THE ACTION OF "BAYER 205" ON TRYPANOSOMA EQUIPERDUM IN EXPERIMENTALLY INFECTED MICE.

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THOUGH many drugs have been tried in the treatment of trypanosomiasis in man and animals, it is generally admitted that none of them is entirely satisfactory, although cases of the human disease have undoubtedly recovered after their prolonged use. In experimentally inoculated small animals, such as mice, it is usually possible, by means of a single dose of a drug, to bring about the disappearance of the trypanosomes from the peripheral blood, but almost invariably relapses occur in a comparatively short time and the animals die of the infection.

Haendel and Joetten¹ (1920) and Mayer and Zeiss² (1920) published accounts of the trypanosomicidal action of a drug which they referred to as "Bayer 205." They reached the conclusion that the preparation possessed trypanosomicidal powers on various pathogenic trypanosomes in small laboratory animals.

In small doses it cured mice, rats, guinea-pigs and rabbits infected with *T. brucei*, *T. equiperdum*, *T. equinum*, *T. gambiense* and *T. rhodesiense*. The animals which had been cured were for a considerable time immune to further inoculations. A dose of 0.0006 gram (about 0.0024 gram per kilo) would cure mice of their infections, and the animals were not reinoculable for a period of three months. Administered prophylactically before inoculation the drug prevented infection. The drug was then tried by Pfeiler³ (1920) in natural dourine in horses. The results in 200 horses thus treated were highly successful, and it is concluded that "Bayer 205" is efficient in the treatment and prophylaxis of dourine, and that it will be found to be equally successful in the treatment of sleeping-sickness and other trypanosome diseases. Miessner and Berge⁴ (1920) and Ellinger⁵ (1920) confirmed Pfeiler's results. In small animals the German workers employed the subcutaneous or intraperitoneal methods of injection.

Dr. C. R. Hennings gave a sample of the drug to Sir David Bruce, who handed it to me for trial. It was tested on a very virulent strain of *T. equiperdum* in mice.

The animals were inoculated intraperitoneally from another heavily infected animal. In forty-eight hours the blood showed very heavy infections, and if left untreated the animals died on this or the following day. In all cases the drug was given forty-eight hours after inoculation by the intravenous route when trypanosomes were swarming in the blood.

It was found that a dose of 0.0025 gram per kilogram of body weight would cause the trypanosomes to disappear, but that relapse occurred in about one week, the animals then dying of very heavy infections two or three days later. A dose of 0.005 gram per kilogram of body weight, however, has not been followed by any relapse during ten weeks' observation. The mice are quite healthy, and from what I know of the action of other trypanosomicidal drugs if relapse is to occur, as is practically always the case, it does so in mice within ten days. It may fairly safely be assumed that the minimal dose required to produce this apparent *sterilisans magna* in mice lies between 0.0025 and 0.005 gram per kilogram of body weight if the drug is administered intravenously.

These doses do not indicate the limit to which one can go. It is possible to give a mouse with a heavy infection as much as 0.5 gram per kilo of body weight. With this high dose there is, however, a definite and immediate reaction, and some of the animals succumb to its toxic effects within twenty-four hours. With half this dose (0.25 gram) the reaction is slight. The German workers pointed out that the ratio of the minimal therapeutic dose required to bring about a permanent cure to the maximal tolerated dose was 1 to 60, and the experiments just detailed bear this out. Employing the subcutaneous method, their maximal tolerated dose was higher than that obtained here by the intravenous method. The action of the drug is not immediate. The trypanosomes disappear gradually from the blood during the forty-eight hours following the injection. In the case of tartar emetic all trypanosomes may have disappeared in half an hour.

