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STUDIES ON THE TREATMENT OF HUMAN TRYPANOSOMIASIS WITH TRYPARSAMIDE (THE SODIUM SALT OF N-PHENYLGLYCINEAMIDE-*p*-ARSONIC ACID).

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INTRODUCTION.

The work in experimental chemotherapy of certain protozoan infections which has been in progress at the Rockefeller Institute for several years, has resulted in the development of a large series of compounds, of which one at least was found to possess a high degree of therapeutic activity in experimental trypanosomiasis. This substance, *N*-phenylglycineamide-*p*-arsonic acid, was first made in 1915 by Dr. WalterA. Jacobs and Dr. Michael Heidelberger (1 and 2) and studied biologically in collaboration with Dr. Wade H. Brown under its serial number of A 63; its sodium salt has recently been named "Tryparsamide." The biological investigations included toxicologic experiments (3) in which it was shown that the reaction of different species of laboratory animals to the drug was of a favorable character. The substance lends itself well to almost any method of administration and can be given to animals in large doses. Moreover, toxic effects were confined to doses relatively close to the minimum lethal dose and the recovery of animals from sublethal intoxication was remarkably rapid and complete, thus making possible the repetition of large doses at comparatively short intervals of time. The therapeutic activity of the drug in experimental trypanosomiasis (4) was particularly evidenced by the relative speed and sharpness of action in the acute blood infections of mice and rats and by the potency and duration of action in the subacute and chronic tissue infections of guinea pigs and rabbits. The accomplishment of a permanent cure was obtained in the experimental infections produced by five strains of pathogenic trypanosomes, *Tr. brucei*, *Tr. gambiense*, *Tr. evansi*, *Tr. equiperdum*, and *Tr. equinum*, but, on the other hand, infections produced by *Tr. rhodesiense* were more difficult to influence (5). Comparative experiments in laboratory animals with well known drugs such as atoxyl, arsacetin, arsenophenylglycin, salvarsan, neosalvarsan, luargol, and galyl, all of which have been used in the treatment of human trypanosomiasis, showed that tryparsamide was in many respects their superior.

An appraisal of the probable value of any drug, with a view to its use in the treatment of human beings or animals suffering from naturally acquired trypanosomal infections, must be based upon the interpretation of the experimental results obtained with the drug in

the laboratory. The various attributes or features of the toxicologic and therapeutic action of tryparsamide, as brought out by laboratory investigation and briefly enumerated above, constituted a logical basis for its application to the treatment of human and animal trypanosomiasis. This conclusion is emphasized by recalling the results of the use of several drugs in human trypanosomiasis, for which various claims had been made on the basis of limited or mistakenly interpreted experimental data. For instance, arsacetin, arsenophenylglycin, salvarsan, and neosalvarsan all possess a high curative ratio in experimental trypanosomiasis of mice and largely upon this basis were transferred to the field of human therapy and that of the large domestic animals. The regrettable toxic effects sometimes noted and the failure to obtain the desired therapeutic action under the conditions imposed by the disease, might have been foretold if requisite laboratory experiments had been carried out and correctly interpreted. A similar statement may be made of so called trypanocidal tests made *in vitro*. On the other hand, the better therapeutic results obtained with atoxyl are entirely in accord with the results of the laboratory experiments carried out by Thomas and Breinl (6 and 7) and aptly illustrate the point in question.

At the present time, human trypanosomiasis, or the so called African sleeping sickness, is very prevalent in tropical Africa, particularly in the central and western portions of the continent, in the French and Belgian Congos. Epidemics of varying degrees of severity are widespread and constitute one of the most pressing problems confronting colonial governments. Although great progress has been made in the fight against the disease and notably so in the treatment of patients in the early stages of the infection by the use of atoxyl or by the combined treatment with atoxyl and tartar emetic, it is apparent that the means of combating the disease, particularly in its more advanced stages and in prophylaxis against its spread, are not at present adequate. Whether the ideal control of an infection of the nature of trypanosomiasis will ever be accomplished by a single drug, in the sense that quinine is used to control malaria, is problematical. In any event, the various aspects of the situation in Africa today are such that the colonial officials are very ready to try any new remedy, itself harmless, for the treatment of sleeping sickness which holds out

a promise of some degree of success. The biological experiments referred to indicated that tryparsamide might fill some place in the therapy of the disease and consequently a mission was sent by the Rockefeller Institute to the Belgian Congo in May, 1920, to study the effect of the drug in patients suffering with trypanosomiasis.

It is obvious that any extended application of a new remedy for administration in human beings must be preceded by a careful study of its action in relatively few patients irrespective of the scope of the initial investigations in the laboratory. In a problem such as the therapy of human trypanosomiasis as just indicated, it is of the utmost importance to ascertain such fundamental facts as the initial speed of therapeutic activity of various sized single doses, as measured by the length of time required to clear the superficial lymph glands and blood of trypanosomes and the permanency of this effect; the action of the drug, if any, in the advanced stages of the disease as indicated by examination of the spinal fluid and the mental and nervous response of the patient; the general physical reaction of the patient as shown by weight observations, blood counts, etc.; and finally, the determination of any untoward observable effects. On the basis of a series of such facts obtained in a certain number of patients, a rational system of therapeutic procedure can then be logically attempted.

The object of the mission sent to the Belgian Congo was the obtaining of concrete facts and observations as outlined above. All of the work was done at the government laboratory and Hôpital de la Reine in Léopoldville. The helpful cooperation of the Belgian and Colonial Governments made it possible to accomplish a considerable amount of work in a comparatively short time and it is a pleasure to express here our appreciation of the aid so cordially extended to us, first in Brussels and then in the Congo. We also wish to acknowledge the assistance given us by Professor Rodhain, Chief of the Colonial Medical Service, and by Dr. van den Branden, Director, and Dr. van Hoof, Assistant Director of the Laboratory in Léopoldville.

SOURCE AND TYPE OF PATIENTS.

The observations which form the basis of this report were made on 77 native cases of trypanosomiasis caused by *Tr. gambiense* which were treated with tryparsamide in Léopoldville, Belgian Congo. The

civil service of the Belgian Congo has established throughout the colony, medical stations and posts under the charge of government physicians and traveling sanitary agents, in addition to which a considerable amount of medical work is done by various religious missions. The native population is thus examined for trypanosomiasis at more or less regular intervals, the routine procedure consisting of the palpation of the cervical lymph glands and the microscopic examination of lymph gland juice from those individuals having one or more palpable cervical glands. At the present time, there is no widespread epidemic of a severe character in the immediate vicinity of Léopoldville but there are many endemic foci of the disease in this district, while a few days' travel brings one into active epidemic areas. The patients treated with tryparsamide were entirely typical of the routine run of trypanosomiasis cases met with in Léopoldville. The population of the nearby native villages comes *en masse* to the laboratory every 3 months for examination and several cases were obtained in this way. Moreover, Léopoldville is the terminus of one of the large river transportation companies and a medical passport issued after examination for trypanosomiasis, is required of any native traveling from one part of the colony to another. The entire crew of each boat is examined the day before sailing and this source yielded a number of cases from distant parts of the colony. Finally, several advanced cases under treatment in the native Hôpital de la Reine and lazaret in Léopoldville were transferred to us for treatment with tryparsamide. All of the patients studied thus fell into three general classes: First, those who were sent to the lazaret, which is in reality a native village under nominal native police control on the outskirts of Léopoldville, and who came to the laboratory when sent for; second, patients in the Hôpital de la Reine, over whom a closer supervision could be maintained; and third, ambulatory cases, corresponding to dispensary patients, who continued to live in their own villages and who came to the laboratory at certain fixed times.

According to the recognized authorities on human trypanosomiasis, the course of the disease may be divided into two periods, the glandular or blood infection stage and the cerebral stage. The first stage is characterized principally by a polyadenitis, most apparent in the

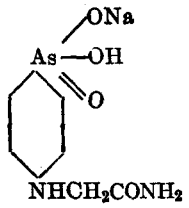
cervical glands, an irregular intermittent fever, a rapid pulse (the rate of which is usually out of proportion to the fever), an enlarged spleen, an erythematous eruption in whites, a fine tremor of the tongue, a deep hyperesthesia, and asthenia. Localized edemas are sometimes seen. Trypanosomes are present in the hypertrophied lymph glands and in the blood. The number of lymphocytes in the spinal fluid is normal. The second period, in which the infection has invaded the cerebrospinal system, is characterized by the aggravation of the general symptoms such as fever, emaciation, loss of strength, and by the predominance of cerebrospinal symptoms such as tremors, paralysis, mental disturbances, apathy, somnolence, lethargy, and finally coma and death. In this period, the spinal fluid is pathologically altered, the conspicuous feature of which is an increase in the lymphocytic (small mononuclear) cell content with other types of cells (large mononuclears and so called mulberry cells) in the more advanced cases (8 and 9). Trypanosomes are present in the spinal fluid of the most advanced cases while they are said to be less numerous in the lymph glands and blood than in the early cases.

The 77 cases treated with tryparsamide represented all grades of the infection and included previously untreated patients as well as several who had been treated with one or more drugs for varying lengths of time. With the exception of 8 patients who were being treated at the time of their transfer to us, trypanosomes were demonstrated in every case as follows: in 67 cases by gland punctures; in 1 case in the centrifuged blood; in 1 case in the spinal fluid. A lumbar puncture was done before treatment in 72 instances—it was omitted in the case of 1 infant and 4 ambulatory patients.

The study of tryparsamide was carried out under the same conditions that prevail in the laboratory, lazaret, and native hospital in Léopoldville, under which the routine treatment with atoxyl and tartar emetic is given. Under the conditions prevailing, complete clinical records were not obtainable and the observations were necessarily confined to certain definite fields. In addition, mention should be made of the fact that the native population of West Africa suffers widely from other affections such as subacute and chronic malaria, filariasis, and intestinal parasites, of which little or no attention could be taken.

ADMINISTRATION OF TRYPARSAMIDE.

Tryparsamide, or the sodium salt of *N*-phenylglycineamide-*p*-arsonic acid, is a pentavalent arsenic compound having the following structural formula:



Its preparation and chemical properties have been fully described by Jacobs and Heidelberger in previous publications (1 and 2). It is a white crystalline substance of stable character and has been kept in ordinary tightly stoppered bottles for long periods of time and under various climatic conditions without appreciable change. It was found that the same procedures of preparation of drug solution employed in the experimental work (3 and 4) were entirely applicable to the preparation of the drug for human therapy.

As the drug is bottled under aseptic conditions, the addition of sterile distilled water with the usual precautions for preventing contamination is all that is required. Sterilization of the drug solution is not necessary. The dose for each patient was in most instances weighed out separately on a balance and dissolved in a small sterile petri dish or flask with the appropriate amount of sterile distilled water. It is entirely feasible, however, to prepare the doses for several patients at one time and to administer the requisite amount of the drug to each. The drug is extremely soluble in water in concentrations as high as 50 per cent. In most instances, a 20 per cent solution was used, but varying strengths, from 10 to 40 per cent, were also employed.

The drug is readily administered intravenously and this route obviously offers the most uniform condition for the observation of various sized doses. When injected directly into the tissues, it is quickly absorbed and produces but slight irritation or local injury. However, the African native exhibits little objection to intravenous

medication while opposing injection into the subcutaneous or intramuscular tissues. In a few patients injections deeply into the muscles of the buttocks could be made and the effects studied.

ADMINISTRATION OF SINGLE DOSES IN EARLY CASES.

Initial Peripheral Sterilization.

The characteristics of human trypanosomiasis would seem to preclude any idea of materially influencing the course of the disease by the administration of a single dose of any drug and the experience of tropical workers indicates that a series of treatments covering a period of months or years is necessary. Untreated cases eventually die and it is the general opinion that only comparatively slight and temporary benefit accrues to patients in the advanced or cerebrospinal stage of the disease from the drugs hitherto in use. Before any system of treatment can be intelligently attempted, it is necessary to determine the duration of therapeutic action of single doses since the

TABLE I.

Results of Early Gland Puncture After Single Doses of Tryparsamide.

Number of patients—55.
Size of doses—0.3 to 7.0 gm. or 4.7 to 112 mg. per kilo of body weight.
Routes of administration—Intravenous 51.
Intramuscular 4.

Results:

All examinations negative within 24 hours after treatment.
20 " " " 4½ to 9 hours after treatment.
10 " " " 10 to 15 " " "
13 " " " 15½ to 20 " " "
12 " " " 21 to 24 " " "

Time of negative examination after treatment.	Doses of 0.3 to 1.0 gm. 4.7 to 25 mg. per kg.	Doses of 1.0 to 3.0 gm. 33 to 50 mg. per kg.	Doses of 2.0 to 5.0 gm. 54 to 70 mg. per kg.	Doses of 4.0 to 7.0 gm. 80 to 112 mg. per kg.
I. 4½ to 9 hours.....		10	4	6
II. 10 to 15 "	3	3	3	1
III. 15½ to 20 "	4	3	3	3
IV. 21 to 24 "	4	4	2	2
Total.....	11	20	12	12

giving of succeeding doses should be governed by this factor. In addition, this information is of importance in the prophylactic use of a drug. Incidentally, it was desirable to ascertain the approximate rapidity of the preliminary or so called sterilizing effect of a given dose as shown by repeated microscopic examinations of lymph gland juice or of centrifuged blood. A number of such observations were made, which are summarized in Tables I and II. The patients represent both early and advanced periods of the disease in which trypanosomes were demonstrated before treatment in the lymph glands or blood.

The gland punctures of 55 patients were all negative within 24 hours after treatment with single doses of tryparsamide varying from 0.3 to 7.0 gm. or 4.7 to 112 mg. per kilo of body weight; 30 examinations were negative within the first 15 hours, 25 from 15 to 24 hours after treatment, irrespective of the size of the dose (Table I). It should be pointed out that these results do not imply that an examination one or more hours previous to the negative finding was positive, as it was not always possible to make a complete series of examinations at frequent intervals since microscopic work could only be done in the daytime and consequently a relative and not absolute interpretation must be placed upon the observations. In 14 cases, trypanosomes were found microscopically in lymph gland juice 3 to 8 hours after doses of 1.0 to 5.0 gm., while the examinations repeated within the succeeding 21 to 16 hours were invariably negative. The following examples are typical of the results obtained:

Makalamba № 49. +. Tryparsamide 1.0 gm. or 19 mg. per kilo.
Gland puncture: 6 hours +; 19½ hours 0.

Mondeke № 47. +. Tryparsamide 2.0 gm. or 33 mg. per kilo.
Gland puncture: 5½ hours +; 6 hours 0.

Masimango № 16. ++. Tryparsamide 2.0 gm. or 42 mg. per kilo.
Gland puncture: 6 hours +; 20 hours 0.

Tono № 14. ++. Tryparsamide 2.0 gm. or 44 mg. per kilo.
Gland puncture: 8 hours +; 9 hours 0.

Loyoko № 18. ++. Tryparsamide 3.0 gm. or 50 mg. per kilo.
Gland puncture: 5 hours +; 8 hours 0.

Kaniki № 58. +++. Tryparsamide 2.5 gm. or 58 mg. per kilo.
Gland puncture: 5 hours +; 21 hours 0.

Tuamene ✱68. ++. Tryparsamide 5.0 gm. or 82 mg. per kilo.
Gland puncture: 3 hours +; 8 hours 0.
N'Siola ✱32. +. Tryparsamide 4.0 gm. or 100 mg. per kilo.
Gland puncture: 4 hours +; 6 hours 0.

In contrast to the above examples, the following 3 cases are of interest in that gland punctures were positive 14 and 19 hours after treatment. The doses used however, in terms of amounts of drug per kilo of body weight were comparatively small and the infection of 2 patients was unusually severe.

Bikoko ✱55. +++. Tryparsamide 0.3 gm. or 4.7 mg. per kilo.
Gland puncture: 19 hours +; 22 hours 0.
Molalo ✱60. +. Tryparsamide 1.0 gm. or 20 mg. per kilo.
Gland puncture: 14 hours +; 16 hours 0.
Tsarjembe ✱74. +++. Tryparsamide 2.0 gm. or 37 mg. per kilo.
Gland puncture: 14 hours +; 15 hours 0.

Thus, it is seen that with amounts above 25 mg. per kilo, 27 of the examinations were negative within the first 15 hours, while 9 were negative in from $15\frac{1}{2}$ to 20 hours. 20 patients were treated with doses of 1.0 to 3.0 gm. or 33 to 50 mg. per kilo of body weight, of which 10 were negative within 9 hours, 3 within 10 to 15 hours, 3 within $15\frac{1}{2}$ to 20 hours, and 4 within 21 to 24 hours. Considering together the doses of from 33 to 70 mg. per kilo of body weight and combining the results of the second and third columns of Table I, it is seen that 14 of the 32 patients, or approximately one half, were negative within the first 9 hours, while there were 6 negative examinations each in the succeeding periods of time. Concerning smaller doses (4.7 to 25 mg. per kilo), all that can be said at present is that the examinations of the 11 patients so treated were all negative within 24 hours and there was practically no difference between the second, third, and fourth periods of time, *i. e.*, it is probable that all 11 were negative within 15 hours after treatment. With the larger doses of 80 to 112 mg. per kilo of body weight 6 of the 12 patients gave negative gland punctures within the first 9 hours after treatment. 4 patients were given doses of 1.0, 2.0, and 3.0 gm. intramuscularly with no delay in negative gland puncture.

The preliminary effect of the drug upon the blood infection may next be considered, since in reality so called peripheral sterilization includes both the superficial lymph glands and the circulating blood. The patients in this group represent both early and advanced periods of the disease of different degrees of severity. Doses of 1.0 to 5.0 gm. or 18 to 109 mg. per kilo of body weight were administered intravenously, and at periods ranging from 15 minutes to 30 hours afterwards 9 cc. of blood were withdrawn in a syringe containing 1 cc.

TABLE II.

Results of Early Blood Examination after Single Doses of Tryparsamide.

Number of patients—35.
Size of dose—1.0 to 5.0 gm. or 18 to 109 mg. per kilo of body weight.
Intravenous administration.

Results:

All negative within 21 hours after treatment.
14 " " 3½ to 9 hours after treatment.
13 " " 10 to 15 hours " "
8 " " 16 to 21 hours " "

Time of negative examination after treatment.	Doses of 1.0 gm. 18 to 25 mg. per kg.	Doses of 1.0 to 2.5 gm. 33 to 48 mg. per kg.	Doses of 3.0 to 5.0 gm. 51 to 70 mg. per kg.	Doses of 2.0 to 5.0 gm. 71 to 109 mg. per kg.
I. 3½ to 9 hours.....	1	5	2	6
II. 10 to 15 "	2	5	3	3
III. 16 to 21 "	3	1	4	
Total.....	6	11	9	9

of a 6 per cent sodium citrate solution and the mixture was then centrifuged three times according to the method described by Broden (10). The three sediments were examined microscopically for trypanosomes. The results of these examinations of 35 patients are condensed in Table II and may be described briefly: All the examinations were negative in 21 hours, 14 were negative in 3½ to 9 hours, 13 in 10 to 15 hours, and 8 in 16 to 21 hours, irrespective of the size of the dose administered. There were 11 patients treated with single doses of 1.0 to 2.5 gm. or 33 to 48 mg. per kilo of body weight and

5 of the 11 showed negative blood examinations within 9 hours after treatment, and 10 were negative within 15 hours. Combining the results of these doses with those of 51 to 70 mg. per kilo as shown in the second and third columns, 15 out of the 20 patients so treated were negative within 15 hours. Somewhat larger doses of 2.0 to 5.0 gm or 71 to 109 mg. per kilo of body weight were given to 9 patients, all of whom were negative in 15 hours and 6 negative within 9 hours after treatment.

As in the microscopic examination of lymph gland juice, it was not possible to make complete series of observations. In these 35 patients, the last positive blood examinations occurred from 3 to 8 hours after treatment with doses of 1.0 to 3.0 gm. or 18 to 51 mg. per kilo. The following examples illustrate these points:

Molalo № 60. Tryparsamide 1.0 gm. or 20 mg. per kilo.
Centrifuged blood: 16 hours 0.
Mafuala № 30. Tryparsamide 1.0 gm. or 25 mg. per kilo.
Centrifuged blood: 6 hours 0.
Mago № 28. Tryparsamide 1.0 gm. or 33 mg. per kilo.
Centrifuged blood: 7½ hours 0.
Messamba № 57. Tryparsamide 2.0 gm. or 39 mg. per kilo.
Centrifuged blood: 7 hours +; 21 hours 0.
Mondi № 75. Tryparsamide 2.0 gm. or 44 mg. per kilo.
Centrifuged blood: 3½ hours 0.
Mulamba № 39. Tryparsamide 3.0 gm. or 51 mg. per kilo.
Centrifuged blood: 3 hours +; 8 hours 0.
Mondeke № 47. Tryparsamide 4.0 gm. or 66 mg. per kilo.
Centrifuged blood: 6½ hours 0.
Mambula № 43. Tryparsamide 2.0 gm. or 71 mg. per kilo.
Centrifuged blood: 6 hours +; 8 hours 0.
Bajaka № 41. Tryparsamide 4.0 gm. or 76 mg. per kilo.
Centrifuged blood: 15 hours 0.
Bikoko № 55. Tryparsamide 5.0 gm. or 80 mg. per kilo.
Centrifuged blood: 5 hours 0.

