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9. Idem. (1957). Idem. (Cinquième Rapport). Ibidem, *37*, 541-550.
10. Idem. (1958). Idem. (Sixième Rapport). Ibidem, *38*, 225-230.
11. VAN OYE, E., DEOM, J., VERCRUYSSE, J. & FASSEAUX, P. (1957). Recherches sur l'incidence des Salmonella chez les animaux de boucherie à Elisabethville. — Ann. Soc. belge Méd. trop., *37*, 551-558.
12. VAN OYE, E. & DEOM, J. (1958). Les Salmonelloses chez les oiseaux de basse-cour au Congo Belge et au Ruanda-Urundi. — Bull. Off. int. Epizoot. (sous presse).
13. STIJNS, J. & CHARLES, P. (1956). La tare thalassémique chez les Bantous d'Afrique centrale. — Ann. Soc. belge Méd. trop., *36*, 763-779.
14. VANDEPITTE, J., COLAERT, J., LAMBOTTE-LEGRAND, J. et C. & PERIN, F. (1953). Les ostéites à Salmonella chez les sicklanémiques. A propos de 5 observations. — Ann. Soc. belge Méd. trop., *33*, 511-522.
15. WIKTOR, T. & VAN OYE, E. (1955). Importance des animaux de boucherie comme propagateurs de salmonelloses humaines à Stanleyville. — Ann. Soc. belge Méd. trop., *35*, 825-831.

Drug Responses of the Sakwa Trypanosome (Heisch 1958).

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Concepts concerning the relationship of human and animal polymorphic trypanosomes evolved from the realm of speculation to experimental investigation when HEISCH, MCMAHON & MANSON-BAHR (1958) transmitted successfully a *brucei*-type trypanosome from bush bucks on Sakwa Peninsula, Lake Victoria, to rats, and from rats to man [2].

The pathogenicity of the Sakwa strain for rats and man favours the notion of a direct relationship between the trypanosomes found in the bush buck and *T. rhodesiense;* but it fails to exclude the thinkable, if remote, possibility suggested by FAIRBAIRN (personal communication), that the trypanosomes of the Sakwa buck derived from a human *T. gambiense* infection.

Additional evidence, supporting one or the other alternative, can be expected from the response of the Sakwa strain to drugs: *T. gambiense* is generally sensitive and *T. rhodesiense* resistant to tryparsamide, while both are sensitive to Mel B, syn. Arsobal (FRIEDHEIM; APTED).

Experiments reported in the following were designed to elucidate this question.

Methods.

107 white rats, weighing from 53 to 64 g., were infected i.p. by blood passage with the Sakwa strain which we received, by courtesy of Dr. HEISCH, in two rats infected in Nairobi. We refer to these two rats as "Nairobi rats" and to the strain received as the "Sakwa strain".

A first group of 41 rats was infected directly with blood from a Nairobi rat,

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[2] Conf. ASHCROFT 1958 & 1959; YORKE & BLACKLOCK 1914.

a second group of 40 rats with blood from a first rat passage [2] and a third group of 25 rats with blood from a fourth rat passage of the Sakwa strain.

Three to six days after infection all rats presented trypanosomes in the blood. The animals were distributed into 13 groups representative as to body weight and the intensity of the parasitemia.

Experiment 1. Four lots of 8 rats from group 1, representing the first blood passage of the Sakwa strain, were treated with a single i.p. dose of 400, 200, 100 and 50 mg./kg. of tryparsamide, respectively.

Experiment 2. Four lots of 8 rats from group 2, representing the second blood passage of the Sakwa strain, were treated with a single i.p. dose of 30, 15, 7.5 and 3.75 mg./kg. Mel B, respectively.

Experiment 3. Two lots of 8 and 9 rats of group 3, representing the fifth blood passage of the Sakwa strain, were treated with a single i.p. dose of 800 and 600 mg./kg. tryparsamide, respectively, followed four days later by a single i.p. dose of 15 mg./kg. Mel B.

Each experiment included an untreated control group of 8 simultaneously infected animals.

