneously and with the same blood, ran the course in the usual way. The possibility of a previous malarial infection either of the malignant or benign form has been definitely excluded by investigation of the man's previous history.

If it serves no other purpose, this phenomenal case illustrates the obscurity

Temperature Chart of Malaria, showing Rigor occurring after Administration of Quinine. Rigors occurring at Daily Intervals (with the exception of the fourth day).

A = parasites in blood film. B = parasites frequent in blood film.
C = quinine given. D = total of five doses of quinine given.

with which the aetiology of blackwater fever is still surrounded. There would have been no hesitation in labelling this case as one of true blackwater fever if the malaria had been of the malignant variety, for in this case most of the characteristic features of this disease made their appearance in the usual sequence. Thus there was the malarial course terminated by quinine, and this, in turn, followed by the intravascular haemolysis, resulting in haemoglobinuria, jaundice, and anaemia. As in most cases, it is very puzzling to assess the importance of the part played by quinine in the production of this condition, but it is very significant that the symptoms appeared immediately after the administration of the drug, a feature of the aetiology which is much emphasized in textbook descriptions. Other causative factors of haemoglobinuria can be dismissed—namely, drugs (for example, potassium chlorate), over-exertion, excessive cold, as in the paroxysmal haemoglobinuria variety, in which in the last-mentioned case there would in all probability have been previous attacks.

Whatever may be the nature and source of the lysis producing such severe haemolysis, it would seem from the experience of this singular case that a condition identical with, or strongly resembling, blackwater fever can arise after benign malaria treated with quinine as well as after the malignant form. The complete absence of any reference to this possibility in all standard textbooks of medicine testifies to the extreme rarity of the condition.

In conclusion, I gratefully acknowledge my indebtedness to Dr. F. Murgatroyd of the Liverpool School of Tropical Medicine for his invaluable advice and interest, and also to Dr. E. F. Reeve for permission to publish this case.