The negative gland and blood findings after treatment were controlled by subsequent examinations as indicated by the following examples:

Bikoko #55.

Admitted to lazaret September 22, 1920. 64.5 kilos.
Cervical lymph glands markedly enlarged. Gland puncture +++.
Lumbar puncture normal.

1920											
Sept. 22,	5 p.m.	Tryparsamide 0.3 gm. (4.7 mg. per kg.) adm. i.v.									
" 23,	7 a.m.	14 hours after treatment				G. P.	+	(2 tryp.)			
	9 a.m.	16	"	"	"	"	"	+	(2 ")		
	12 n.	19	"	"	"	"	"	+	(1 ")		
	3 p.m.	22	"	"	"	"	"	0			
	5 p.m.	24	"	"	"					C.B.	0
" 24,	9 a.m.	40	"	"	"	"	"	0			
" 25,		3 days		"	"	"	"	0			
" 27,		5	"	"	"	"	"	+	(1 tryp.)	" "	+
" 27,	11.30 a.m.	Tryparsamide 5.0 gm. (80 mg. per kilo) adm. i.v.									
	4.30 p.m.	5 hours after treatment								C.B.	0
	5 p.m.	5½	"	"	"	G. P.	0				
" 28,	7 a.m.	19½	"	"	"					" "	0
	10 a.m.	22½	"	"	"	"	"	0			
Oct. 2,		4 days		"	"	"	"	0			
" 4,		6	"	"	"	"	"	0		" "	0

Tsarjembe #74.

Admitted for ambulatory treatment October 11, 1920. 53½ kilos.
Cervical lymph glands enlarged, typical chains. Gland puncture +++.
Centrifuged blood ++.
Lumbar puncture 19 lymphocytes per cmm. Large mononuclears ++.

1920										
Oct. 11,	5 p.m.	Tryparsamide 2.0 gm. (37 mg. per kg.) adm. i.v.								
" 12,	7 a.m.	14 hours after treatment				G. P.	+	(2 tryp.)		
	8 a.m.	15	"	"	"	"	"	0	C. B.	0
	9 a.m.	16	"	"	"	"	"	0		
	10 a.m.	17	"	"	"				" "	0
	11 a.m.	18	"	"	"	"	"	0		
" 13,		7 days after treatment				"	"	0	" "	0

Mondongo # 5.

Admitted to lazaret July 14, 1920. 47 kilos.
Cervical lymph glands enlarged. Gland puncture +.
Lumbar puncture 7.5 lymphocytes per cmm.

1920											
July	14,	10 a.m.	Tryparsamide 2.0 gm. (43 mg. per kg.) adm. i.v.								
		11 a.m.	1 hour	after	treatment		G. P.	+			
		12 m.	2	"	"	"	"	"	+		
		3 p.m.	5	"	"	"	"	"	+		
		5 p.m.	7	"	"	"	"	"	+		
"	15,	7 a.m.	21	"	"	"	"	"	0		
		9 a.m.	23	"	"	"	"	"	0		
		11 a.m.	25	"	"	"	"	"	0		
"	16,		2 days	"	"	"	"	"	0		
"	19,		5	"	"	"	"	"	0		
"	20,		6	"	"	"	"	"	0		
"	21,		7	"	"	"	"	"	0		
"	22,		8	"	"	"	"	"	0		
"	27,		13	"	"	"	"	"	0		
Aug.	3,		20	"	"	"	"	"	0	C. B.	0
"	9,		26	"	"	"	"	"	0		
"	17,		34	"	"	"	"	"	0	" "	0
"	24,		41	"	"	"	"	"	0	" "	0
"	31,		48	"	"	"	"	"	0		
Sept.	2,		50	"	"	"				" "	0
"	7,		55	"	"	"	"	"	0		
"	14,		62	"	"	"	"	"	0	" "	0
"	22,		70	"	"	"	"	"	0	" "	0
"	29,		77	"	"	"	"	"	0	" "	0
Oct.	5,		83	"	"	"	"	"	0		
"	6,		84	"	"	"				" "	0
"	13,		91	"	"	"	"	"	0		
"	15,		93	"	"	"				" "	0
"	21,		99	"	"	"				" "	0
"	23,		Tryparsamide 0.5 gm. (Provocative dose).								
"	26,						G. P.	0	C. B.	0	
"	30,		Tryparsamide 0.5 gm. (2nd Provocative dose).								
Nov.	2,						G. P.	0	C. B.	0.	

Mondi #75.

Admitted for ambulatory treatment October 22, 1920. 45 kilos.
Cervical lymph glands enlarged. Gland puncture +.
Centrifuged blood +.
Lumbar puncture not done.

1920							
Oct. 22,	11.45 a.m.	Tryparsamide 2.0 gm. (44 mg. per kg.) adm. i.v.					
	3.15 p.m.	3½ hours after treatment				C. B.	0
	4 p.m.	4¼	"	"	G. P.	0	
	5 p.m.	5¼	"	"		C. B.	0
" 23,	7 a.m.	18¾	"	"		" "	0
	9 a.m.	20¾	"	"	" "	0	

Victor Makau #77.

Admitted as ambulatory patient October 27, 1920. 57 kilos.
Cervical lymph glands enlarged. Gland puncture +++.
Centrifuged blood +++.
Lumbar puncture 3.8 lymphocytes per cmm. (1 large mononuclear seen.)

1920							
Oct. 28,	9 a.m.	Tryparsamide 1.0 gm. (18 mg. per kg.) adm. i.v.					
	9.15 a.m.	15 minutes after treatment				C. B.	+++
	10 a.m.	1 hour	"	"		" "	+++
	11 a.m.	2 hours	"	"		" "	+
	12 n.	3	"	"		" "	+
	3.30 p.m.	6½	"	"		" "	+++
	4 p.m.	7	"	"	G. P.	+++	
	5 p.m.	8	"	"		" "	++
" 29,*	8 a.m.	23	"	"	" "	0	
	3 p.m.	30	"	"		" "	0

* Patient was quite ill the second day and only a gland puncture could be done at 8 a. m.

Itoma № 78.

Admitted for ambulatory treatment October 29, 1920. 52 kilos.
Cervical lymph glands enlarged. Gland puncture ++.
Lumbar puncture deferred. Very advanced stage.

1920						
Oct. 29, 5.30 p.m.	Tryparsamide 1.0 gm. (19 mg. per kg.) adm. i.v.					
" 30, 6.30 a.m.	13 hours after treatment				C. B.	0
7 a.m.	13½ "	"	"	G. P. 0		
9 a.m.	15½ "	"	"	" " 0	" "	0

Tuamene № 68.

Admitted to lazaret October 5, 1920. 62.5 kilos.
Cervical lymph glands enlarged.
Gland puncture ++. Centrifuged blood ++.
Lumbar puncture 5 lymphocytes per cmm. (1 large mononuclear seen.)

1920								
Oct. 5, 11 a.m.	Tryparsamide 5.0 gm. (80 mg. per kg.) adm. i.v.							
5 p.m.	6 hours after treatment			G. P.	0	C. B.	0	
" 6, 8 a.m.	21 "	"	"	"	"	0		
" 14,	9 days	"	"	"	"	0		
" 21,	16 "	"	"	"	"	0		
" 22,	17 "	"	"			"	"	0
" 28,	23 "	"	"	"	"	0	"	" 0
" 30,	25 "	"	"	"	"	+	"	" +
Nov. 1, 8 a.m.	Tryparsamide 5.0 gm. (82 mg. per kilo) adm. i.v.							
11 a.m.	3 hours after treatment			G. P.	+			
12 n.	4 "	"	"			C. B.	+	
3 p.m.	7 "	"	"			"	"	+
4 p.m.	8 "	"	"	"	"	0		
5 p.m.	9 "	"	"			"	"	0
" 2, 8 a.m.	24 "	"	"			"	"	0

The deduction from this series of observations on the effect of a single dose of tryparsamide administered intravenously to a mixed group of patients infected with *Tr. gambiense* is, briefly expressed, as follows: Doses of tryparsamide of 1.0 to 5.0 gm. bring about peripheral sterilization as indicated by negative findings for trypanosomes in lymph gland juice and centrifuged blood in an average of 6 to 12 hours. It would appear that a similar speed of action follows the intramuscular injection of the drug.

Duration of Peripheral Sterilization after Single Doses.

21 patients were treated with single doses of tryparsamide of 0.5 to 5.0 gm. or from 9 to 83 mg. per kilo of body weight and followed with frequent microscopic examinations of lymph gland juice and centrifuged blood to ascertain the permanence of therapeutic effect as expressed by the duration of the peripheral sterilization. Table III summarizes the protocols of the 12 patients who relapsed after single doses of from 0.5 to 5.0 gm. of tryparsamide or from 17 to 83 mg. per kilo of body weight, while Table IV summarizes the records of 9 patients who showed no demonstrable relapse following treatment with single doses of 0.5 to 3.0 gm. or 9 to 68 mg. per kilo. All patients were either in the first period of the disease or at the beginning of the second as shown by the slight excess in the cell count of the spinal fluid, 3 lymphocytes per cmm. being considered normal (10). The drug was administered intravenously except in 4 cases in which the intramuscular route was employed.

TABLE III.

Relapses after Single Doses of Tryparsamide.
Intravenous Administration.

Case No.	Name.	Weight.	Spinal fluid.	Dose.	Dose.	Relapse.	Time after treatment.
		kg.		*gm.*	*mg. per kg.*		*days*
50	Moangolo.....	29.5	Normal.	0.5	17	C. B. + G. P. −	29
48	M'Bondo.....	50	5	1.0	20	C. B. + G. P. +	23
28	Mago.....	33	5	1.0	33	C. B. + G. P. +	19
47	Mondeke.....	61	7.5	2.0	33	C. B. + G. P. +	26
43	Mambula.....	27	7.5	1.0*	37	C. B. + G. P. −	58
36	Sudila.....	46	20	2.0	44	C. B. + G. P. −	50
63	N'Kaka.....	42.5	Normal.	2.0	47	C. B. + G. P. +	17
39	Mulamba.....	55.5	4	3.0*	54	C. B. + G. P. −	45
41	Bajaka.....	53	15	3.0*	57	C. B. + G. P. −	37
42	N'Keta.....	36	10	2.0*	57	C. B. + G. P. +	51
68	Tuamene.....	62.5	5	5.0	80	C. B. + G. P. +	25
53	Ganzema.....	36	3.4 (1 l. m.)	3.0	83	C. B. + G. P. +	21

l. m.—Large mononuclear.
* Intramuscular administration.

In the first group as shown in Table III, there were 2 relapses at 17 and 19 days (Mago #28 and N'Kaka #63), 5 from 21 to 29 days (Ganzema #53, M'Bondo #48, Mondeke #47, Tuamene #68, and Moangolo #50), 2 at 37 and 45 days (Bajaka #41 and Mulamba #39), and 3 from 50 to 58 days (Sudila #36, N'Keta #42, and Mambula #43). The following protocols illustrate the method of determining the time of relapse after treatment.

Moangolo # 50.

Admitted to hospital September 7, 1920. 29.5 kilos.
Cervical lymph glands enlarged. Gland puncture +.
Lumbar puncture normal.

1920										
Sept.	7,	11.30	a.m.	Tryparsamide 0.5 gm. (17 mg. per kg.) adm. i.v.						
"	10,	3	days	after	treatment	G. P.	0			
"	15,	8	"	"	"	" "	0			
"	17,	10	"	"	"	" "	0			
"	20,	13	"	"	"	" "	0			
"	24,	17	"	"	"	" "	0			
"	25,	18	"	"	"	" "	0	C. B.	0	
Oct.	1,	24	"	"	"	" "	0			
"	4,	27	"	"	"	" "	0	" "	0	
"	5,	28	"	"	"	" "	0			
"	6,	29	"	"	"	" "	+	" "	+	

M'Bondo # 48.

Admitted to lazaret August 30, 1920. 50 kilos.
Cervical lymph glands enlarged. Gland puncture +++.
Lumbar puncture 5 lymphocytes per cmm.

1920										
Aug	31,	11.45	a.m.	Tryparsamide 1.0 gm. (20 mg. per kg.) adm. i.v.						
		3.15	p.m.	3½	hours	after	treatment	G. P.	++	
		4.45	p.m.	5	"	"	"	" "	++	
Sept.	1,	7	a.m.	19	"	"	"			C. B. 0
		9	a.m.	21	"	"	"	" "	0	
"	6,			6	days	"	"	" "	0	
"	11,			11	"	"	"			" " 0
"	17,			17	"	"	"	" "	0	" " 0
"	20,			20	"	"	"	" "	0	
"	23,			23	"	"	"	" "	+	" " +

Mondeke #47

Admitted to lazaret August 28, 1920. 61 kilos.
Cervical lymph glands enlarged. G. P. +.
Lumbar puncture 7.5 lymphocytes per cmm.

1920											
Aug.	28,	11 a.m.	Tryparsamide 2.0 gm. (33 mg. per kg.) adm. i.v.								
		4.30 p.m.	5½	hours	after	treatment	G. P.	+ (1 tryp.)			
		5 p.m.	6	"	"	"	"	" 0	C. B.	0	
Sept.	6		9	days	"	"	"	" 0			
"	10,		13	"	"	"	"	" 0			
"	11,		14	"	"	"			"	"	0
"	17,		20	"	"	"	"	" 0	"	"	0
"	20,		23	"	"	"	"	" 0			
"	23,		26	"	"	"	"	" + (1 tryp.)	"	"	+ (2 tryp.)

Sudila #36.

Admitted for ambulatory treatment August 19, 1920. 46 kilos.
Gland puncture +.
Lumbar puncture 20 lymphocytes per cmm.

1920										
Aug.	19,	5 p.m.	Tryparsamide 2.0 gm. (44 mg. per kg.) adm. i.v.							
"	20,	6 a.m.	13	hours	after	treatment	G. P.	0		
		6.30 a.m.	13½	"	"	"			C. B.	0
"	26		7	days	"	"	"	" 0		
"	31,		12	"	"	"	"	" 0		
Sept.	2,		14	"	"	"			"	" 0
"	7,		19	"	"	"	"	" 0		
"	14,		26	"	"	"	"	" 0		
"	21,		33	"	"	"	"	" 0		
"	22,		34	"	"	"			"	" 0
"	28,		40	"	"	"	"	" 0		
Oct.	5,		47	"	"	"	"	" 0		
"	8,		50	"	"	"			"	" +
"	9,		51	"	"	"	"	" 0		

It so happens that 8 of the 12 relapsed cases, including Tuamene #68 and Ganzema #53, who were given the largest amounts of drug per kilo, came from so called "virulent" districts or villages[1] and that

[1] Certain sections of the Belgian Congo are known as "severe" or "virulent" districts because the infection acquired there is more difficult to influence therapeutically than that of other places.

M'Bondo #48, Mago #28, and Tuamene #68 showed an unusually heavy gland infection at the time of treatment, in fact the most marked of any of the 21 patients considered in these two groups. The spinal fluids of the relapsed cases, moreover, showed greater abnormality than those of the non-relapses (Table IV). Doubtless these factors contribute towards the shortening of the duration of action of the drug but it is not possible to define their effects with accuracy and the point is merely alluded to here.

The duration of negative gland and blood examinations resulting from the intramuscular injection of tryparsamide in 4 patients was appreciably longer than that observed after the intravenous route and since this mode of administration possesses obvious advantages, particularly in field work, abstracts of these cases are given:

Mambula ✻43.—Young boy from a "virulent" region. Severe lymph gland infection. Spinal fluid, 7.5 lymphocytes per cmm. Treated with 1.0 gm. tryparsamide (37 mg. per kilo of body weight) in 3.0 cc. of water, injected into the deep muscles of the left buttock. Slight transitory local tenderness lasting a few hours.

Gland puncture negative 21½ hours after treatment; 12 subsequent microscopic gland examinations and 5 examinations of centrifuged blood were negative during 56 days. A second lumbar puncture 34 days after treatment showed a normal cell count (2.1 lymphocytes per cmm.)—a decrease from the initial count.

A relapse was finally detected 58 days after treatment by the finding of 1 trypanosome in the centrifuged blood. Gland puncture was negative.

Mulamba ✻39.—Soldier who had been in a "virulent" region during the previous year. Moderate lymph gland infection; spinal fluid contained 4 lymphocytes per cmm. Treated with 3.0 gm. tryparsamide (54 mg. per kilo) in 10 cc. of water injected deeply into muscles of the right buttock. The following morning, 14½ hours after treatment, gland puncture was negative and there was no induration or tenderness of the injection area. Patient reported slight local discomfort after the injection lasting a few hours. No cells were found in the spinal fluid examined 35 days after treatment, contrasting with the 4 per cmm. before treatment. 9 gland punctures and 3 examinations of centrifuged blood during the succeeding 42 days were negative but on the 45th day after treatment, one trypanosome was found in the centrifuged blood. Gland puncture negative.

Bajaka ✻41.—Adult man from a "virulent" region. Severe lymph gland infection; spinal fluid contained 15 lymphocytes per cmm. Treated with 3.0 gm. tryparsamide in 9 cc. of water (57 mg. per kilo), injected deeply into the muscles of the left buttock. Gland puncture negative 6 hours later at which time patient complained of soreness in the injection area. During the next 2 days,

soreness disappeared and 6 days after injection, there was only a slight induration and slight tenderness on deep pressure of this area.

During 35 days after treatment, the microscopic examination of 8 gland punctures and 3 centrifuged bloods were negative but on the 37th day, 2 trypanosomes were found in the centrifuged blood. Gland puncture was negative.

A second examination of the spinal fluid 35 days after treatment showed 7.5 lymphocytes—a 50 per cent decrease—but 2 large mononuclear cells were also seen indicating the continued involvement of the cerebrospinal system.

N'Keta # 42.—Young woman from a "virulent" region Suffering from extensive craw-craw. Severe lymph gland infection. Spinal fluid contained 10 lymphocytes per cmm. Treated with 2.0 gm. tryparsamide (57 mg. per kilo) in 6.0 cc. of water injected deeply into the muscles of the left buttock. Gland puncture negative 7 hours later.

During the following week, injection area became considerably indurated and quite tender although patient was able to walk; there was considerable loss of weight (2.5 kilos), a rapid pulse, subnormal temperature and patient appeared ill. By the end of the second week after treatment, there was but slight residual tenderness on deep pressure, very little induration of a small area and patient's general condition had improved.

Microscopic examination of 9 specimens of lymph gland juice and 5 of centrifuged blood over a period of 48 days were negative but 51 days after treatment 1 trypanosome was found in both the lymph gland and centrifuged blood examinations.

A second spinal fluid examination 34 days after treatment showed a normal cell content (0.6 lymphocytes per cmm.), contrasting with the original count of 10 lymphocytes per cmm.

Several points of interest are brought out in the above four abstracts: In only 1 patient was there any considerable discomfort lasting more than a few hours in the area of intramuscular injection. This patient had a marked case of craw-craw and in addition was indescribably dirty. Although the skin of the injection area was cleansed with iodine and alcohol, probably an infection of some kind was set up in the deep muscles, resulting in a tender area of induration which was absorbed within 2 weeks. Similar effects following the intramuscular injection of other drugs are not unusual under such circumstances according to the experience of the physicians in Léopoldville. Next, the time of initial therapeutic action of the drug is comparable with that observed after intravenous administration of the drug. Thus in these 4 cases with severe lymph gland infection, negative punctures were obtained within 21½ hours and, in the cases in which earlier

examination could be made, 6 to 14½ hours after intramuscular injections of doses of 54 and 57 mg. per kilo of body weight. Moreover, the action of single doses of from 1.0 to 3.0 gm. (37 to 57 mg. per kilo of body weight) lasted from 37 to 58 days. These 4 patients came from a region in which the trypanosomal disease is recognized as more difficult to influence than in other places and, although all 4 patients ultimately suffered relapses, it is noteworthy that moderate sized doses controlled the recurrence of lymph gland and blood infection for from 5 to 8 weeks. Finally, a distinct effect was observed in the spinal fluid in that the cell count was decreased in all four patients, the second lumbar puncture being done 5 weeks after treatment. Thus, Mambula #43, showed a decrease from 7.5 to 2.1 lymphocytes per cmm.; Mulamba #39 from 4.0 to 0 lymphocytes; N'Keta #42 from 10 to 0.6 lymphocytes and Bajaka #41 from 15 to 7.5 lymphocytes per cmm. Although the patients treated intramuscularly are comparatively few in number, the results obtained are clear cut and suggest that with this method of administration the drug may remain available in a biologically active state for a period of time perhaps exceeding that of the intravenous route.