Blood was examined daily for trypanosomes during two weeks, then once a week up to two months after treatment (except Experiment 2). Schedules and findings are reported in tables 1-3.

Findings.

Effect of tryparsamide (Experiment 1, table I). Doses of 50-400 mg./kg. tryparsamide had no significant trypanocidal effect. Unabated, the parasitemia increased and all treated animals died 9-23 days after the infection (3-17 days after the treatment). The untreated control animals died 10-13 days after the infection. Individual survival-times vary, but in treated and untreated animals

TABLE I.

Effect of a single i.p. dose of tryparsamide.

Number of negative animals over the number of surviving animals.

Days after treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
I. Control	0/8	0/8	0/8	0/6	0/5	0/2	0										
II. 400 mg./kg.	0/8	0/8	0/5	0/5	0/3	0/3	0/3	0/3	0/2	0/2	0						
III. 200 mg./kg.	0/8	0/8	0/8	0/5	0/4	0/2	0/1	0									
IV. 100 mg./kg.	0/8	0/8	0/6	0/6	0/4	0/4	0/3	0/1	0/1	0							
V. 50 mg./kg.	0/8	0/8	0/8	0/7	0/7	0/4	0/3	0/2	0/2	0/2	0/2	0/1	0/1	0/1	0/1	0/1	0

[2] The number of passages mentioned in this paper means those realised since the strain has been received in Basle. Previously in Nairobi the strain had undergone 5 or 6 rat-passages since its isolation from a human volunteer.

alike the number of survivors fell to or below the 50% mark on the 11th or 12th day after the infection. It follows that tryparsamide had no significant effect on the life span of the treated animals.

Effect of Mel B (Experiment 2, table II). Single i.p. doses of 3.75 to 30 mg./kg. Mel B cleared the blood from trypanosomes in all animals, within 24 hours in doses of 7.5 mg./kg. and up, within 72 hours in the dose of 3.75 mg./kg. During the follow-up period of two months the relapse rate was nil for 30 mg./kg., one out of eight for 15 mg./kg., 2 out of 7 for 7.5 mg./kg. and 7 out of 8 for 3.5 mg./kg.

Effect of Mel B following tryparsamide (Experiment 3, table III). Confirming experiment 1, the blood of all 17 rats, distributed in two lots, was swarming with trypanosomes four days after a treatment with 800 and 600 mg./kg. tryparsamide, respectively. At this time all animals received an additional treat-

TABLE II.

Effect of a single i.p. dose of Mel B.

Number of negative animals over the number of surviving animals.

Days after treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	29	36	46	56
I. Control	0/8	0/8	0/8	0/8	0/4	0/3	0/1	0											
II. 30 mg./kg.	7/7									*				7/7	7/7	7/7	7/7	7/7	7/7
III. 15 mg./kg.	8/8									*				7/8	7/8	7/8	7/8	7/8	7/7
IV. 7.5 mg./kg.	7/7									7/7			6/7	6/7	4/5	4/4	4/4	4/4	4/4
V. 3.75 mg./kg.	6/8	6/8	8/8	8/8		6/8	6/8	4/8	2/8	2/8	3/7		2/7	1/6	1/5	1/3	1/3	1/2	1/2

* Probes.

TABLE III.

Effect of a single i.p. dose of tryparsamide (T) followed after four days by a single i.p. dose of Mel B (A).

Number of negative animals over the number of surviving animals.

Days after treatment	0 T	1	2	3	4 A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	28	35	42	49	56	63
I. Control	0/8	0/8	0/8	0/8	0/4	0/1	0/1	0																		
II. 800 mg./kg. T 15 mg./kg. A	0/8	0/8	0/8	0/8	0/8	8/8	8/8	8/8	8/8	8/8	8/8	8/8	8/8	6/6	—	6/6	5/6	4/6	4/6	4/6	3/6	3/5	3/5	3/5	3/5	3/3
III. 600 mg./kg. T 15 mg./kg. A	1/9	1/9	1/9	0/9	0/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9	—	9/9	8/9	7/9	7/9	5/9	5/6	5/5	5/5	4/4	4/4	4/4

ment with 15 mg./kg. Mel B i.p., which cleared the blood of all animals within 24 hours. In the course of the next three weeks two animals relapsed from the group of 8 pre-treated with 800 mg./kg., and four animals from the group of 9 pre-treated with 600 mg./kg. tryparsamide. The former survived for 34 and 37 days respectively after onset of the relapse, the latter for 10 to 15 days only.