"Bayer 205" thus has a remarkable action on the trypanosomes, in that in every instance (over 50 mice) a single injection of a suitable dose has apparently brought about a *sterilisans magna*, and this in a dose which is considerably lower than that which can be given without killing the animals. There seems every reason to suppose that this drug, whatever may be its constitution—and this has not yet been made public—will be found to be a more efficient remedy than those hitherto used in cases of human and animal trypanosomiasis, if not in other diseases, such as kala-azar. I have tried

in animals most of the remedies which have previously been employed for the treatment of trypanosome diseases, and in no case has a permanent cure been obtained with single doses. The animals have invariably relapsed and have died of their infections. Thus, in the case of sodium antimony tartrate it is necessary to give mice intravenously a dose of 0.015 gram per kilo to cause the trypanosomes to disappear in twenty-four hours, while a dose of 0.05 will kill the animal in less than two days. The toxic dose is thus barely four times as great as the therapeutic dose. If a man of 70 kilograms is to receive the same proportionate dose he should be given $0.015 \times 70 = 1.05$ grams. In practice man is rarely given as much as 0.2 gram as a single dose, and this is often followed by marked reaction. The usual dose for a man is 0.1 gram (10 c.cm. of 1 per cent. solution), which, as will be seen, is about one-tenth of that required by the calculation based on mouse dosage. In the case of neo-salvarsan and its allies 0.02 gram per kilo of body weight may be taken as the minimal therapeutic dose for mice, while a dose of 0.3 gram per kilo of body weight may be tolerated. A man of 70 kilograms should then have a dose of $0.02 \times 70 = 1.4$, but in practice he is only given about half this amount, as larger doses produce severe reactions. In the case of these drugs, however, the therapeutic dose in mice does not effect a cure, but only brings about a temporary disappearance of trypanosomes. If the minimal therapeutic dose of "Bayer 205" is 0.005 gram per kilo of body-weight for mice the corresponding dose for man would be $0.005 \times 70 = 0.35$ gram. If the doses of sodium antimony tartrate and neo-salvarsan which can be tolerated by mice and man bear any relation to the doses of "Bayer 205" which can be given to mice and man, then there is every prospect that human beings will be able to tolerate a dose of 0.35 gram or even more, which is well up to the therapeutic dose required to bring about a permanent cure in animals. The dosage of "Bayer 205" for man, however, has to be determined by direct trial, as calculations based on animal dosage are full of fallacies. It is understood that this is now being done. It is also possible that different samples of the same drug may vary in their action, and the statements made here refer, of course, only to that particular one used by me.

The claims made for this drug by the German investigators, and which have been confirmed by the results detailed above, demonstrate that in experimental animals it has a remarkable trypanosomicidal action. There can be no doubt that the drug should be given a trial in naturally occurring cases of human and animal trypanosomiasis with a view to discovering if it will have in these as definite an action as it apparently has in that produced experimentally in small animals.

REFERENCES.

- ¹ Haendel and Joetten (1920): *Berliner klin. Wochenschrift*, No. 35 p. 821. ² Mayer and Zeiss (1920): *Archiv f. Schiff- und Tropenhygiene* vol. xxiv, No. 9. ³ Pfeiler (1920): *Veröffentlichungen der Tierseuchen stelle*, Jena, Nos. 5-6. ⁴ Miessner and Berge (1920): *Deutsche Tierärztliche Wochenschrift*, No. 11, p. 133. ⁵ Ellinger (1920): *Berliner Tierärztliche Wochenschrift*, p. 492.

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

GLYCOSURIA OF MALARIAL ORIGIN.

It may be of interest to record the fact, of which I became aware at the cost of a mistaken diagnosis, that transient glycosuria may occur during a malarial paroxysm.

The patient was a man of 30, suffering from bilateral apical subacute pulmonary tuberculosis, and confined to bed with mild intermittent pyrexia, the evening temperature being from 99° to 100° F. Tubercle bacilli were present in the sputum, and the urine was free from albumin or sugar. He had been under treatment in hospital for three weeks with this condition when, at 10 o'clock one morning, I found him confused, complaining of severe headache, and with a temperature of 104.2° F. There was no history of rigor. Having in mind the possibility of meningitis I sought for further physical signs, but, apart from the above condition, the only sign suggesting meningitis was the presence of sugar in the urine. According to Frew and Garrod,¹ glycosuria occurs

¹ *Lancet*, 1913, vol. i, p. 15.