TABLE IV.

Non-Relapses after Single Doses of Tryparsamide. Intravenous Administration.

Case No.	Name.	Weight.	Spinal fluid.	Dose.	Dose.	Non-relapse.	Time after treatment.
		kg.		*gm.*	*mg. per kg.*		*days*
40	Esombo.....	51	Normal.	0.5	9	C. B. — G. P. —	109
38	Daie.....	46	(?)R.B.C.	1.0	22	C. B. — G. P. —	40*
30	Mafuala.....	39.6	5	1.0	25	C. B. — G. P. —	75
46	Bokao.....	50	5	2.0	40	C. B. — G. P. —	67
5	Mondongo.....	47	7.5	2.0	43	C. B. — G. P. —	111
45	K. Georges.....	38.5	Normal.	2.0	52	C. B. — G. P. —	68
37	Bukasa.....	54.5	12.5	3.0	55	C. B. — G. P_1 —	69
51	Gwamuntele....	44	Normal.	3.0	67	C. B. — G. P. —	54
31	Lubaki.....	44.5	Normal.	3.0	68	C. B. — G. P. —	75

* Considered a relapse because of probable increase of cell content of spinal fluid, 37 days after treatment.

Table IV summarizes the records of 9 patients treated intravenously with single doses of tryparsamide of from 0.5 to 3.0 gm. or from 9 to 68 mg. per kilo of body weight, in whom return of trypanosomes in the lymph glands or blood from 40 to 111 days after treatment was not demonstrable. As will be seen by comparing Tables III and IV, similar sized doses were given to the two groups of patients. The type and stage of the infection of the non-relapsed patients were as follows: 4 showed slightly abnormal spinal fluids, Mafuala #30, 5; Bokao #46, 5; Mondongo #5, 7.5; and Bukasa #37, 12.5 lymphocytes per cmm.; while 4 had normal spinal fluid cell counts—Esombo #40, K. Georges #45, Gwamuntele #51, and Lubaki #31. In one instance, Daie #38, the spinal fluid was contaminated with blood so that an accurate cell count could not be made. Although trypanosomes were readily found by microscopic examination of the lymph gland juice or of centrifuged blood before treatment, in general, the lymph gland infection was not a heavy one except in the case of Bukasa #37. In addition, none of these patients had come, as far as could be ascertained, from the "virulent" regions referred to. Hence, these cases may represent a less advanced period of the disease and a somewhat less virulent type of infecting organism than the majority of patients listed in Table III.

Although patient Daie #38 is included in Table IV because no trypanosomes were found in the lymph gland juice, centrifuged blood, or centrifuged spinal fluid for 40 days after treatment with 1.0 gm. of tryparsamide, the probable increase in the cells of the spinal fluid, together with an increased pulse rate, loss of weight, and negative malarial examination made it seem probable that a relapse had really occurred and consequently a system of repeated dose therapy was begun.

With this exception, the 8 patients who were under close observation for 54 to 111 days and who received a single dose of tryparsamide of from 9.0 to 68 mg. per kilo suffered no relapse as far as could be discovered. For comparison, one other case may be mentioned in which no relapse occurred although the period of observation was only 26 days. This patient, Talamene #73, came from an active epidemic area with a severe lymph gland infection; his spinal fluid was normal. He was given 4.0 gm. of tryparsamide or 109 mg. per

kilo intravenously. Gland puncture was negative 14 hours and centrifuged blood 15 hours after treatment. Subsequent examinations were also negative for 26 days but as it was feared that he would run away, the drug was repeated systematically. The observations on this patient may be compared with those on 2 others, Tuamene #68 and Ganzema #53, who relapsed (Table III); the lymph gland infection of Talamene #73 and Tuamene #68 were both severe, while Ganzema #53 came from a village known to furnish particularly difficult cases. They were given doses of 80 and 83 mg. per kilo which produced peripheral sterilization for 25 and 21 days respectively. In the case of Talamene #73, the larger dose of 109 mg. per kilo resulted in negative lymph gland and blood examinations for at least 26 days.

The following protocols illustrate the time and frequency of examinations carried out with the patients who showed no return of trypanosomes during the period of observation:

Esombo # 40.

Admitted for ambulatory treatment August 24, 1920. 51.0 kilos.
Cervical lymph glands enlarged. Gland puncture +.
Lumbar puncture normal.

1920						
Aug. 24, 4.30 p.m.	Tryparsamide 0.5 gm. (9.0 mg. per kg.) adm. i.v.					
" 25, 7.30 a.m.	15 hours after treatment	G. P. 0				
Sept. 1,	8 days	"	"	"	" 0	
" 7,	14 "	"	"	"	" 0	
" 13,	20 "	"	"			C. B. 0
" 14,	21 "	"	"	"	" 0	
" 21,	28 "	"	"	"	" 0	
" 22,	29 "	"	"			" " 0
" 25,	32 "	"	"	"	" 0	
" 28,	35 "	"	"	"	" 0	
Oct. 5,	42 "	"	"	"	" 0	
" 8,	45 "	"	"			" " 0
" 12,	49 "	"	"	"	" 0	
" 19,	56 "	"	"	"	" 0	" " 0
" 20,	57 "	"	"			" " 0
" 21,	58 "	"	"	"	" 0	
" 26,	63 "	"	"			" " 0
Dec. 11,	109 "	"	"			" " 0

Mafuala # 30.

Admitted to lazaret August 16, 1920. 39.6 kilos.
Cervical lymph glands enlarged. Gland puncture +.
Centrifuged blood +. Lumbar puncture normal.

1920												
Aug.	16,	11 a.m.	Tryparsamide 1.0 gm. (25 mg. per kg.) adm. i.v.									
		5 p.m.	6	hours	after	treatment	G.	P.	0	C.	B.	0
"	17,	8 a.m.	21	"	"	"	"	"	0			
"	19,		3	days	"	"				"	"	0
"	24,		8	"	"	"	"	"	0			
"	31,		15	"	"	"	"	"	0			
Sept.	3,		18	"	"	"				"	"	0
"	6,		21	"	"	"	"	"	0			
"	14,		29	"	"	"	"	"	0			
"	20,		35	"	"	"				"	"	0
"	23,		38	"	"	"	"	"	0	"	"	0
"	27,		42	"	"	"	"	"	0			
Oct.	1,		46	"	"	"	"	"	0			
"	6,		51	"	"	"				"	"	0
"	12,		57	"	"	"	"	"	0			
"	15,		60	"	"	"				"	"	0
"	19,		64	"	"	"	"	"	0			
"	20,		65	"	"	"				"	"	0
"	21,		66	"	"	"	"	"	0			
"	25,		70	"	"	"				"	"	0
"	30,		75	"	"	"	"	"	0	"	"	0

Bukasa # 37.

Admitted to lazaret August 21, 1920. 54.5 kilos.
Cervical lymph glands enlarged. Gland puncture ++.
Lumbar puncture 12.5 lymphocytes per cmm.

1920												
Aug.	21,	5.30 p.m.	Tryparsamide 3.0 gm. (55 mg. per kg.) adm. i.v.									
"	22,	6 a.m.	12½	hours	after	treatment	G.	P.	0			
		7 a.m.	13½	"	"	"				C.	B.	0
Sept.	3,		13	days	"	"				"	"	0
"	10,		20	"	"	"	"	"	0			
"	17,		27	"	"	"	"	"	0			
"	20,		30	"	"	"				"	"	0
"	28,		38	"	"	"	"	"	0			
Oct.	4,		44	"	"	"	"	"	0			
"	6,		46	"	"	"	"	"	0			
"	7,		47	"	"	"				"	"	0
"	14,		54	"	"	"	"	"	0			
"	15,		55	"	"	"	"	"	0			
"	19,		59	"	"	"				"	"	0
"	25,		65	"	"	"				"	"	0
"	29,		69	"	"	"				"	"	0

Lubaki ♯ 31.

Admitted to lazaret August 16, 1920. 44.5 kilos.
Cervical lymph glands palpable. Gland puncture 0.
Centrifuged blood +. Lumbar puncture normal.

1920					
Aug. 16,	11.15 a.m.	Tryparsamide 3.0 gm. (68 mg. per kg.) adm. i.v.			
" 17,	8.30 a.m.	21 hours after treatment			C. B. 0
" 24,		8 days " "	G. P. 0	" "	0
Sept. 4,		19 " " "		" "	0
" 14,		29 " " "	" " 0	" "	0
" 23,		38 " " "	" " 0	" "	0
" 30,		45 " " "	" " 0		
Oct. 7,		52 " " "		" "	0
" 12,		57 " " "	" " 0		
" 15,		60 " " "		" "	0
" 21,		66 " " "	" " 0		
" 25,		70 " " "		" "	0
" 30,		75 " " "	" " 0	" "	0

TABLE V.

Summary of Relapses and Non-Relapses after Single Doses of Tryparsamide.

Doses of from 9 to 33 mg. per kg. of body weight.			Doses of from 37 to 52 mg. per kg. of body weight.			Doses of from 54 to 83 mg. per kg. of body weight.		
Name.	Dose.	Result.	Name.	Dose.	Result.	Name.	Dose.	Result.
	gm.	*days*		*gm.*	*days*		*gm.*	*days*
40 Esombo....	0.5	0 109	43 Mambula...	1.0	+ 58	39 Mulamba...	3.0	+ 45
50 Moangolo..	0.5	+ 29	46 Bokao.....	2.0	0 67	37 Bukasa.....	3.0	0 69
48 M'Bondo...	1.0	+ 23	5 Mondongo..	2.0	0 111	41 Bajaka.....	3.0	+ 37
30 Mafuala...	1.0	0 75	36 Sudila.....	2.0	+ 50	42 N'Keta.....	2.0	+ 51
28 Mago.....	1.0	+ 19	63 N'Kaka	2.0	+ 17	51 Gwamuntele	3.0	0 54
47 Mondeke...	2.0	+ 26	45 K. Georges.	2.0	0 68	31 Lubaki.....	3.0	0 75
						68 Tuamene...	5.0	+ 25
						53 Ganzema...	3.0	+ 21
2 Non-relapses. 4 Relapses in average of 24 days or 3 weeks.			3 Non-relapses. 3 Relapses in average of 42 days or 6 weeks.			3 Non-relapses. 5 Relapses in average of 36 days or 5 weeks.		

In considering the length of time of peripheral sterilization in relation to the size of the dose, it will be of assistance to glance at Table V which groups together the instances of relapse and non-

relapse of Tables III and IV according to the amount of drug administered. Daie #38 is not included since we were uncertain of the result. The first column of Table V contains the results of the treatment of 6 patients with doses of from 9 to 33 mg. per kilo of body weight or, with the usual size of the native in the lower Congo, a dose of from 0.5 to 2.0 gm. Of these 6 patients, 4 suffered a relapse in from 19 to 29 days or on an average of 24 days, a little over a 3 weeks' period. The 2 non-relapsed patients, of whom one had received the small dose of 9.0 mg. per kilo of body weight, were still clear 109 and 75 days after treatment. In the second group, 6 patients were treated with amounts ranging from 37 to 52 mg., usually a 2.0 gm. dose, and 3 relapsed in from 17 to 58 days or on an average of 42 days or 6 weeks. The instances of non-relapse in this group had been under observation respectively for 67, 68, and 111 days. In the third group comprising 8 patients who received 2.0, 3.0, and 5.0 gm. doses, or from 54 to 83 mg. per kilo of body weight, 5 relapsed in from 21 to 51 days or on an average of 36 days or practically 5 weeks. The 3 non-relapsed patients were clear 54, 69, and 75 days after treatment.

Speaking generally, there is apparently not a great deal of difference between the results obtained with what might be called average doses, that is, 2.0 and 3.0 gm.—as shown in columns 2 and 3 of Table V—since the average negative period for trypanosomes was 6 and 5 weeks respectively. There is a distinct shortening of this period, however, after the smaller doses of 0.5 and 1.0 gm. as shown by the average figure of 3 weeks. Thus it appears that once a certain amount of drug is biologically available for therapeutic action, it may be unnecessary to increase the size of the dose above this amount which represents a favorable ratio between rate of absorption and elimination and duration of action on the parasites.

However, from the point of view of planning a system of repeated doses, especially with a new or little tried drug, one is not justified in the beginning in working with averages of duration of peripheral sterilization. The shortest period of sterilization was 17 days after a dose of 2.0 gm. or 47 mg. per kilo of body weight and accordingly two principal systems of therapy were planned. These consisted in giving average doses of 2.0, 3.0, and 4.0 gm. according to the weight

of the patient at weekly or fortnightly intervals for 4 to 8 injections. A number of patients were thus treated toward the end of our stay in the Congo, the results of which will be sent to us by the Belgian physician in charge of the cases in Léopoldville.

Effect of Single Doses upon the Spinal Fluid.

The effect of a drug upon the spinal fluid of patients suffering from trypanosomiasis is of great importance, since the natural evolution of the disease is toward involvement of the cerebrospinal system. The ultimate outcome of certain cases is at once problematical if the therapeutic field of action of a drug is limited, practically speaking, to that of so called peripheral sterilization, while if the cerebrospinal system is included in its sphere of action and the effect of its administration is reflected in the spinal fluid, the therapeutic possibilities of the drug are at once extended. Thus, in cases of human trypanosomiasis in the first stage in which the spinal fluid is normal, it is essential to ascertain if that condition continues so or whether, despite the negative blood and lymph gland examination, the cerebrospinal axis may be invaded.

Moreover, in those cases in which some invasion has already taken place as indicated by a slight pleocytosis, the selection of a drug which tends to limit the further progress of the disease is urgently called for. Finally, in the advanced cases with more or less cerebrospinal involvement and alteration of the spinal fluid, such an agent is obviously indicated.

Broden and Rodhain (8, 9, and 10) have shown that in human trypanosomiasis, the cell content of the spinal fluid may be looked upon as an index of the extent of cerebrospinal involvement, thus serving as a diagnostic criterion and a therapeutic guide. They consider that a normal spinal fluid contains no more than 3 lymphocytes (small mononuclears) per cmm.;[2] and that in the cerebrospinal stage of the disease, the first abnormality to be noted is an increase in the lymphocytes which is followed in the more advanced cases by

[2] The cells are counted directly by means of a Fuchs-Rosenthal chamber, immediately after the withdrawal of a few cubic centimeters of spinal fluid which is not centrifuged.

the appearance of medium sized mononuclear cells and so called mulberry cells or large vacuolated mononuclear cells (*cellules en mûre*). The very advanced cases, on the other hand, may show extremely large vacuolated cells, rare polymorphonuclear cells with eosinophilic granules and cells which apparently have become detached from the surface of the meninges. Although minor variations in the cell count of the spinal fluid occurs from time to time, in general, once the cerebrospinal system has become affected, progress tends to be continuous with increasing abnormality of the spinal fluid. Trypanosomes may be found in the centrifuged spinal fluid of the more advanced cases, but it is not always practical to withdraw the necessary amounts of fluid for this procedure. The nature of the infection in these cases is usually readily established by gland puncture or examination of centrifuged blood so that demonstration of trypanosomes in the spinal fluid was not attempted as a routine measure.

The effect, therefore, of the administration of tryparsamide upon the spinal fluid was carefully followed. The usual procedure was: A lumbar puncture was done before treatment and from 3 to 10 cc. of fluid removed and the cells counted. The period of the disease was based on the results obtained irrespective of other clinical findings. The manner of treatment was also determined by this procedure since when a moderate or marked alteration in the cell content was found more vigorous treatment than a single dose of the drug was indicated. A second lumbar puncture was done about 5 weeks later, and when possible, again at some more remote date; more frequent punctures were not made as the patients were ambulatory, and, in addition, we wished to avoid so called drainage changes which might result from such a procedure.

In Table VI are given the cell counts of 14 patients before and after treatment with single doses of tryparsamide. This number includes 9 patients in whom no return of trypanosomes in the blood or lymph glands was detected during the period of observation after treatment and 5 who eventually relapsed but whose second lumbar puncture was done before this occurred. The cell content of the spinal fluids was normal or showed a slight increase up to 20 lymphocytes per cmm. Single does of 0.5 to 3.0 gm. or 9 to 68 mg. per kilo of body weight were administered intravenously to 10 and intramuscularly to 4 patients.

The second lumbar puncture was done approximately 5 weeks after treatment in all the patients except Sudila #36 and Gwamuntele #51, in whom the interval between the first and second lumbar puncture was 40 and 47 days and in the case of Mondongo #5, in which it was 26 days. It will be noted that with the exception of Daie #38, the second examinations showed no increase in the cell

TABLE VI.

Cell Content of Spinal Fluid after Single Doses.

Case No.	Name.	Weight.	Dose.	Dose.	Cell content before treatment.	Cell content after treatment.	Interval between treatment and 2nd L. P.	Remarks.	
		kg.	*gm.*	*mg. per kg.*			*days*		*days*
40	Esombo.....	51	0.5	9	Normal.	Normal.	35	No relapse	109
38	Daie.....	46	1.0	22	(?)R.B.C.	35 (1 l.m.)	37	No relapse (?)†	
30	Mafuala....	39.6	1.0	25	5	4.6	37	No relapse	75
43	Mambula...	27	1.0*	37	7.5	Normal.	34	Relapse	58
46	Bokao.....	50	2.0	40	5	Normal.	34	No relapse	67
5	Mondongo..	47	2.0	43	7.5	5	26	No relapse	111
						3 (2 l.m.)	93		
36	Sudila.....	46	2.0	44	20	Normal.	40	Relapse	50
45	K. Georges..	38.5	2.0	52	Normal.	Normal.	34	No relapse	68
39	Mulamba...	55.5	3.0*	54	4	Normal.	35	Relapse	45
37	Bukasa.....	54.5	3.0	55	12.5	Normal.	38	No relapse	69
42	N'Keta.....	36	2.0*	57	10	Normal.	34	Relapse	51
41	Bajaka	53	3.0*	57	15	7.5 (2 l.m.)	35	Relapse	37
51	Gwamuntele.	44	3.0	67	Normal.	Normal.	47	No relapse	54
31	Lubaki	44.5	3.0	68	Normal.	Normal.	37	No relapse	75

l.m.—Large mononuclears.

* Intramuscular administration.

† Cf. Table IV.

content; but 4, Esombo #40, K. Georges #45, Gwamuntele #51, and Lubaki #31, continued to be normal; and 2, Mafuala #30 and Mondongo #5, whose original counts were 5 and 7.5 lymphocytes per cmm., showed practically no change, 4.6 and 5 lymphocytes per cmm. respectively. On the other hand, 6 patients whose spinal fluids showed slight changes before treatment (Mambula #43, 7.5; Bokao

#46, 5; Sudila #36, 20; Mulamba #39, 4; Bukasa #37, 12.5; N'Keta #42, 10) all had normal cell counts at the time of the second examination. One patient, Bajaka #41, with an initial cell content of 15, showed 7.5 lymphocytes 35 days after treatment but as 2 large mononuclears were seen in the counting chamber, it is probable that the influence of the drug was less marked than in the other cases. This patient came from a "virulent" region and at the time of treatment had a very severe lymph gland infection. A third lumbar puncture done 93 days after a single dose of 2.0 gm. in one patient, Mondongo #5, showed 3 lymphocytes or a normal count but, as in the case of Bajaka #41, 2 large mononuclears having been seen, according to the standards established by Broden and Rodhain, the possibility of some degree of cerebrospinal involvement must be considered. Finally, one patient, Daie #38, showed what was apparently a progression of the disease. An accurate initial cell count was impossible because the spinal fluid was contaminated with blood but the second cell count, done 37 days after treatment with the small dose of 22 mg. per kilo of body weight, showed 35 lymphocytes per cmm., and 1 large mononuclear in the counting chamber. No trypanosomes were found in centrifuged specimens of the spinal fluid and repeated examinations of lymph glands and blood had been negative since treatment. As there had been a loss of 1.5 kilos in weight and no malarial parasites were found and as 4 days before the second lumbar puncture the pulse had risen from the usual rate of 72 to 80 to 92, this man was transferred to the group of patients being treated with repeated doses of tryparsamide.