Discussion.

While experiments 1 and 2 indicate that the Sakwa trypanosome is tryparsamide resistant and Mel B sensitive, it might be argued that the infections treated in these two experiments are not exactly comparable, representing in the tryparsamide experiment 1 a first, in the Mel B experiment a second blood passage of the strain received from Dr. HEISCH. This objection is countered by experiment 3, demonstrating the same (fifth) passage of the Sakwa strain, in identical animals, to be resistant to maxima doses of tryparsamide and sensitive to medium doses of Mel B.

Although the number of animals used precludes an exhaustive interpretation of variations in the course of the infection taken in individual animals, some particularities of experiment 3 are noteworthy: the relapse rate following a treatment with 15 mg./kg. Mel B on top of a massive tryparsamide treatment was higher — 2 out of 6 and 4 out of 9 (table III) — than in the infections of experiment 2 — 1 out of 8 (table II) — treated exclusively with 15 mg./kg. Mel B.

The infections studied in experiments 1, 2 and 3 represent respectively first, second and fifth blood passage of the strain received. The particularities appearing in experiment 3 point to incipient changes of the drug response in connection with an increasing number of blood passages. This is in keeping with the fundamental findings of MURGATROYD & YORKE 1937, that the response of trypanosomes to arsenicals is modified by repeated blood passages, but maintained by cyclic transmission. In particular, blood passages tend to decrease tryparsamide resistance.

While the detailed history of the Sakwa strain received is not on our record, it is reasonably certain that the tryparsamide resistance and Mel B sensitivity observed reflect properties of the original Sakwa trypanosome. Indeed, a secondary tryparsamide resistance could only be due to a systematic application of increasing doses of tryparsamide, or an unheard of mutation. Mechanisms of artificial sensibilisation to Mel B are unknown. To our knowledge, the strain received was previously not submitted to drugs of any description.

It appears that the experiments reported here were carried out, in the nick of time, before or at the brink of critical changes of the drug response, induced by blood passages. Additional blood passages significantly modified the drug response.

Summary and conclusions.

The Sakwa strain of man-pathogenic bush buck trypanosomes, isolated by Dr. HEISCH, transmitted by blood passages to rats, is highly resistant to tryparsamide and sensitive to Mel B, supporting the view of a close relationship between this polymorphic animal trypanosome and human *T. rhodesiense*. Indications prevail that the drug response is modified by repeated blood passages.

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References.

APTED, F. I. C. (1953). The treatment of advanced cases of Rhodesian sleeping sickness by Mel B and Arsobal. — Trans. roy. Soc. trop. Med. Hyg. *47,* 387-398.

ASHCROFT, M. T. (1958). An attempt to isolate *Trypanosoma rhodesiense* from wild animals. — Trans. roy. Soc. trop. Med. Hyg. *52,* 276-282.

— (1959). *Trypanosoma rhodesiense* in bushbuck. — Brit. med. J., Jan. 17, 173-174.

FRIEDHEIM, E. A. H. (1949). Mel B in the treatment of human trypanosomiasis. — Amer. J. trop. Med. *29,* 173-180.

HEISCH, R. B., MCMAHON, J. P. & MANSON-BAHR, P. E. C. (1958). The isolation of *Trypanosoma rhodesiense* from a bushbuck. — Brit. med. J., Nov. 15, 1203-1204.

MURGATROYD, F. & YORKE, W. (1937). Studies in Chemotherapy. XIII. The changes observed in *T. brucei* during five years maintenance in the laboratory. — Ann. trop. Med. Parasit. *31,* 145.

YORKE, W. & BLACKLOCK, B. (1914). The identity of *T. rhodesiense* with the trypanosome of the same appearance found in game. — Brit. med. J., June 6, 1234-1236.