The observations just described indicate that in the first period of the disease or in the very early stages of the second period, single small and medium doses of tryparsamide will in nearly all cases be followed by beneficial effects as indicated by the influence upon the cell content of the cerebrospinal fluid. Perhaps it may be permissible to go even further than this and to state that in these early stages an arrest of the disease has been achieved although it must be remembered that there is no criterion of the time of occurrence of cerebrospinal involvement and no prediction of the duration of the observed effect can be made.

Effect of Single Doses upon the Blood.

The blood condition of natives suffering from trypanosomiasis is often complicated by the presence of one or more other infections. In the lower and middle Congo regions, almost every native shows an enlarged spleen and chronic malaria; moreover, skin infections, filariasis, intestinal parasites, and amœbiosis are common, and venereal disease is frequent. Keeping in mind these facts, most authorities agree that the blood changes in human trypanosomiasis consist of diminution of red cells, decrease in hemoglobin, and normal or slightly subnormal white cells associated with a relative increase of mononuclear cells and a decrease of granular leukocytes.

Blood counts were followed in 12 patients in the early period of the disease or at the period of slight abnormality of the cerebrospinal fluid. Single doses of tryparsamide, ranging from 0.5 to 5.0 gm. were given intravenously to 10 and intramuscularly to 2 patients (Table VII) including 8 non-relapsed subjects who had negative lymph gland and blood examinations during the period of observation; 1 patient, who had not relapsed 26 days after treatment but who was transferred to the series of repeated doses at this time and 3 relapsed patients from whom a second blood count had been obtained before trypanosomes were again found in the lymph glands or blood. The time of the second blood examination in relation to the first, taken on the day of treatment, ranged from 26 to 63 days.

At the first count, there was in these cases a marked decrease in hemoglobin and a somewhat less decrease in the red cells or an anemia of the secondary type. Only 2 patients showed an original increased or normal red cell count; 4 showed counts of 4 million; 4 showed counts between 3 and 4 million, and 2 patients showed only 2 and $2\frac{1}{2}$ million red cells.

The injection of a single dose of tryparsamide (0.5 to 5.0 gm.) was followed in 41 to 63 days by an increase in the number of red cells in 7 patients ranging from 10 to 60 per cent as shown in Table VIII. One patient, Tuamene #68, showed an increase of 15 per cent in 28 days, while in two others, Bukasa #37 and Mondongo #5, the increase was 47 and 60 per cent in 60 and 41 days respectively. In 3 patients with initial counts of 4 million, Talamene #73, Lubaki #31, K. Georges

TABLE VII.

Changes in Blood Counts after Single Doses of Tryparsamide.

Case No.	Name.	Dose adm. i. v.	1st blood count.	2nd blood count.	Change.	Time after treatment of 2nd count.
					per cent	*days*
40	Esombo.....	0.5 gm.	R. B. C. 5,760,000	6,400,000	+10	63‡
	51 kg.	9.0 mg.	Hb. 55 %	70 %	+27	
		per kg.	W. B. C. 10,800	9,600	−11	
30	Mafuala	1.0 gm.	R. B. C. 4,960,000	4,048,000	−18	37§
	39.6 kg.	25 mg.	Hb. 65 %	70 %	+ 8	
		per kg.	W. B. C. 6,400	8,000	+20	
				4,480,000†	−10†	66†
				65 %	−	
				8,000	+20	
43	Mambula	1.0 gm.*	R. B. C. 4,000,000	4,800,000	+20	48‡
	27 kg.	37 mg.	Hb. 60 %	80 %	+33	
		per kg.	W. B. C. 4,200	6,000	+43	
46	Bokao	2.0 gm.	R. B. C. 3,840,000	4,640,000	+21	54
	50 kg.	40 mg.	Hb. 60 %	70 %	+17	
		per kg.	W. B. C. 5,000	6,600	+32	
5	Mondongo.....	2.0 gm.	R. B. C. 2,000,000	3,200,000	+60	41‖
	47 kg.	43 mg.	Hb. 35%	55 %	+57	
		per kg.	W. B. C. 5,400	9,800	+81	
				3,360,000†	+68†	105†
				55 %	+57	
				12,000	+122	
45	K. Georges.....	2.0 gm.	R. B. C. 4,032,000	4,000,000	−	56‡
	38.5 kg.	52 mg.	Hb. 50 %	60 %	+20	
		per kg.	W. B. C. 8,200	9,000	+10	
37	Bukasa.....	3.0 gm.	R. B. C. 2,490,000	3,656,000	+47	60
	54.5 kg.	55 mg.	Hb. 40 %	70 %	+75	
		per kg.	W. B. C. 5,200	6,000	+15	
42	N'Keta	2.0 gm.*	R. B. C. 3,200,000	3,200,000	−	30**
	36 kg.	57 mg.	Hb. 35 %	45 %	+29	
		per kg.	W. B. C. 4,000	7,600	+90	

TABLE VII—*Continued.*

Case No.	Name.	Dose. adm. i. v.	1st blood count.	2nd blood count.	Change.	Time after treatment of 2nd count.
					per cent	*days*
51	Gwamuntele....	3.0 gm.	R. B. C. 3,200,000	4,000,000	+25	51‡
	44 kg.	67 mg.	Hb. 40 %	55 %	+38	
		per kg.	W. B. C. 3,600	5,000	+39	
31	Lubaki.....	3.0 gm.	R. B. C. 4,000,000	4,000,000	−	37††
	44.5 kg.	68 mg.	Hb. 65 %	70 %	+8	
		per kg.	W. B. C. 4,700	5,600	+19	
				4,800,000†	+20†	70†
				65 %	−	
				8,000	+70	
68	Tuamene.....	5.0 gm.	R. B. C. 3,680,000	4,240,000	+15	28
	62.5 kg.	80 mg.	Hb. 50 %	60 %	+20	
		per kg.	W. B. C. 8,000	8,000	−	
73	Talamene.....	4.0 gm.	R. B. C. 4,000,000	4,000,000	−	26
	36.5 kg.	109 mg.	Hb. 50 %	65 %	+30	
		per kg.	W. B. C. 4,000	6,000	+50	

* Administered intramuscularly.
† 3rd blood count.
‡ Estivo-autumnal malaria.
§ Estivo-autumnal malaria (?).
‖ Multiple skin ulcers; filariasis; chronic amœbiosis (?).
** Craw-craw; intramuscular abscess.
†† Filariasis.

#45, and in one, N'Keta #42, with a count of 3 million red cells, there was no change noted after 26 to 56 days; 2 of these patients, K. Georges #45 and N'Keta #42, suffered from acute concurrent infections during this period; Lubaki #31 ultimately showed an increase of 20 per cent, 70 days after treatment; and in the case of Talamene #73 the interval between the counts was comparatively short, 26 days. One patient, Mafuala #30, whose first count was 5 million red cells, showed a decrease of 18 per cent in 37 days but in a third count 66 days after treatment the decrease amounted to 10 per cent.

TABLE VIII.

Changes in the Red Blood Cell Counts of Patients Treated with Single Doses of Tryparsamide.

Case No.	Name.	Dose.	Original R. B. C. before treatment.	R. B. C. after treatment.	Change.	Interval between counts.
		mg. per kg.			*per cent*	*days*
5	Mondongo	43	2,000,000	3,200,000 3,360,000	+60 +68	41 105
37	Bukasa	55	2,490,000	3,656,000	+47	60
42	N'Keta	57	3,200,000	3,200,000	—	30
51	Gwamuntele	67	3,200,000	4,000,000	+25	51
68	Tuamene	80	3,680,000	4,240,000	+15	28
46	Bokao	40	3,840,000	4,640,000	+21	54
43	Mambula	37	4,000,000	4,800,000	+20	48
31	Lubaki	68	4,000,000	4,000,000 4,800,000	— +20	37 70
73	Talamene	109	4,000,000	4,000,000	—	26
45	K. Georges	52	4,032,000	4,000,000	—	56
30	Mafuala	25	4,960,000	4,048,000 4,480,000	−18 −10	37 66
40	Esombo	9	5,760,000	6,400,000	+10	63

TABLE IX.

Changes in Hemoglobin Content of Blood after Single Doses of Tryparsamide.

Case No.	Name.	Dose.	Original hemoglobin content before treatment.	Hemoglobin content after treatment.	Change +.	Interval between examinations.
		mg. per kg.	*per cent*	*per cent*	*per cent*	*days*
5	Mondongo	43	35	55	57	41
42	N'Keta	57	35	45	29	30
37	Bukasa	55	40	70	75	60
51	Gwamuntele	67	40	55	38	51
45	K. Georges	52	50	60	20	56
68	Tuamene	80	50	60	20	28
73	Talamene	109	50	65	30	26
40	Esombo	9	55	70	27	63
43	Mambula	37	60	80	33	48
46	Bokao	40	60	70	17	54
30	Mafuala	25	65	65	—	66
31	Lubaki	68	65	65	—	70

The hemoglobin content of the blood, determined by a Sahli hemoglobinometer, was generally increased after treatment with tryparsamide as shown in Table IX. In 10 of the patients in this group, the hemoglobin content rose from 17 to 75 per cent during periods of from 26 to 63 days after single dose treatment while 2 patients each with an original hemoglobin of 65 per cent showed no change. As might be expected, the greatest gains were in those patients with the lowest hemoglobin. Thus, in the first 4 cases with 35 and 40 per cent hemoglobin, the average gain was 50 per cent and in 6

TABLE X.

Changes in the White Blood Cell Counts after Single Doses of Tryparsamide.

Case No.	Name.	Dose.	Original W. B. C. before treatment.	W. B. C. after treatment.	Change +.	Interval between counts.
		mg. per kg.			*per cent*	*days*
51	Gwamuntele.....	67	3,600	5,000	39	51
42	N'Keta.....	57	4,000	7,600	90	30
73	Talamene.....	109	4,000	6,000	50	26
43	Mambula.....	37	4,200	6,000	43	48
31	Lubaki.....	68	4,700	5,600 8,000	19 70	37 70
46	Bokao.....	40	5,000	6,600	32	54
37	Bukasa.....	55	5,200	6,000	15	60
5	Mondongo.....	43	5,400	9,800 12,000	81 122	41 105
30	Mafuala.....	25	6,400	8,000 8,000	20 20	37 66
68	Tuamene.....	80	8,000	8,000	—	28
46	K. Georges.....	52	8,200	9,000	10	56
40	Esombo.....	9	10,800	9,600	−11	63

patients with original values of 50 to 60 per cent the increase was 25 per cent in an average of 46 days.

No direct relation was detected between the size of the dose of tryparsamide and the changes in the red cells or the hemoglobin; it is probable, however, that such improvement as takes place results from the trypanocidal action of the drug.

The initial leucocyte counts of this group were less than 8,000 in 9 of the 12 patients; there were 2 counts of 8,000 and 8,200 and one of 10,800 (Table X). Examinations made at varying intervals of time

after treatment with single doses of tryparsamide showed an increase of white blood cells of from 10 to 122 per cent in 10 patients, no change in an original count of 8,000 cells per cmm. and a 11 per cent decrease in the patient who had an original slight leucocytosis.

The upshot of the observations of these patients is that, despite other concurrent infections, a tendency is to be discerned toward a normal blood picture once the trypanosomal infection is controlled for even a few weeks by a single dose of tryparsamide.

Effect of Single Doses upon the Weight.

The effect upon the weight of all patients treated with tryparsamide was followed and the observations made on 21 patients treated with single doses are shown in Table XI. These patients were in the first period or in the beginning of the second stage of the disease as indicated by the cell content of the spinal fluid and were treated with single doses of from 0.5 to 5.0 gm. given intravenously in 17 and intramuscularly in 4 cases. The group includes 9 non-relapsed cases in whom no trypanosomes were demonstrated microscopically in lymph glands, centrifuged blood or centrifuged spinal fluid, 11 relapsed cases and 1 in whom the result was uncertain.

Considering the group as a whole, 5 patients showed no change of weight in 3 to 12 weeks, 2 showed a loss of 0.5 and 1.5 kilos respectively in 3 and 6 weeks and 14 showed a gain of 0.5 to 8.4 kilos in from 3 to 10 weeks after treatment. Generally speaking, patients who gained little or no weight had intercurrent infections or suffered an ultimate relapse.

Of the 14 patients who gained weight, 7 remained negative during the period of observation and 7 ultimately relapsed. These cases are contrasted in Table XII. The increase in weight of the 7 non-relapsed patients ranged from 0.5 to 8.4 kilos or an average of 3.3 kilos in 4 to 10 weeks. The relapsed patients on the other hand showed smaller gains ranging from 0.5 to 2.5 kilos or an average of 1.4 kilos in 3 to 8 weeks.

General Effects Following Single Doses.

The preceding sections of this paper have dealt with a series of observations carried out on a number of patients suffering with

trypanosomiasis treated with single doses of tryparsamide. These observations consisted of the results of microscopic examinations for trypanosomes in aspirated lymph gland juice and in centrifuged blood,

TABLE XI.

Changes in Weight after Single Doses of Tryparsamide.

Case No.	Name.	Dose tryparsamide.	Day of treatment.	1st week.	2nd week.	3rd week.	4th week	6th week.	8th week.	10th week.	12th week.	Total change.	Relapse.
		gm.	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	
40	Esombo.....	0.5	51.0	49.5	51.5	51.0	51.0	51.0	51.5			+0.5	0†
50	Moangolo.....	0.5	29.5	29.5	30.0	30.5	30.5					+1.0	+
48	M'Bondo.....	1.0	50.0	51.0	51.0	51.5	52.0					+2.0	+‡
38	Daie.....	1.0	46.0	46.5	44.0	44.5	44.5	44.5				−1.5	0(?)
30	Mafuala.....	1.0	39.6	40.0	40.0	40.5	44.0	43.0	45.5	48.0		+8.4	0
28	Mago.....	1.0	33.0	33.0	32.5	33.5						+0.5	+
47	Mondeke.....	2.0	61.0	61.5	61.0	60.5						−0.5	+‡
43	Mambula.....	1.0*	27.0	26.5	26.5	25.5	26.0	27.5	27.5			+0.5	+†
46	Bokao.....	2.0	50.0	49.0	49.5	49.0	50.0	50.5	55.0			+5.0	0
5	Mondongo....	2.0	47.0	47.0	47.0	45.0	44.0	44.5	45.5	46.5	47.0	None.	0‖
36	Sudila.....	2.0	46.0	46.0	46.5	47.0	49.0	48.0				+2.0	+
45	K. Georges....	2.0	38.5	39.0	38.5	36.5	37.0	38.5	43.0			+4.5	0†
39	Mulamba.....	3.0*	55.5	56.5	57.0	58.5	57.5	58.0				+2.5	+‡
37	Bukasa.....	3.0	54.5	54.0	55.0	54.0	52.5	53.0	53.5	54.5		None.	0
41	Bajaka.....	3.0*	53.0	53.0	52.5	52.5	53.0	53.0				None.	+§
42	N'Keta.....	2.0*	36.0	35.0	33.5	34.5	34.0	34.5	36.0			None.	+**
51	Gwamuntele..	3.0	44.0	45.0	44.0	44.0	44.5	45.0	44.5			+0.5	0†
31	Lubaki.....	3.0	44.5	43.5	42.5	43.0	44.5	46.0	46.0	47.0		+2.5	0‡
68	Tuamene.....	5.0	62.5	62.0	61.5	62.5						None.	+
53	Ganzema.....	3.0	36.0	37.0	37.0	37.0						+1.0	+
73	Talamene.....	4.0	36.5	36.5	37.0	37.5	38.0					+1.5	0

* Intramuscular administration.

† Estivo-autumnal malaria.

‡ Filariasis.

§ Filariasis; malaria (?).

‖ Diffuse skin infection; filariasis; chronic diarrhoea.

** Craw-craw; intramuscular abscess.

cell counts of the spinal fluid, cell counts and hemoglobin estimations of the blood, and finally weight determinations—information of a fundamental character to be used in devising an effective system of

repeated dose therapy. In addition, other effects of treatment may be briefly considered.

Adenitis.—Polyadenitis is a constant symptom of human trypanosomiasis and of all of the superficial lymph glands those of the neck are most regularly involved. Palpation of these glands constitutes the general diagnostic method for the disease in the Belgian Congo, and enlarged cervical glands were present in all cases treated with tryparsamide except in 4 advanced patients who were being treated with other drugs. The glands most frequently hypertrophied

TABLE XII.

Increases in Weight of Non-Relapsed and Relapsed Patients after Single Doses of Tryparsamide.

Non-relapses.					Relapses.				
Case No.	Name.	Dose.	Total gain.	Time.	Case No.	Name.	Dose.	Total gain.	Time.
		mg. per kg.	*kg.*	*weeks*			*mg. per kg.*	*kg.*	*weeks*
40	Esombo.....	9	0.5	8†	50	Moangolo.....	17	1.0	4
30	Mafuala.....	25	8.4	10	48	M'Bondo.....	20	2.0	4*
46	Bokao.....	40	5.0	8	28	Mago.....	33	0.5	3
45	K. Georges....	52	4.5	8†	43	Mambula.....	37	0.5	8†
51	Gwamuntele...	67	0.5	8†	36	Sudila.....	44	2.0	6
31	Lubaki.....	68	2.5	10*	39	Mulamba.....	54	2.5	6*
73	Talamene.....	109	1.5	4	53	Ganzema.....	83	1.0	3
Average gain of 3.3 kg. in 4 to 10 weeks.					Average gain of 1.4 kg. in 3 to 8 weeks.				

* Filariasis.

† Estivo-autumnal malaria.

in our series were those of the posterior cervical triangle; in several cases a chain of enlarged glands were felt along one or both sides of the posterior portion of the neck, while the majority showed one or more enlarged glands at the base, either in the anterior or posterior cervical triangle. Usually the glands were about the size of a large pea or filbert, often slightly fusiform and of a peculiar soft but elastic consistency which has been compared to that of a ripe plum. In the cerebrospinal cases, the glands were usually smaller and firmer. Other superficial lymph glands are not commonly used as diagnostic signs.

Under treatment with single doses of tryparsamide, a marked reduction of the enlarged cervical glands was observed in all cases which did not relapse. They became much smaller and firmer and in certain patients whom we were able to follow for 2 or 3 months gland puncture was carried out with considerable difficulty. In relapsed patients, the condition of the glands was directly related to the duration of the peripheral sterilization; if this extended over 4 or 5 weeks, a distinct reduction was noticeable.

Temperature.—An irregular intermittent fever and rapid pulse are characteristic of human trypanosomiasis and during febrile periods the temperature is more often elevated in the afternoon than morning. Because one is obliged to take the temperatures in the axilla of the natives, correct readings are difficult to obtain and the readings are lower than they should be. The highest fever noted was usually around 38.5° C.; after treatment, a sharp drop occurred as shown in Charts I to III. The temperature charts of Bikoko #55 (Chart I) is interesting as it shows the prompt cessation of fever after the administration of the dose of only 0.3 gm. or 4.7 mg. per kilo; this patient had an unusually severe lymph gland infection but the dose was sufficient to produce a negative gland examination in 19 hours. Three other patients, M'Bondo #48, Yala #70, and Kakuma #65 (Chart I), show a similar drop in the temperature curve following the administration of 1.0, 3.0, and 4.0 gm. doses of tryparsamide. The charts of Esombo #40 (Chart II) and K. Georges #45 (Chart III) treated with single doses of 0.5 and 2.0 gm. cover periods of $6\frac{1}{2}$ and 9 weeks in which no trypanosomes were found in the lymph glands or blood. The intercurrent fever with increased pulse rate in these patients was due to an acute attack of estivo-autumnal malaria. K. Georges #45 was admitted during an afebrile period but it should be noted that his pulse rate was increased to 96 per minute.

Pulse.—The pulse rate in human trypanosomiasis is of considerable importance in diagnosis and in many of our cases it served as an index of the effect and duration of action of tryparsamide. The pulse itself is regular with a small volume and generally a lowered tension. The rate is usually disproportionately increased in relation to the fever and may persist above normal in afebrile periods.

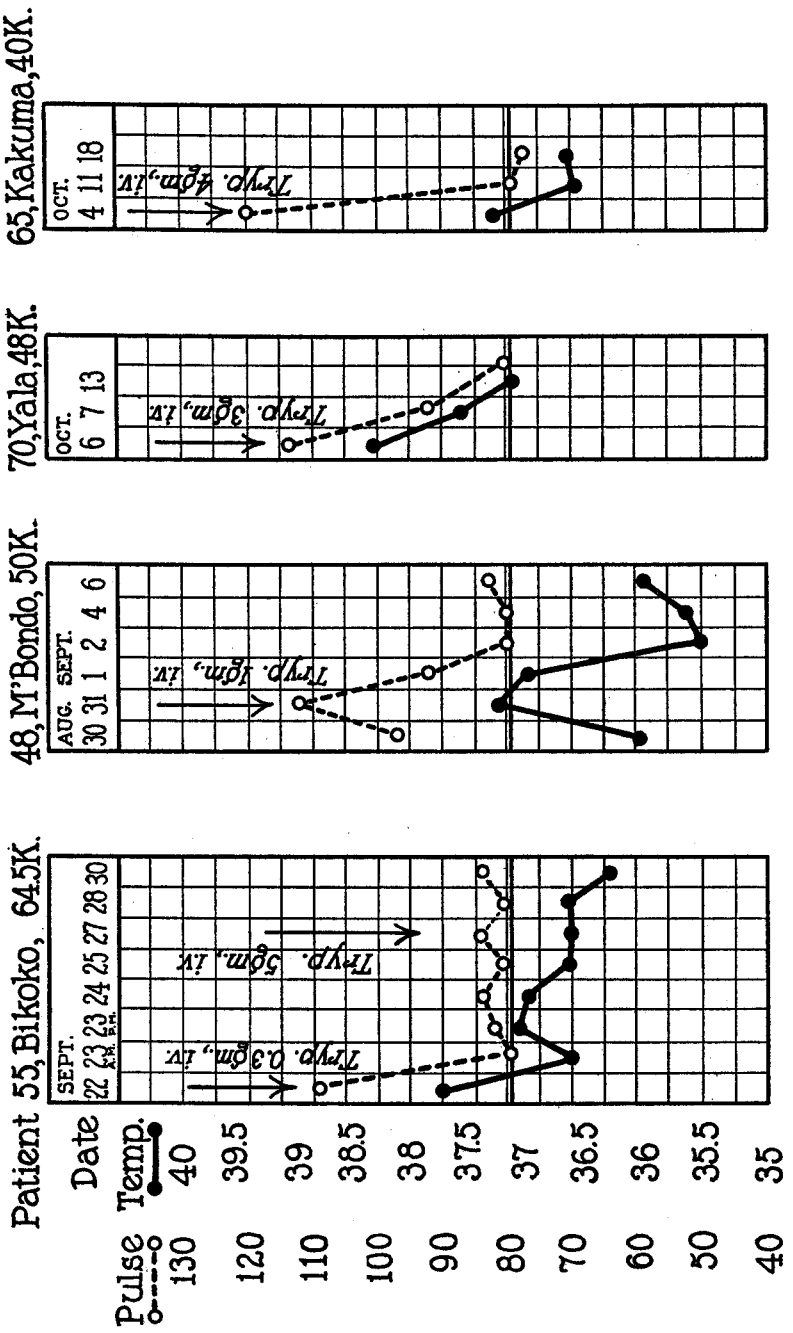

Patient 55, Bikoko, 64.5K.
48, M'Bondo, 50K.
70, Yala, 48K.
65, Kakuma, 40K.
Date
Temp.
Pulse
Trvp. 0.3gm., iv.
Trvp. 5gm., iv
Trvp. 1gm., iv.
Trvp. 3gm., iv.
Trvp. 4gm., iv.
SEPT.
AUG. SEPT.
OCT.
OCT.

CHART I.

In the charts of the above 6 patients (Charts I to III), the effects of tryparsamide upon the pulse rate may be seen. Usually within 24 to 48 hours after treatment with a single dose, the pulse rate became normal or subnormal, unless some complicating infection or pathological condition existed—as for instance an acute or subacute malaria which was the case with Esombo #40 (Chart II) and K. Georges #45

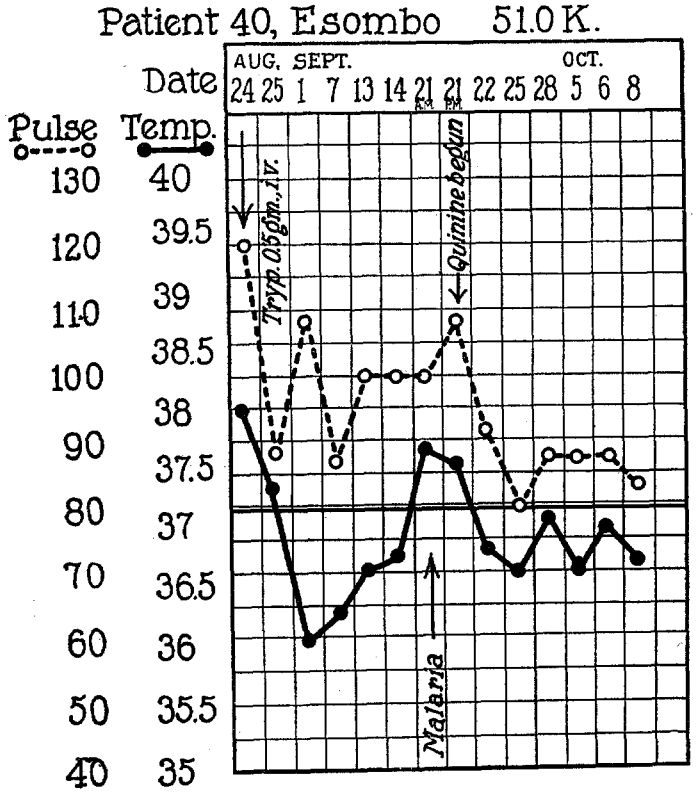


CHART II.

(Chart III). In a few patients in whom no complicating condition was found, the possibility of a still operative trypanosomal infection must be considered, although repeated microscopic examinations of lymph gland juice and centrifuged blood were negative. Such cases ultimately relapsed but the duration of peripheral sterilization varied widely. An increased pulse rate with slight or no fever during the

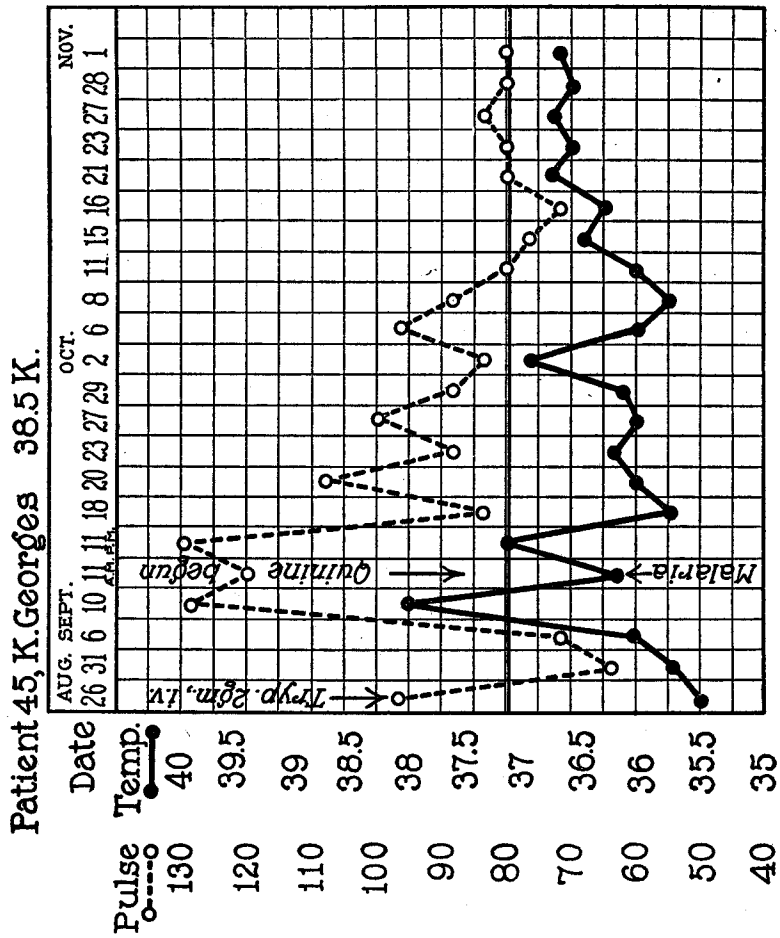

Patient 45, K. Georges 38.5 K.
Date
Temp.
Pulse
AUG. SEPT. OCT. NOV.
26 31 6 10 11 11 18 20 23 27 29 2 6 8 11 15 16 21 23 27 28 1
Tryp. 2gm., Iv
Quinine begun
Malaria
40 39.5 39 38.5 38 37.5 37 36.5 36 35.5 35
130 120 110 100 90 80 70 60 50 40

CHART III.

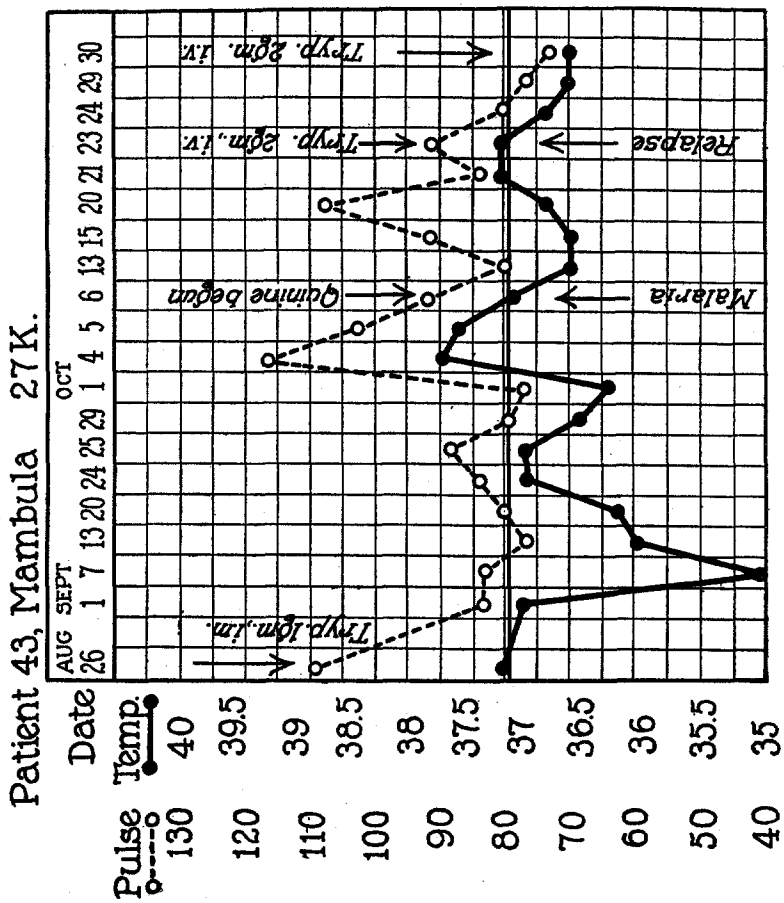

Patient 43, Mambula 27 K.
Date
Temp.
Pulse
AUG 26
SEPT 1 7 13 20 24 25 29
OCT 1 4 5 6 13 15 20 21 23 24 29 30
40 39.5 39 38.5 38 37.5 37 36.5 36 35.5 35
130 120 110 100 90 80 70 60 50 40
Tryp. 10cm. i.m.
Quinine begun
Tryp. 20cm. i.v.
Tryp. 20cm. i.v.
Malaria
Relapse

CHART IV.

period of peripheral sterilization was found to possess considerable importance as an indication of a relapse, provided that other pathological factors were excluded as shown in Charts IV to VII.

Mambula #43 (Chart IV) after treatment on August 26, 1920, with 1.0 gm. of tryparsamide administered intramuscularly, showed a subnormal temperature and fairly normal pulse rate with negative

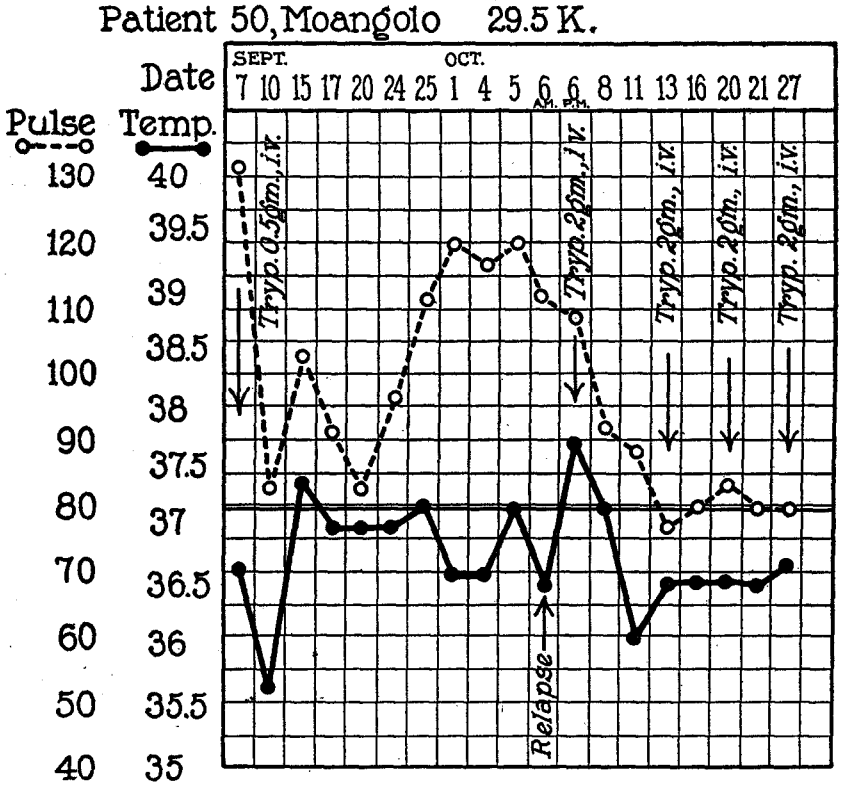


CHART V.

lymph gland and blood examinations until October 4, 1920, at which time he developed fever and a pulse rate of 116 per minute. Malarial parasites were found on October 6 and quinine therapy resulted in the return to a normal pulse rate until October 15, when an increase again occurred. During the following week, the pulse rate was irregularly increased without a proportionate rise in temperature and

trypanosomes were found on October 23. After retreatment, the pulse rate promptly fell to normal.

The chart of Moangolo #50 (Chart V) illustrates the type of case which leads one to suspect that the trypanosomal infection may still be active within the body although no organisms can be found in the lymph glands or blood. This boy was given 0.5 gm. of tryparsa-

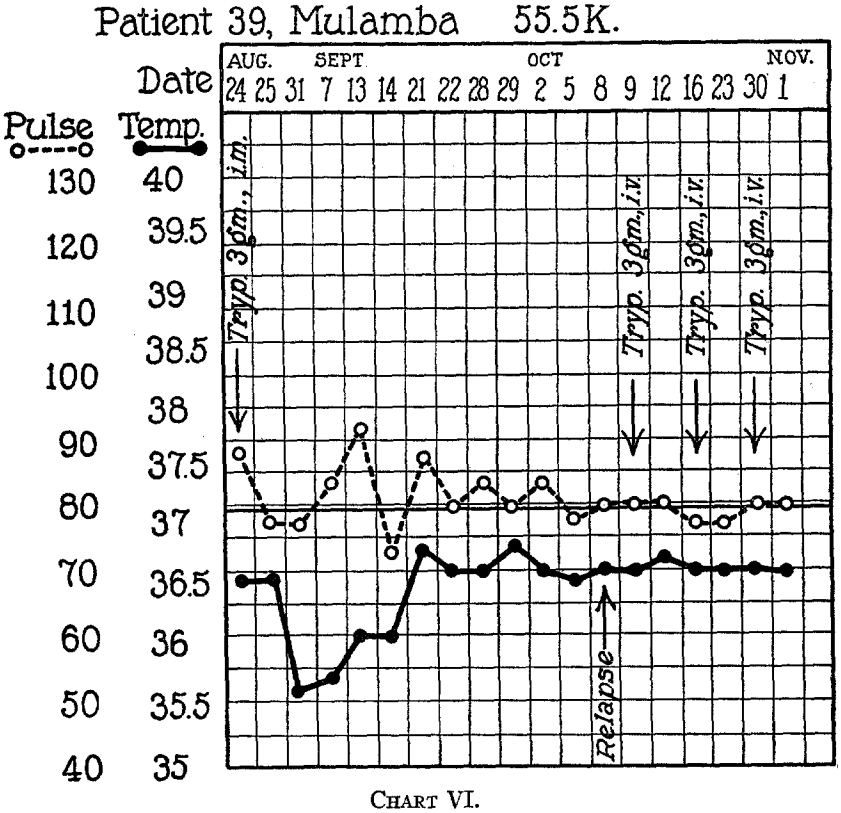


CHART VI.

mide on September 7. After an initial drop in pulse rate and temperature the pulse became disproportionately rapid, varying from 96 to 120 per minute for 16 days, and the temperature was somewhat irregular. No complicating infections could be found, however, and trypanosomes were not seen until October 6, 29 days after treatment. Retreatment had a very prompt effect upon both pulse and temperature as may be seen by referring to Chart V.

Charts VI and VII are illustrative of the less common type of reaction in which little or no increase in pulse rate takes place with a return of trypanosomes to the lymph glands or blood. Mulamba #39 (Chart VI) was treated August 24 with 3.0 gm. and during the following 6 weeks the pulse rate was irregular, varying from 72 to 92, but on the whole was not remarkable and no fever was observed.

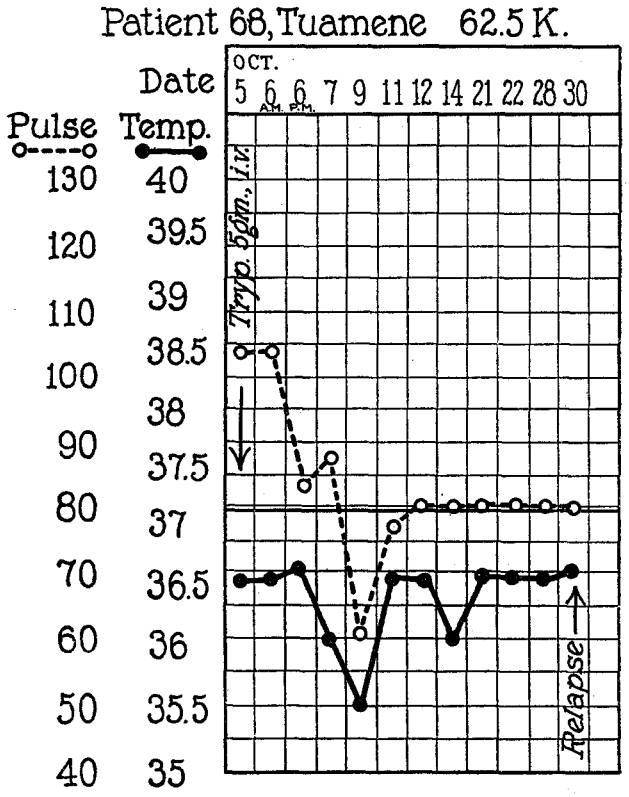


CHART VII.

Trypanosomes were found on October 8 and retreatment with tryparsamide caused a prompt cessation of pulse rate irregularity. A somewhat similar course of events is seen in the chart of Tuamene #68 (Chart VII), in whom a peripheral relapse was detected 25 days after treatment although the pulse rate had not been above normal for 23 days.

Symptoms.—Finally, as a result of the single dose treatment, a noticeable and continuous general improvement occurred in all patients in the first or beginning of the second stage of sleeping sickness leading them to wish to leave the lazaret or hospital or to cease coming to the laboratory. Conspicuous improvement was naturally most apparent in those patients whose ill appearance on admittance was most noticeable. The more definite symptoms of pains in the legs, arms, and joints, headaches, weakness, and general malaise disappeared during the first week after treatment and did not return even in those cases which eventually relapsed, presumably because retreatment was immediately instituted. Within 1 or 2 weeks, all the patients in this group appeared well and it was in many instances only with the greatest difficulty that further visits were secured.

ADMINISTRATION OF REPEATED DOSES IN EARLY CASES.

The consensus of opinion is that human trypanosomiasis can best be influenced by a system of repeated doses of the drugs commonly employed and several courses of atoxyl alone or combined with tartar emetic are recommended both in early and late cases. Treatment with repeated doses of tryparsamide given intravenously was regularly carried out as soon as the duration of action of single doses was determined in a number of instances. The patients thus treated fall into two main groups according to the period of the disease as determined by the spinal fluid. The first group consisted of patients in the first stage of the disease or in the beginning of the second period and included those who suffered a relapse after single doses as well as a number of previously untreated cases and the observations carried out on this group will be considered first.

Early Cases Previously Treated with One Dose.

This group consists first of 12 patients treated with a single dose of tryparsamide of from 17 to 83 mg. per kilo, who showed a return of trypanosomes in the blood and lymph glands after periods of peripheral sterilization varying from 17 to 58 days, and were retreated with repeated doses of the drug given at weekly or fortnightly intervals as shown in Table XIII. 2 other patients are also considered in this

TABLE XIII.

Treatment of Relapsed Early Cases with Repeated Doses of Tryparsamide. Weekly Administration.

Case No.	Name.	Original weight.	No. of cells in spinal fluid per cmm. before treatment.	Doses of tryparsamide adm. i. v.	Remarks.
		kg.		*gm.*	
28	Mago.....	33	5 (1 l.m.)	1.0 (33 mg. per kg.) Aug. 16 2.0 Sept. 4, 11, 18, 25 Total 9.0 gm.	L. P. Oct. 16 Normal. 2.5 lymph.
50	Moangolo..	29.5	Normal.	0.5 (17 mg. per kg.) Sept. 7 2.0 Oct. 6, 13, 20, 27 Total 8.5 gm.	L. P. Oct. 16 1.2 lymph. 1 l.m.
39	Mulamba..	55.5	4	3.0 (54 mg. per kg.) Aug. 24* 3.0 Oct. 9, 16, 23, 30 Total 15.0 gm.	L. P. Sept. 28 Normal.
36	Sudila.....	46	20	2.0 (44 mg. per kg.) Aug. 19 3.0 Oct. 9 2.0 Oct. 16, 23, 30 2.0 to be given Nov. 6, 13, 20 Total 17.0 gm.	L. P. Sept. 28 Normal. 2.5 lymph.
42	N'Keta....	36	10	2.0 (57 mg. per kg.) Aug. 26* 2.0 Oct. 16, 23, 30 2.0 to be given Nov. 6, 13 Total 12.0 gm.	L. P. Sept. 29 Normal. 0.6 lymph.
43	Mambula..	27	7.5	1.0 (37 mg. per kg.) Aug. 26* 2.0 Oct. 23, 30 2.0 to be given Nov. 6, 13, 20 Total 11.0 gm.	L. P. Sept. 29 Normal. 2.1 lymph.
53	Ganzema...	36	3.4 (1 l.m.)	3.0 (83 mg. per kg.) Sept. 13 4.0 Oct. 4, 18, 25 4.0 to be given Nov. 4 Total 19.0 gm.	
68	Tuamene...	62.5	5 (1 l.m.)	5.0 (80 mg. per kg.) Oct. 5 5.0 Nov. 1 3.0 to be given Nov. 8, 15, 23, 30 Total 22.0 gm.	

TABLE XIII—*Continued.*

Case No.	Name.	Original weight.	No. of cells in spinal fluid per cmm. before treatment.	Doses of tryparsamide adm. i. v.	Remarks.
		kg.		*gm.*	
63	N'Kaka....	42.5	Normal.	2.0 (47 mg. per kg.) Oct. 4 3.0 Oct. 21. Did not return Oct. 28 3.0 to be given weekly for 5 inj. Total 20.0 gm.	
38	Daie.....	46	(?) R. B. C.	1.0 (22 mg. per kg.) Aug. 21 3.0 Sept. 30 1.0 Oct. 7, 14, 21, 28 1.0 to be given Nov. 4, 11, 18, 25 Total 12.0 gm.	L. P. Sept. 27 35 lymph. 1 l.m.
			Fortnightly Administration.		
48	M'Bondo..	50	5.0	1.0 (20 mg. per kg.) Aug. 31 2.5 Sept. 24, Oct. 8, 22 2.5 to be given Nov. 5 Total 11.0 gm.	L. P. Oct. 6 Normal. 1 lymph.
47	Mondeke...	61	7.5	2.0 (33 mg. per kg.) Aug. 28 4.0 Sept. 24, Oct. 8, 22 4.0 to be given Nov. 5 Total 18.0 gm.	L. P. Oct. 6 Normal. 3 lymph.
41	Bajaka.....	53	15.0	3.0 (57 mg. per kg.) Aug. 26* 4.0 Oct. 2, 16, 30 4.0 to be given Nov. 13 Total 19.0 gm.	L. P. Sept. 30 7.5 lymph. 2 l. m.
55	Bikoko.....	64.5	Normal.	0.3 (4.7 mg. per kg.) Sept. 22 5.0 Sept. 27, Oct. 11, 25 5.0 to be given Nov. 5 Total 20.3 gm.	

* Intramuscular administration.

section: Bikoko #55, who was given the small dose of 0.3 gm. (4.7 mg. per kilo) which produced a peripheral sterilization for 5 days and Daie #38, whose second spinal fluid examination showed an increased cell content, although no trypanosomes were detected in the lymph

glands, blood, or spinal fluid. 10 of these patients were treated at weekly intervals with 4 to 9 injections of doses varying from 20 to 111 mg. per kilo, while 4 were placed on a fortnightly schedule. The drug was given intravenously in all instances.

The observations at present available may be considered briefly. In 8 patients who could be examined shortly after the administration of the first dose, no trypanosomes were found in the lymph glands or centrifuged blood at 5, 6, 7, 8, and 15 hours after treatment, showing that the initial effect of the drug in retreatment is similar to that observed in previously untreated cases. Several examinations for trypanosomes carried out on all the patients during the course of retreatment were uniformly negative. In one case, Mago #28, the course of 4 doses of 2.0 gm. given at weekly intervals, was completed so that subsequent observation can be reported here. During the following 6 weeks, examinations of lymph glands and blood were negative and in addition a lumbar puncture done 61 days after the first single dose showed a normal spinal fluid—2.5 lymphocytes per cmm.—whereas the original count was 5 lymphocytes per cmm. with 1 large mononuclear in the preparation (Table XIV).

The spinal fluid of 3 other patients, Moangolo #50, M'Bondo #48, and Mondeke #47, examined 10 and 12 days after the beginning of the course of repeated doses and approximately 5 weeks after the initial single dose, showed that the disease had not progressed to the second stage and in 2 patients the slightly increased cell counts had become normal (Table XIV).

Thus in these 4 instances the administration of 2 to 5 small or medium sized doses of tryparsamide, though widely spaced apart and covering a period in which a peripheral relapse occurred, had an apparent effect in arresting further cerebrospinal involvement.

Effect on Blood Count.—The blood was studied in 10 patients retreated with repeated doses at weekly or fortnightly intervals following a relapse after a previous single dose. The first blood examination was made before the initial single dose while the second occurred about 2 months later during or at the end of the course of repeated doses, as shown in Table XV. A marked secondary anemia was the outstanding abnormality of the blood count on admittance.

For convenience of comparison, the changes noted in the red and white cell counts and hemoglobin estimation have been tabulated separately (Tables XVI to XVIII). It was found that after treatment with tryparsamide, an increase in the number of red cells of from 3 to 47 per cent occurred in 8 patients. The most marked improvement was usually observed in those patients who had the lowest original counts. In 2 patients, Moangolo #50 and Bikoko #55, the first count was practically normal and the second count made 50 and 33 days

TABLE XIV.

Changes in Cell Count, Spinal Fluid of Relapsed Cases During Retreatment with Repeated Doses of Tryparsamide.

Case No.	Name.	Initial weight.	Doses adm. i. v.	Cell count spinal fluid initial L.P.	Cell count spinal fluid 2nd L. P.	Interval between L. P.
		kg.	*gm.*			*days*
28	Mago.....	33	1 x 1.0 9.0 4 x 2.0 in 40 days.	5 (1 l.m.)	Normal.	61
50	Moangolo.....	29.5	1 x 0.5 4.5 2 x 2.0 in 36 days.	Normal.	1.2 lymph. 1 l.m.	39
48	M'Bondo.....	50	1 x 1.0 3.5 1 x 2.5 in 25 days.	5	Normal.	37
47	Mondeke.....	61	1 x 2.0 6.0 1 x 4.0 in 27 days.	7.5	Normal.	39

after the administration of the single dose of tryparsamide showed a slight decrease of 5 and 8 per cent respectively.

The improvement in hemoglobin content of the blood was even more striking as may be seen in Table XX. Each patient showed a gain ranging from 7 to 71 per cent. As was the case after the administration of single doses, the most marked increase occurred in those patients whose hemoglobin was below 60 per cent before treatment, while the two patients, Moangolo #50 and Bikoko #55, with normal red cell counts showed an improvement of 45 and 7 per cent respectively.

TABLE XV.

Changes in Blood Count of Relapsed Early Cases after Retreatment.

Case No.	Name.	Total No. of doses adm. i. v.	1st blood count.	2nd blood count.	Changes.	Time after 1st treatment of 2nd B. C.
		gm.			*per cent*	*days*
28	Mago.....	1 x 1.0	R. B. C. 4,320,000	4,800,000	+ 11	68
	33 kg.	4 x 2.0	Hb. 55 %	70 %	+ 27	
			W. B. C. 5,700	8,000	+ 40	
50	Moangolo.....	1 x 0.5	R. B. C. 5,056,000	4,800,000	− 5	50
	29.5 kg.	3 x 2.0	Hb. 55 %	80 %	+ 45	
			W. B. C. 11,200	10,000	− 11	
39	Mulamba.....	1 x 3.0*	R. B. C. 3,840,000	4,000,000	+ 4	59
	55.5 kg.	2 x 3.0	Hb. 52 %	80 %	+ 54	
			W. B. C. 12,800	7,000	− 45	
36	Sudila.....	1 x 2.0	R. B. C. 4,160,000	5,120,000	+ 23	65†
	46 kg.	1 x 3.0	Hb. 60 %	65 %	+ 8	
		1 x 2.0	W. B. C. 8,600	8,000	− 7	
42	N'Keta.....	1 x 2.0*	R. B. C. 3,200,000	4,000,000	+ 25	65‡
	36 kg.	2 x 2.0	Hb. 35 %	60 %	+ 71	
			W. B. C. 4,000	8,000	+100	
38	Daie.....	1 x 1.0	R. B. C. 3,720,000	4,000,000	+ 8	67
	46 kg.	1 x 3.0	Hb. 60 %	70 %	+ 17	
		3 x 1.0	W. B. C. 7,000	6,000	− 14	
48	M'Bondo.....	1 x 1.0	R. B. C. 3,200,000	3,680,000	+ 15	53§
	50 kg.	2 x 2.5	Hb. 50 %	65 %	+ 30	
			W. B. C. 9,200	8,000	− 13	
47	Mondeke.....	1 x 2.0	R. B. C. 4,480,000	4,640,000	+ 3	55§
	61 kg.	2 x 4.0	Hb. 65 %	75 %	+ 15	
			W. B. C. 8,400	8,000	− 5	
41	Bajaka.....	1 x 3.0*	R. B. C. 3,044,000	4,480,000	+ 47	60**
	53 kg.	2 x 4.0	Hb. 45 %	75 %	+ 67	
			W. B. C. 4,800	9,000	+ 88	
55	Bikoko.....	1 x 0.3	R. B. C. 5,240,000	4,830,000	− 8	33‖
	64.5 kg.	3 x 5.0	Hb. 75 %	80 %	+ 7	
			W. B. C. 8,000	8,000	—	

* Intramuscular administration.

† Malaria (?).

‡ Intramuscular abscess; craw-craw.

§ Filariasis.

‖ Malaria.

** Filariasis; malaria (?).

TABLE XVI.

Changes in Red Blood Cell Counts of Patients Previously Treated with Single Doses—Retreated with Repeated Doses.

Case No.	Name.	Total amount tryparsamide.	Time between 1st and 2nd R. B. C.	1st R. B. C. before treatment.	R. B. C. after treatment.	Change.
		mg. per kg.	*days*			*per cent*
41	Bajaka	209	60	3,044,000	4,480,000	+47
42	N'Keta	171	65	3,200,000	4,000,000	+25
48	M'Bondo	120	53	3,200,000	3,680,000	+15
38	Daie	154	67	3,720,000	4,000,000	+ 8
39	Mulamba	162	59	3,840,000	4,000,000	+ 4
36	Sudila	154	65	4,160,000	5,120,000	+23
28	Mago	297	68	4,320,000	4,800,000	+11
47	Mondeke	165	55	4,480,000	4,640,000	+ 3
50	Moangolo	201	50	5,056,000	4,800,000	− 5
55	Bikoko	244.7	33	5,240,000	4,830,000	− 8

TABLE XVII.

Changes in Hemoglobin Content of Patients Previously Treated with Single Doses—Retreated with Repeated Doses.

Case No.	Name.	Total amount tryparsamide.	Interval between 1st and 2nd hemoglobin examinations.	1st hemoglobin.	2nd hemoglobin.	Increase.
		mg. per kg.	*days*			*per cent*
42	N'Keta	171	65	35	60	+71
41	Bajaka	209	60	45	75	+67
48	M'Bondo	120	53	50	65	+30
39	Mulamba	162	59	52	80	+54
50	Moangolo	201	50	55	80	+45
28	Mago	297	68	55	70	+27
38	Daie	154	67	60	70	+17
36	Sudila	154	65	60	65	+ 8
47	Mondeke	165	55	65	75	+15
55	Bikoko	244.7	33	75	80	+ 7

The white cells in practically all cases were within normal limits after retreatment as shown in Table XVIII. 3 patients, N'Keta #42, Bajaka #41, and Mago #28, who originally had a leukopenia, showed an increase in the number of white cells of 100, 88, and 40 per cent respectively—in the others, the white cells remained or approached normal.

These observations are in accord with those noted after single doses and indicate that the blood picture of patients suffering with trypanosomiasis tends to return to normal limits after treatment with tryparsamide.

Effect upon the Weight.—The changes in weight of 12 patients during the period of peripheral sterilization and subsequently after retreatment with repeated doses of tryparsamide, are shown in Table XIX. The majority of observations extend over a period of 10 weeks during which time from 2 to 6 doses were given. Doses of 2.0, 3.0, and 4.0 gm. were used in most instances.

TABLE XVIII.

Changes in White Blood Cell Counts of Patients Previously Treated with Single Doses—Retreated with Repeated Doses.

Case No.	Name.	Total amount tryparsamide.	Interval between 1st and 2nd W. B. C.	1st W. B. C. before treatment.	2nd W. B. C. after treatment.	Change.
		mg. per kg.	*days*			*per cent*
42	N'Keta.....	171	65	4,000	8,000	+100
41	Bajaka.....	209	60	4,800	9,000	+ 88
28	Mago.....	297	68	5,700	8,000	+ 40
38	Daie.....	154	67	7,000	6,000	− 14
55	Bikoko.....	244.7	33	8,000	8,000	−
47	Mondeke.....	165	55	8,400	8,000	− 5
36	Sudila.....	154	65	8,600	8,000	− 7
48	M'Bondo.....	120	53	9,200	8,000	− 13
50	Moangolo.....	201	50	11,200	10,000	− 11
39	Mulamba.....	162	59	12,800	7,000	− 45

The effect of tryparsamide treatment upon the weight of these patients was as follows: 6 patients gained from 1.5 to 3.5 kilos, 4 showed no change, and 2 showed a loss of 1.5 kilos. Concurrrent infections were present in 5 of the 6 patients who did not gain, while in the case of Daie #38 the explanation is not entirely clear.

In general, it may be said that the physical improvement of these patients which occurred after treatment with single doses of tryparsamide continued during the course of repeated doses as shown by an increase of weight in uncomplicated cases and by the beneficial effect upon the blood picture.

TABLE XIX.

Changes in Weight of Relapsed Early Cases after Retreatment with Repeated Doses of Tryparsamide.

Case No.	Name.	Total no. of doses.	Original weight.	2nd week.	4th week.	6th week.	8th week.	10th week.	Total change.
		gm.	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*
28	Mago.....	1 x 1.0 4 x 2.0	33.0	32.5	33.0	34.5	33.5	34.5	+1.5
50	Moangolo.....	1 x 0.5 3 x 2.0	29.5	30.0	30.5	31.5	31.5		+2.0
39	Mulamba.....	1 x 3.0* 3 x 3.0	55.5	57.0	57.5	58.0	58.5	59.0	+3.5‖
36	Sudila.....	1 x 2.0 1 x 3.0 2 x 2.0	46.0	46.5	49.0	48.0	47.5	46.0	0†
42	N'Keta.....	1 x 2.0* 2 x 2.0	36.0	33.5	34.0	34.5	35.5	36.0	0§
43	Mambula.....	1 x 1.0* 1 x 2.0	27.0	26.5	26.0	27.5	27.5	27.0	0‡
53	Ganzema.....	1 x 3.0 3 x 4.0	36.0	37.0	37.0	37.0	37.5		+1.5
38	Daie.....	1 x 1.0 1 x 3.0 4 x 1.0	46.0	44.0	44.5	44.5	44.5	44.5	−1.5
48	M'Bondo.....	1 x 1.0 3 x 2.5	50.0	51.0	52.0	52.0	52.5	53.5	+3.5‖
47	Mondeke.....	1 x 2.0 3 x 4.0	61.0	61.0	60.5	61.0	61.0	61.0	0‖
41	Bajaka.....	1x 3.0* 2 x 4.0	53.0	52.5	53.0	53.0	53.0	51.5	−1.5**
55	Bikoko.....	1 x 0.3 3 x 5.0	64.5	63.5	65.0	66.0			+1.5‡

* Intramuscular administration.

† Malaria (?).

‡ Malaria.

§ Intramuscular abscess; craw-craw.

‖ Filariasis.

** Filariasis; malaria (?)

Previously Untreated Early Cases.

13 previously untreated patients in the first period of trypanosomiasis were treated with repeated doses of from 1.0 to 5.0 gm. of tryparsamide given at weekly and fortnightly intervals (Tables XX

TABLE XX.

Repeated Dose Treatment of Early Previously Untreated Cases. Weekly Administration.

Case No.	Name.	Weight.	No. cells spinal fluid per cmm.	Doses of tryparsamide adm. i. v.	Total.
		kg.			*gm.*
72	N'Ganzobo..	26	Normal.	1.0 gm. (38 mg. per kg.) Oct. 6, 13, 20, 27 1.0 " to be given on Nov. 3, 10	6.0
78	Itoma.....	52		1.0 " (19 mg. per kg.) Oct. 29 2.0 " (38 " " ") Nov. 4, 11, 18, 25, Dec. 2, 9, 16	15.0
71	Madeele....	24	Normal.	1.0 " (42 " " ") Oct. 6, 13, 20, 27	4.0
64	Dano.....	40	0.6	2.0 " (50 " " ") Oct. 4, 21, 28 2.0 " to be given Nov. 4, 11	10.0
69	Sabole.....	67.5	7.5 1 l.m.	3.0 " (44 mg. per kg.) Oct. 5, 12, 19, 26 Nov. 2	15.0
77	V. Makau...	57.0	3.8 1 l.m.	1.0 " (18 " " ") Oct. 28 3.0 " (54 " " ") Oct. 29 3.0 " to be given Nov. 5, 12, 19, 26	16.0
58	Kaniki.....	42.5	1.2	2.5 " (58 mg. per kg.) Sept. 28, Oct. 7, 14, 21, 28 2.5 " to be given Nov. 4	15.0
70	Yala.....	48.0	8.0	3.0 " (63 mg. per kg.) Oct. 6, 13, 20, 27	12.0
62	Sawa.....	57.0	5.3	4.0 " (70 " " ") Oct. 4, 12, 19 4.0 " to be given Nov. 3	16.0

and XXI). Trypanosomes were found in lymph gland juice before treatment in all instances; spinal fluid examination showed a normal cell count in 6 cases and a slight increase of cells in 5; lumbar puncture was not done in 2 cases.

The observations of this group at present available were made during the first month of treatment and are summarized as follows: The preliminary sterilization of lymph glands and blood together with a sharp drop in the accelerated pulse rate and fever occurred as previously described and in those patients under observation for 3 or 4 weeks a decrease in size and induration of the cervical lymph glands was observed; subsequent examinations for trypanosomes in each patient made at various times were uniformly negative. With the

TABLE XXI.

Repeated Dose Treatment of Early Previously Untreated Cases. Fortnightly Administration.

Case No.	Name.	Weight.	No. cells spinal fluid per cmm.	Doses of tryparsamide adm. i. v.	Total.
		kg.			*gm.*
56	Yaya.....	49.5	1	2.0 gm. (40 mg. per kg.) Sept. 24, Oct. 8, 25 2.0 " to be given Nov. 8, 22	10
65	Kakuma.....	40.0	4	4.0 " (100 mg. per kg.) Oct. 4, 18, Nov. 1 4.0 " to be given Nov. 15, 29	20
67	M'Bwongo...	27.0		3.0 " (111 mg. per kg.) Oct. 4, 18 Nov. 1 3.0 " to be given Nov. 15, 29	15
66	Popa.....	42.5	2.5	5.0 " (118 mg. per kg.) Oct. 4, 18 5.0 " to be given Nov. 3, 15	20

exception of Kaniki #58, who had syphilis, and Yaya #56, who had malaria, there was prompt cessation of the pains, weakness, and general malaise complained of on admittance.

The changes in weight of 11 patients are given in Table XXII; 6 patients gained from 0.5 to 2.5 kilos, 1 lost 2 kilos from no apparent cause, while 4 showed no change. It was not possible to carry out a detailed study of this group and blood counts of only 2 patients were made; these, however, showed a marked improvement during the period of treatment comparable to that previously described.

This group of patients has been included in the present paper to illustrate the application of a preliminary system of repeated dose therapy based upon the information obtained from the use of single doses. It is probable that various modifications will be made in the future; but just as it was necessary to determine the effect of single doses before proceeding to the use of repeated doses, so it is imperative to study the results of a few repeated doses in a certain number of cases before attempting a more complicated method of therapy. Further observations on these patients will be reported later.

TABLE XXII.

Changes in Weight of Early Cases Treated with Repeated Doses of Tryparsamide.

Case No.	Name.	Doses.	Initial weight.	1st week.	2nd week.	3rd week.	4th week.	Total change.
		gm.	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*
72	N'Ganzobo.....	3 x 1.0	26	27	27.5	27.5		+1.5
71	Madeele.....	4 x 1.0	24	24.5	24.5	24.5		+0.5
64	Dano.....	2 x 2.0	40		40.0	38.0		−2.0
58	Kaniki.....	5 x 2.5	42.5	42.5	44.0	44.5	45.0	+2.5*
70	Yala.....	4 x 3.0	48	48.5	49.0	49.0	49.5	+1.5
62	Sawa.....	3 x 4.0	57	57.8	58.0			+1.0
69	Sabole.....	4 x 3.0	67.5	66.0	66.5	67.0	67.5	0
56	Yaya.....	3 x 2.0	49.5	49.5	48.5	49.0	49.5	0†
65	Kakuma.....	2 x 4.0	40.0		40.0			0
67	M'Bwonga.....	2 x 3.0	27.0	27.5	27.5	27.5	28.0	+1.0
66	Popa.....	2 x 5.0	42.5	43.0	42.5			0

* Syphilis.

† Malaria.

ADMINISTRATION OF REPEATED DOSES IN ADVANCED CASES.

35 patients whose spinal fluid showed that the disease had involved the cerebrospinal system represent the second group treated with repeated doses of tryparsamide given intravenously. Of these, 2 patients deserted after the first injection of the drug, 2 were practically moribund on admittance, and 3 others were under observation for such a short time that their records are not included. The remaining 28 patients may be conveniently considered in two subdivisions: 18 who had not previously been treated so far as known and 10 who had been treated before. The spinal fluids of the patients examined before

the administration of tryparsamide showed from 15 to 572 lymphocytes per cmm., and large mononuclears and *cellules en mûre* in most instances, while most of the patients suffered from pronounced nervous and mental symptoms and were anemic and debilitated. Trypanosomes were found in the cervical lymph nodes of 21 patients; they were not found in 7 patients who were being treated with atoxyl and tartar emetic at the time of transfer to tryparsamide therapy. Certain outstanding effects of the tryparsamide treatment as measured by changes in the spinal fluid, the blood, and body weight will be considered in the following sections and the size and number of doses of tryparsamide given to each patient will be described in connection with these observations.

Previously Untreated Advanced Cases.

1 Course of Treatment.

Effect upon the Spinal Fluid.—The most conspicuous concrete effect of the treatment of advanced cases of trypanosomiasis with tryparsamide was the marked and rapid decrease in the cell content of the spinal fluid accompanied by a definite clinical improvement. The cell changes observed in 7 previously untreated, advanced patients are shown in Table XXIII. The first examination before treatment showed an increase of lymphocytes in the spinal fluid varying from 17.5 to 285 per cmm. and in addition large mononuclear and mulberry cells were seen in 4 instances, indicating a considerable degree of cerebrospinal involvement. The diagnosis of trypanosomiasis was made by finding the organisms in the cervical lymph glands of all 7 patients; negative examinations followed the first treatment as previously described.

The system of therapy employed in these patients consisted of 3 to 9 intravenous injections of tryparsamide of from 1.0 to 5.0 gm. doses usually at weekly or semi-weekly intervals over an average period of 30 days. The following abstracts indicate the outstanding features of individual cases.

Loyoko № 18.—Soldier on sick leave from a "virulent" region. Good state of nutrition but very anemic. Mental condition normal. Marked filariasis. 60 kilos. General glandular enlargement. Gland puncture ++. Spinal fluid 17.5 lympho-

TABLE XXIII.

Cell Changes of Spinal Fluid in Advanced Cases Treated with Repeated Doses of Tryparsamide.
(No Previous Treatment.)

Case No.	Name.	Course of tryparsamide. Total.	Cell content spinal fluid before treatment.	Cell content spinal fluid after treatment. Per cent change.	3rd L. P. after treatment. Per cent change.	Remarks.
18	Loyoko..... 60 kg.	3 x 3.0 gm. 9.0 gm. in 28 days. 150 mg. per kg.	17.5	3.4 (35 days) 80%	2.5 (82 days) 1 l.m.	Marked improvement.
49	Makalamba... 52.5 kg.	9 x 1.0 gm. 9.0 gm. in 29 days. 171 mg. per kg.	22.0	4.2 (38 days) 80%		Marked improvement.*
9	Bolendo..... 49.0 kg.	5 x 2.0 gm. 10.0 gm. in 34 days. 204 mg. per kg.	47.5	10 (39 days) 1 l.m. 70%		Marked improvement.*
44	N'Kusu..... 38.5 kg.	4 x 4.0 gm. 16.0 gm. in 29 days. 416 mg. per kg.	47.5 l.m.+	15 (32 days) 1 l.m. 68%	22 (55 days)	Improvement.*
32	N'Siola..... 40 kg.	4 x 4.0 gm. 16.0 gm. in 32 days. 400 mg. per kg.	52.5 l.m.+	15 (36 days) 70%	3.1 (66 days)	Marked improvement.
29	Fulu..... 25.5 kg.	8 x 1.0 gm. 8.0 gm. in 33 days. 314 mg. per kg.	142.5 l.m.+	22.5 (36 days) 84%		Marked improvement.*
35	Koloshi..... 44.5 kg.	4 x 5.0 gm. 20.0 gm. in 29 days. 449 mg. per kg.	285.0 l.m.+ m.+	12.5 (35 days) 1 l.m. 96%	8 (64 days) 1 l.m.	Marked improvement.

l.m.—Large mononuclears.
m.—Mulberry cells.
* Tryparsamide treatment resumed.

cytes per cmm. He was given 3 doses of 3.0 gm. (150 mg. per kilo) at intervals of 2 weeks or a total of 9.0 gm.; 5 weeks after the beginning of treatment, the cell count had fallen to 3.4 per cmm., a decrease of 80 per cent. As his general condition had materially improved, he returned to his military duties and during the following 2 months he continued to work each day. A third lumbar puncture done 12 weeks after the first dose of tryparsamide showed a cell content of 2.5 lymphocytes per cmm. with, however, 1 large mononuclear; at this time, a few tiny hard cervical lymph glands could be palpated; his blood count had materially improved. No further treatment is to be given this patient unless trypanosomes are found in the blood or lymph glands or unless there is an increase in the cells of the spinal fluid.

Makalamba # 49.—Fisherman. Good physical and mental condition; had not stopped work. 52.5 kilos. General glandular enlargement. Gland puncture +. Spinal fluid 22 lymphocytes per cmm. He was treated with 9 doses of 1.0 gm. each (19 mg. per kilo) administered twice a week, or a total of 9.0 gm. in 29 days. The second lumbar puncture done 38 days after the first showed a cell content of 4.2 lymphocytes per cmm. or a decrease of 80 per cent. After the course of tryparsamide was finished, he wished to return home but as the duration of the effect of his treatment was not known, a second course was begun. Despite an acute attack of malaria which developed under observation and the detection of a positive Wassermann reaction, he remained in excellent physical condition. There was a marked regression of the cervical adenitis.

Bolendo # 9.—Wife of a soldier. Well nourished but anemic and weak and had been unable to work. Mental condition normal. 49 kilos. General glandular enlargement. Gland puncture ++. Spinal fluid 47.5 lymphocytes per cmm. She was given 5 doses of 2.0 gm. in 34 days—a total of 10.0 gm. or 204 mg. per kilo. 39 days after the first dose of tryparsamide, her spinal fluid contained 10 lymphocytes per cmm., a decrease of 70 per cent, with 1 large mononuclear seen in the counting chamber. After a month's intermission, a second course of 3 doses of 4.0 gm. each was given in 18 days; a subsequent lumbar puncture was refused. There was a noticeable physical improvement, with a marked gain in weight during the first course of treatment which continued during the period of observation. The cervical lymph glands became very small and indurated.

N'Kusu # 44.—Laborer from a "virulent" region. Undernourished and anemic; unable to work. Uncertain mental state. 38.5 kilos. Typical chains of enlarged lymph glands on both sides of neck. Gland puncture ++. Spinal fluid 47.5 lymphocytes per cmm.; large mononuclears +. He was given 4 doses of 4.0 gm. of tryparsamide at 14, 7, and 8 day intervals or 416 mg. per kilo in 29 days, with no untoward effects. A second lumbar puncture, 32 days after the first, showed a cell content of 15 lymphocytes with 1 mononuclear, a decrease of 68 per cent. A third examination, 55 days after admittance, showed 22 lymphocytes per cmm. indicating that the effect of the drug had not continued to produce a further diminution of cells but on the other hand had sufficed to prevent a return to the original condition. A second course of tryparsamide was begun. Physically,

there was a moderate improvement during the period of observation and he wished to return home; the cervical glands decreased markedly in size and became very indurated; mentally, there was definite improvement to a normal status.

N'Siola # 32.—Workman; suspected case. Good state of nutrition. Mental condition normal. 40 kilos. General glandular enlargement. Gland puncture +. Spinal fluid 52.5 lymphocytes per cmm.; large mononuclears +. Treatment consisted of 4 doses of 4.0 gm. at 8, 17, and 7 day intervals or 400 mg. per kilo in 32 days. There were no untoward effects and during the period of observation patient was in excellent physical condition. The cervical lymph glands were reduced to a few shotty masses. A second examination of spinal fluid 5 weeks after the first showed 15 lymphocytes per cmm. and no large mononuclears were seen—a decrease of 70 per cent. A third examination, 66 days after admittance, showed a practically normal count of 3.1 lymphocytes per cmm., and no large mononuclears, and this value represented a decrease of 95 per cent from the original count. No further treatment is to be given this patient unless trypanosomes are found in the lymph glands or blood or the cell content of the spinal fluid increases.

A comparison of the amount of drug administered to the last 3 patients and the effect upon the spinal fluid obtained in each shows that in the case of Bolendo #9 10.0 mg. given in 5 doses of 2.0 gm. over a period of 34 days accomplished the same numerical result as 16.0 gm. in 4 doses of 4.0 gm. in 29 and 32 days given to N'Kusu #44 and N'Siola #32—that is, decreases of 68 and 70 per cent in the cell counts. However, it should be noted that the original examination of the spinal fluids of N'Kusu #44 and N'Siola #32 showed a more serious cerebrospinal involvement as indicated by the presence of large mononuclears. In addition, the effect of the treatment given to N'Siola #32 extended over a longer period than that of the same amount given to N'Kusu #44; the latter patient, however, presumably had a more difficult infection to influence as he came from a "virulent" district.

Fulu # 29.—Small, undernourished, debilitated, and anemic boy. Mental condition normal; tongue tremor. Scabies; pustular skin infection; filariasis. 25.5 kilos. Marked general glandular enlargement. Gland puncture ++. Spinal fluid 142.5 lymphocytes per cmm.; large mononuclears +. He was given 8 doses of 1.0 gm. at intervals of 3 to 9 days over a period of 33 days—so that he received a total amount of 8.0 gm. or 314 mg. per kilo. The second lumbar puncture, 5 weeks after the beginning of treatment, showed a cell count of 22.5 lymphocytes per cmm.—a decrease of 84 per cent and no large mononuclears were seen. A second course of treatment of 1.0 gm. per week for 7 injections was begun a month later. During the period of observation, the tongue tremor disappeared, and there

was a marked reduction in size and induration of the lymph glands with a moderate improvement in general physical condition.

Koloshi # 35.—Laborer. Very weak and anemic; unable to work. Dull mental state. Slight edema of upper eyelids and suggestive fullness of lower jaw. Marked tongue tremor; slight tremor of extended hands; greatly exaggerated knee jerks. Ankylostomiasis; chronic amœbiosis. 44.5 kilos. Slight general glandular enlargement. Gland puncture +. Spinal fluid 285 lymphocytes per cmm.; large mononuclears +; mulberry cells +. He was given 4 doses of 5.0 gm. at intervals of 7, 15, and 7 days, or 20.0 gm. in 29 days (449 mg. per kilo). No untoward effects were observed after individual doses or following the course of treatment. 5 weeks after the beginning of treatment, a second spinal fluid examination showed a cell count of 12.5 lymphocytes per cmm., a decrease of 96 per cent, and in addition only 1 large mononuclear cell was seen. Clinically, there was also a marked improvement; the tremors had disappeared, the knee jerks were practically normal, the edema of the eylids and lower jaw had disappeared, his mental condition appeared normal, and he was much stronger. The change was so striking that it was decided to defer further treatment until a third examination of the spinal fluid could be made. This was accomplished a month later and showed a cell count of 8 lymphocytes per cmm. with 1 large mononuclear seen in the counting chamber. Apparently the disease had not advanced during this time and, therefore, it was decided to omit further treatment until indicated by lymph gland, blood, or spinal fluid findings.

These patients represent typical cases of various degrees of advanced trypanosomiasis. The outstanding features of the treatment of the group are the marked and rapid diminution of the cells of the spinal fluid after 3 or 4 medium sized doses of tryparsamide and a conspicuous physical and mental improvement. Amounts of from 150 to 449 mg. per kilo of body weight given in an average of 4 weeks caused a prompt decrease in the cell content of from 68 to 96 per cent in 3 patients representing slight, moderate, and marked cerebrospinal involvement who showed continued improvement with no further treatment as indicated by lumbar punctures 12 and 9 weeks after admittance. In one patient, a third count showed a slight increase in cells above the second so that treatment was resumed. The 3 remaining patients of the group were given further treatment as the spinal fluids were slightly abnormal after the first course of tryparsamide and there was no means of ascertaining the duration of the therapeutic effect.

Previously Untreated Advanced Cases.

2 Courses of Treatment.

The effect of repeated doses of tryparsamide upon the spinal fluid of a second group of previously untreated patients is shown in Table XXIV. The cell content of the spinal fluid varied from 15 to 450 lymphocytes per cmm. and 6 specimens contained large mononuclears and mulberry cells. The order of arrangement of cases in the accompanying table corresponds to the initial cell count. In general, those patients with less marked abnormality of the spinal fluid showed a secondary anemia, some loss of weight, weakness, an increased pulse rate, and fever with slight nervous symptoms, while in the more advanced cases these symptoms were markedly exaggerated with the addition in certain individuals of pronounced mental disturbances. Trypanosomes were found in the cervical lymph glands of each patient.

Two general systems of treatment were followed in this group—the administration of 2 to 5 doses of 2.0 to 4.0 gm. at weekly intervals or semi-weekly injections of 2.0 gm. A second course of treatment was given approximately a month later. The first dose of the drug produced a sterilization of lymph glands and peripheral blood as previously described. The following abstracts include the important features of individual cases.

Effect upon the Spinal Fluid.—The first 3 patients in Table XXIV showed a slight increase in the cells of the spinal fluids, while the second 3 showed more of an increase and in addition came from a "virulent" district. The last 5 patients are examples of very advanced cases of trypanosomiasis as the cell counts of the spinal fluid indicate.

Bose # 22.—Adult woman complaining of indefinite pains and general malaise. Fair state of nutrition; markedly anemic; exaggerated deep reflexes; mental condition normal. Marked cervical adenitis. Gland puncture +. Spinal fluid 15 lymphocytes per cmm. 56 kilos. She was given 6.0 gm. of tryparsamide or 107 mg. per kilo in 2 doses of 3.0 gm. a week apart. 33 days after the first dose, a second lumbar puncture was done; as the spinal fluid was considerably contaminated with blood, the only comment upon the approximate count of 22 lymphocytes per cmm., is that the pathological condition of the spinal fluid had not materially altered. Physically, there was considerable improvement during this

TABLE XXIV.

Cell Changes of Spinal Fluid in Advanced Cases Treated with Repeated Doses of Tryparsamide.
(No Previous Treatment.)

Case No.	Name.	First course of tryparsamide. Total.	Spinal fluid before treatment.	Spinal fluid after treatment. Per cent change.	2nd course tryparsamide.	3rd L. P. Per cent change.
22	Bose..... 56 kg.	2 x 3.0 gm. 6.0 gm. in 7 days. 107 mg per kg.	15	22(?) (33 days) R.B.C.	4 x 5.0 gm. 20.0 gm. in 19 days. 357 mg. per kg.	6.2 (70 days) 59% ‡
26	M'Pala .... 62 kg.	3 x 3.0 gm. 9.0 gm. in 14 days. 145 mg. per kg.	15	5.6 (30 days) 63%	4 x 5.0 gm. 20.0 gm. in 27 days. 323 mg. per kg.	4.0 (71 days) 73% ‡
6	Nembezi.... 46 kg.	5 x 2.0 gm. 10.0 gm. in 27 days. 220 mg. per kg.	(?)R.B.C.	20 (41 days)	4 x 4.0 gm. 16.0 gm. in 21 days. 348 mg. per kg.	2.0 (98 days) 90% ‡
14	Tono..... 45 kg.	4 x 2.0 gm. 8.7 gm. 1 x 0.7 " 193 mg. per kg. in 28 days.	20.2	7.5 (35 days) 1 l.m. 62%	3 x 4.0 gm. 12.0 gm. in 14 days. 267 mg. per kg.	9.4 (79 days) 53% §
16	Masimango.. 48 kg.	5 x 2.0 gm. 10.0 gm. in 28 days. 208 mg. per kg.	35	7(?) (37 days)† 80%	3 x 4.0 gm. 12.0 gm. in 14 days. 250 mg. per kg.	9.4 (79 days) 4 l.m. 73% ‡
15	Babuli..... 57.5 kg.	5 x 2.0 gm. 10.0 gm. in 28 days. 174 mg. per kg.	70 l.m+	30 (37 days) 2 l.m. 57%	4 x 4.0 gm. 16.0 gm. in 21 days. 278 mg. per kg.	20 (81 days) 1 l.m 71% ‡

24	Miaku*..... 46.5 kg.	2 x 4.0 gm. in 7 days.	8.0 gm. 172 mg. per kg.	305 l.m.++, m.++	25 (35 days) 2 l.m. 92%	5 x 2.0 gm. 10.0 gm. in 29 days. 239 mg. per kg.	16 (80 days) 4 l.m. 95% ‡
25	Madina..... 48 kg.	3 x 4.0 gm. in 14 days.	12.0 gm. 250 mg. per kg.	300 l.m.++, m.++	57.5 (37 days) 81%	8 x 2.0 gm. 16.0 gm. in 24 days. 333 mg. per kg.	14 (74 days) 4 l.m. 95% ‡
20	Kiale*..... 47 kg.	4 x 4.0 gm. in 21 days.	16.0 gm. 340 mg. per kg.	387.5 l.m.+, 2m.	35 (32 days) 91%	8 x 2.0 gm. 16.0 gm. in 24 days. 340 mg. per kg.	33 (78 days) 3–4 l.m. 9 % ‡
17	Bwaba..... 51.5 kg.	4 x 3.0 gm. in 21 days.	12.0 gm. 233 mg. per kg.	450 l.m.++, m.++		1 x 2.0 gm. 2.0 gm. 38 mg. per kg.	22.5 (60 days) 2 l.m. 95% §
10	Makengo.... 41.5 kg.	1 x 1.0 gm. 1 x 2.0 " 1 x 3.0 " 1 x 4.0 " 1 x 5.0 " in 24 days.	15.0 gm. 361 mg. per kg.	247.5 l.m.++, m.++	70 (3 days) 71%	1 x 2.0 gm. 1 x 0.5 " 5 x 1.0 " } 7.5 gm. in 30 days. 180 mg. per kg.	20.4 (86 days) 3 l.m. 92% ‡

* Previous treatment suspected.
† Trace of microscopic blood.
‡ Marked clinical improvement.
§ Moderate clinical improvement.

period and the reflexes had become normal. A second course of approximately 3 times the amount of the first was begun after an intermission of 4 weeks; 4 doses of 5.0 gm. or 357 mg. per kilo were given in 19 days. Her general condition continued to be good and she left the hospital. The cervical lymph glands were reduced to small, indurated masses. The third lumbar puncture 10 weeks after the beginning of treatment showed 6.2 lymphocytes per cmm. in the spinal fluid—a decrease of 59 per cent from the original cell count.

M'Pala № 26.—Wife of a laborer. Good general physical and mental condition; anemic; malaria; general glandular enlargement. Gland puncture +. Spinal fluid 15 lymphocytes per cmm. 62 kilos. She was given 3 weekly doses of 3.0 gm., or 145 mg. per kilo in 14 days. The second examination of the spinal fluid, 30 days after the beginning of treatment, showed a cell content of 5.6 lymphocytes per cmm., or a decrease of 63 per cent. The second course of tryparsamide consisted of 4 weekly doses of 5.0 gm. or 323 mg. per kilo in 27 days—double the amount of the first course and given in twice the time. The succeeding spinal fluid examination 10 weeks after admittance was practically normal, 4 lymphocytes per cmm. During the period of observation, she was in excellent physical condition except for a short malarial attack; there was a marked regression of the adenitis.

Nembezi № 6.—Wife of a soldier. Complained of deep pains in forearms and legs and of feeling sick for 2 months. Well nourished but markedly anemic; normal mental status. Slight cervical adenitis. Gland puncture +. Spinal fluid contaminated with blood. 46 kilos. Treatment was begun with 5 weekly doses of 2.0 gm. or 220 mg. per kilo in 27 days; the subjective symptoms rapidly disappeared and there was a marked improvement in the blood count. A lumbar puncture 6 weeks after admittance showed a cell count of 20 lymphocytes per cmm. A second course of tryparsamide of 4 weekly doses of 4.0 gm. was started after an intermission of 5 weeks; 16.0 gm. or 348 mg. per kilo was given in 21 days. The third lumbar puncture, 14 weeks after admittance, revealed a normal cell count—2 lymphocytes per cmm. She continued in excellent physical condition; the cervical lymph nodes became small and indurated.

Tono № 14.—Boy from a "virulent" region. Fair state of nutrition but extremely weak and anemic. Discrete papulo-vesicular eruption over arms, wrists, backs of hands, and thighs. Normal mental status. Marked cervical adenitis. Gland puncture ++. Spinal fluid 20.2 lymphocytes per cmm. 45 kilos. He was given 5 weekly doses of 2.0 gm. or 193 mg. per kilo in 28 days (one injection incomplete). The eruption cleared during the first 2 weeks and there was a well marked general physical improvement; the cervical lymph glands became small and indurated. The second spinal fluid examination made 5 weeks after admittance showed 7.5 lymphocytes per cmm. (1 large mononuclear)—a decrease of 62 per cent. After an intermission of 2 weeks, treatment was resumed with 3 weekly doses of 4.0 gm. or 267 mg. per kilo, a slightly larger amount than the first course and administered in 2 weeks as contrasted with 4. The third lumbar puncture, 11 weeks after admittance and approximately 3 weeks after the last dose of tryparsamide showed practically no change in the spinal fluid—9.4 lymphocytes per

cmm. No trypanosomes were found in the centrifuged specimens of the spinal fluid. Tryparsamide treatment was resumed.

Masimango # 16.—Laborer from a "virulent" region. Fair state of nutrition but anemic and weak; unable to work. Dulled mental condition; tremor of tongue and extended hands; marked exaggeration of deep reflexes. Cervical glands enlarged and firm. Gland puncture ++. Spinal fluid 35 lymphocytes per cmm. 48 kilos. He was given 5 weekly doses of 2.0 gm. or 208 mg. per kilo in 28 days. There was a prompt physical and mental improvement with disappearance of tremors and exaggerated reflexes during the period of treatment. A second lumbar puncture 5 weeks after admittance showed 7 lymphocytes per cmm., a decrease of 80 per cent. After an interval of 2 weeks, a second course was begun in which 3 doses of 4.0 gm. or 250 mg. per kilo were given in 14 days. A third lumbar puncture was done 11 weeks after admittance and approximately 3 weeks after the last dose of tryparsamide; the spinal fluid contained 9.4 lymphocytes per cmm. and 4 large mononuclears were seen; no trypanosomes were found in centrifuged specimens. Although the third spinal fluid examination showed no improvement beyond that observed in the second, the clinical change was well marked, and the patient returned to work during the second course of treatment. Tryparsamide treatment was resumed.

Babuli # 15.—Laborer from a "virulent" district. Weak and anemic but not emaciated; unable to work. Irritable mental state; leg abscess and malaria; enlarged soft cervical glands. Gland puncture ++. Spinal fluid 70 lymphocytes per cmm.; large mononuclears +. 57.5 kilos. He was given 5 weekly doses of 2.0 gm. or 174 mg. per kilo in 28 days. In spite of a large leg abscess which developed during this period, there was a pronounced physical and mental improvement and a lumbar puncture 5 weeks after admittance showed a cell count of 30 lymphocytes per cmm.—a decrease of 57 per cent and in addition, only 2 large mononuclears were seen. No trypanosomes were found in centrifuged specimens of spinal fluid. The cervical adenitis had disappeared leaving a few tiny indurated glands. Treatment was resumed in 2 weeks with a second course of 4 weekly doses of 4.0 gm. or 278 mg. per kilo in 21 days, that is, 6.0 gm. more than his first course. His spinal fluid examined 12 weeks after admittance showed a further diminution of lymphocytes from 30 to 20 per cmm. or a decrease of 71 per cent from the original count of 70. In this last examination, moreover, only 1 large mononuclear was seen as compared with several in the first and 2 in the second examination. The clinical improvement was well marked and patient was able to return to work. Tryparsamide treatment was resumed because of the continued abnormal cell content of the spinal fluid.

Miaku # 24.—Soldier on sick leave. Complained of headache, indefinite pains in arms and legs, general malaise. Thin but not emaciated; very weak and anemic; dull mental status; beginning lethargy (?), marked tongue tremor, and inconstant tremor of extended hand; greatly exaggerated knee jerks; marked general glandular enlargement. Gland puncture +++. Spinal fluid 305 lymphocytes per cmm.; large mononuclears ++; mulberry cells ++. 46.5 kilos. He was given 2 doses of

4.0 gm. or 172 mg. per kilo of body weight in 7 days. Treatment was then stopped because of the development of visual disturbances; the nervous and mental symptoms, however, had materially improved and he felt much better physically. A second lumbar puncture 5 weeks after admittance showed a remarkable drop in the cells of the spinal fluid, from 305 to 25 or 92 per cent, and in addition no mulberry cells and only 2 large mononuclears were seen. Following an intermission of 6 weeks, treatment was resumed during a febrile attack which had lasted 2 weeks (trypanosomiasis?). Weekly doses of 2.0 gm. were given with beneficial results, for after 2 doses, there was a definite general improvement with cessation of fever. After 5 doses had been given in 29 days, a third lumbar puncture showed a further diminution of cells—16 lymphocytes per cmm. with 4 large mononuclears seen.

Madina № 25.—Laborer. Well nourished but very anemic; mentally affected with beginning lethargy; pronounced tremors of tongue and extended hands; malaria; marked cervical adenitis. Gland puncture ++. Spinal fluid 300 lymphocytes per cmm.; large mononuclears ++; mulberry cells ++. 48 kilos. He was given 3 doses of 4.0 gm. in 14 days or 250 mg. per kilo, which caused a decrease from 300 to 57.5 lymphocytes or 81 per cent. In addition, there was a gradual disappearance of the tremors present on admission and a pronounced mental and physical improvement. The cervical lymph glands were reduced to a few tiny indurated nodules. A second course of smaller doses was begun after an intermission of 4 weeks, consisting of 8 semi-weekly doses of 2.0 gm. or 333 mg. per kilo in 24 days. The third lumbar puncture 74 days after admittance showed the further marked diminution of cells to 14 lymphocytes per cmm., a drop of 95 per cent from the original count; 4 large mononuclears, however, were seen; no trypanosomes were found in centrifuged specimens. The clinical improvement beginning with the first course of tryparsamide was particularly marked and he returned to work, although in view of the residual abnormality of his spinal fluid further treatment was recommended.

Kiale № 20.—House servant. Complained of generalized pains and feeling very ill; not emaciated but weak and asthenic. Extremely dull mental state; marked tremor of tongue and of hands at rest; deep reflexes greatly exaggerated; tinea versicolor. Pronounced cervical adenitis. Gland puncture +. Spinal fluid 387.5 lymphocytes per cmm.; large mononuclears +; 2 mulberry cells. 47 kilos. He was given 4 weekly doses of 4.0 gm. or 340 mg. per kilo in 21 days. The second examination of his spinal fluid made 5 weeks after the first showed a decrease from 387.5 to 35 lymphocytes per cmm. or 91 per cent. At this time his mental condition appeared normal, there were no tremors and the knee jerks were but slightly exaggerated; there was also a well marked physical improvement. A second course of treatment, begun 25 days after the first, consisted of 2 doses of 2.0 gm. per week for 8 injections so that he received the same amount of drug, 16.0 gm., in practically the same time as the first course. The third lumbar puncture 11 weeks after admittance showed no further change in the number of lymphocytes, 33 per cmm.; but 3 or 4 large mononuclear cells were seen and further treatment was recommended. He returned to work and seemed mentally and physically able to do so.

Bwaba # 17.—Laborer from a "virulent" region. Poor state of nutrition, very weak and anemic. Discrete papulo-vesicular eruption over extensor surfaces of forearms. Mental deterioration but no lethargy; marked tremor of tongue and hands at rest; greatly exaggerated knee jerks; slightly enlarged firm cervical glands. Gland puncture +. Spinal fluid 450 lymphocytes per cmm.; large mononuclears ++; mulberry cells ++. 51.5 kilos. He was given 4 weekly doses of 3.0 gm. or 233 mg. per kilo in 21 days with a marked initial clinical improvement. The tremors disappeared, his knee jerks became normal, and the eruption cleared rapidly. During the week following the last dose, however, visual disturbances developed and ultimately there occurred a brawny, indurated swelling of the lower left leg of an uncertain nature and a considerable loss of weight; lumbar puncture was deferred. A second course of smaller doses was begun 5 weeks later; 2 days after the first injection of 2.0 gm., a lumbar puncture was done. It was found that the spinal fluid contained only 22.5 lymphocytes per cmm., a decrease of 95 per cent; 2 large mononuclears were seen. Treatment was continued for 5 additional weekly injections with no further ill effects. There was definite improvement of the mental and nervous symptoms of this patient but less physical benefit than in the other patients of the group.

Makengo # 10.—Young adult laborer. Thin, anemic, and weak; slight edema upper eyelids; discrete papular eruption over forearms, thighs, and legs; uncertain confused mental state; slight lethargy. Tremor of tongue; exaggerated deep reflexes. Cervical adenitis; gland puncture +++. Spinal fluid 247.5 lymphocytes per cmm.; large mononuclears ++; mulberry cells ++. 41.5 kilos. He was given 5 doses of tryparsamide increasing in size from 1.0 to 5.0 gm. so that he received 15.0 gm. or 361 mg. per kilo in 24 days. The second dose of 2.0 gm. was given 3 days after the first, while the succeeding doses of 3.0, 4.0, and 5.0 gm. were given at weekly intervals. There were no untoward effects until after the last dose when visual disturbances appeared and treatment was stopped. A marked clinical improvement, however, had occurred, with disappearance of lethargic symptoms, edema of eyelids, cutaneous eruption, and tongue tremor, and there was a considerable increase in weight. 38 days after admittance, the spinal fluid contained 70 lymphocytes per cmm., a decrease of 71 per cent with no large mononuclears and mulberry cells. A second course of smaller doses of tryparsamide was begun after an interval of 5 weeks, consisting of one 2.0, one 0.5, and five 1.0 gm. doses given on an average of every 5 days so that the patient received 7.5 gm. or 180 mg. per kilo in 30 days. A third lumbar puncture, 12 weeks after admittance, showed a further marked diminution of cells—20.4 lymphocytes per cmm., or a decrease of 92 per cent from the original cell count (3 large mononuclears were seen in the last examination). The physical improvement of this patient was pronounced as indicated by a gain in weight of 7.5 kilos, while the tongue tremor and mental symptoms present on admittance were alleviated.

Considering this group as a whole, the outstanding feature of the treatment is the extremely rapid and marked diminution in the number

of cells of the spinal fluid together with a physical and mental improvement after short courses of tryparsamide. Decreases of from 57 to 92 per cent in the cell counts occurred in from 4 to 5 weeks after the beginning of treatment which in most cases consisted of 2, 3, or 4 doses of 3.0 to 4.0 gm. given at weekly intervals. Second courses of treatment given to 10 patients were followed by further improvement of the spinal fluid in 7 cases while in 3 the diminished cell count remained approximately unchanged. Associated with the changes of the cell content of the spinal fluid was a pronounced beneficial effect upon the physical condition and a similar improvement of nervous and mental symptoms.

Previously Treated Advanced Cases.

This group consisted of 10 patients, 7 of whom were being treated with atoxyl and tartar emetic and 3 the nature of whose previous treatment was unknown. The cell counts of the spinal fluid ranged from 32 to 572 lymphocytes per cmm. and in 6 instances large mononuclears and mulberry cells were seen. The majority of the patients showed pronounced clinical manifestations of an advanced condition. Trypanosomes were found in the cervical lymph glands of the 3 patients who had been treated at some previous time, so they may be considered both as relapsed and non-cured cases; the usual preliminary sterilizing action of tryparsamide was shown by negative examinations of the lymph gland juice of these patients. No one system of treatment was followed in this group but in general doses of various sizes were given at weekly or semi-weekly intervals.

Effect upon the Spinal Fluid.—The effect of treatment with tryparsamide will be considered first in regard to the changes produced in the spinal fluid as shown in Table XXV.

Yali # 13 had received 2.0 gm. soamin and 0.4 gm. tartar emetic during the 4 weeks previous to his admittance. He was weak, anemic, and unable to work. Dull mental condition; marked coarse tremor of the tongue and extended hands; exaggerated deep reflexes. Spinal fluid contained 32 lymphocytes per cmm. 51.5 kilos. He was treated at weekly intervals with 2 doses of 3.0 gm. and 2 doses of 4.0 gm. of tryparsamide, a total of 14.0 gm. or 272 mg. per kilo in 21 days. Clinical improvement was extremely striking by the third week; he was appreciably stronger and mentally seemed normal; there were no tremors and the reflexes

were normal. A second lumbar puncture, 32 days after the first showed 4.6 lymphocytes per cmm. or a decrease of 86 per cent. He remained in excellent condition over an observation period of 3 months during which time examinations of gland juice and centrifuged blood were negative. A third examination of the spinal fluid 74 days after admittance showed the practically normal cell count of 3.4 lymphocytes per cmm. He was able to return to work.

Eali # 1 had received 1 dose of 0.75 gm. of atoxyl 4 days previously. On that day, his spinal fluid contained 80 lymphocytes per cmm. He was thin, weak, and anemic; general glandular enlargement and slightly exaggerated deep reflexes. Mental condition normal. 57 kilos. He was given 2 doses of 2.0 gm. of tryparsamide with a two weeks' interval, or 70 mg. per kilo. Spinal fluid examination 4 weeks after beginning treatment showed a cell content of 62.5 lymphocytes per cmm.—a decrease of 22 per cent, thus indicating that small amounts of tryparsamide, may, in certain cases, have a slight but definite effect upon the spinal fluid and that this effect may endure for an appreciable time. The patient's physical condition had definitely improved; there was a marked reduction of the cervical adenitis and the red cells and hemoglobin of the blood had increased considerably. Treatment was resumed at weekly intervals with 1 dose of 2.0 gm. and 2 doses of 4.0 gm., a total of 10 gm. or 175 mg. per kilo in 14 days. 2 days after the last dose, patient complained of visual dimness and treatment was stopped. During the next 3 weeks, he became quite ill; the condition was diagnosed clinically as an exacerbation of trypanosomiasis and death occurred 5 weeks after the cessation of treatment.

Bibaba # 2 had been treated with 2.5 gm. soamin and 0.4 gm. tartar emetic for 43 days but still showed marked weakness, anemia, general glandular enlargement, greatly exaggerated deep reflexes, and mental apathy. 59 kilos. Spinal fluid contained 37.5 lymphocytes per cmm. He was given 4 doses of 3.0 gm. at 2, 4, and 3 day intervals, a total of 12.0 gm. or 203 mg. per kilo in 9 days. 2 days after the last dose, patient complained of visual impairment and treatment was stopped. A second lumbar puncture done 4 weeks after the beginning of treatment showed 20 lymphocytes per cmm.—a decrease of 47 per cent. A month later, the patient became ill (trypanosomiasis relapse?) and 2 weekly doses of 2.0 gm. were given. There was no increase of residual visual symptoms but the general condition became worse and death occurred.

M'Boyo # 3 had received 2.0 gm. soamin and 0.2 gm. tartar emetic during 26 days preceding tryparsamide treatment. She was undernourished, anemic, and weak; there was a coarse tremor of the hands and greatly exaggerated deep reflexes; she showed mental deterioration and apathy and frequent periods of lethargy; cervical lymph glands barely palpable. 49 kilos. Spinal fluid contained 92.5 lymphocytes per cmm. with many large mononuclears (+++). She was given 4 doses of 3.0 gm. at 2, 4, and 3 day intervals—a total of 12.0 gm. or 245 mg. per kilo in 9 days. Visual disturbance began 2 to 3 days after the last dose and the drug was stopped. The spinal fluid examined 4 weeks after beginning treatment was found to contain only 7.5 lymphocytes per cmm.—a decrease of

TABLE XXV

Cell Changes of the Spinal Fluid of Previously Treated Advanced Cases, Treated with Repeated Doses of Tryparsamide.

Case No.	Name.	First course of tryparsamide. Total.		Spinal fluid before treatment.	Spinal fluid after treatment. Per cent change.	2nd course of tryparsamide. Total.		3rd L. P. Per cent change.
13	Yali*..... 51.5 kg.	2 x 3.0 gm. 2 x 4.0 " in 21 days.	14.0 gm. 272 mg. per kg.	32	4.6 (32 days) 86%			3.4 (74 days) 89%‖
1	Eali*..... 57.0 kg.	2 x 2.0 gm. in 13 days.	4.0 gm. 70 mg. per kg.	80	62.5 (27 days) 22%	1 x 2.0 gm. 2 x 4.0 " in 14 days.	10 gm. 175 mg. per kg.	†
2	Bibaba*..... 59.0 kg.	4 x 3.0 gm. in 9 days.	12.0 gm. 203 mg. per kg.	37.5	20 (27 days) 47% 1 m.	2 x 2.0 gm. in 8 days.	4.0 gm. 67 mg. per kg.	†
3	M'Boyo*.... 49.0 kg.	4 x 3.0 gm. in 9 days.	12.0 gm. 245 mg. per kg.	92.5 l.m.+++	7.5 (27 days) 92%	3 x 4.0 gm. in 14 days.	12.0 gm. 245 mg. per kg.	3.1 (90 days) 97%‖
4	Etumbu*.... 48.5 kg.	3 x 2.0 gm. 1 x 3.0 " in 9 days.	9.0 gm. 185 mg. per kg.	142.5 l.m.+	17.5 (27 days) 88%			‡
8	Tokamba*.. 39.0 kg.	1 x 4.0 gm. 8 x 2.0 " in 28 days.	20.0 gm. 513 mg. per kg.	100 l.m.++	7.5 (39 days) 93% 1 l.m.	6 x 2.0 gm. in 36 days.	12.0 gm. 286 mg. per kg.	§

7	Engondo*... 45.0 kg.	4 x 4.0 gm. in 32 days.	16.0 gm. 356 mg. per kg.	572 l.m.+++ m.+		4 x 2.0 gm. in 21 days.	8.0 gm. 178 mg. per kg.	25 (86 days) 3 l.m. 96%§
21	Monololo... 60.0 kg.	4 x 4.0 gm. in 21 days.	16.0 gm. 267 mg. per kg.	37.5	17.5 (32 days) 3 l.m. 53%	2 x 6.0 gm. 1 x 4.0 " in 29 days.	16.0 gm. 267 mg. per kg.	33 (77 days) l.m+ 12%††
27	K. Lukas... 48.0 kg.	3 x 5.0 gm. in 14 days.	15.0 gm. 313 mg. per kg.	327.5 l.m.+++ m.++	15 (31 days) 95%	8 x 2.0 gm. in 26 days.	16.0 gm. 333 mg. per kg.	41.5 (79 days) 8–9 l.m. 87%§
34	Langomo... 62.5 kg.	3 x 7.0 gm. in 21 days.	21.0 gm. 336 mg. per kg.	467.5 l.m.+++ m.+++	10 (35 days) 98%			**

* Under atoxyl and tartar emetic treatment when transferred to tryparsamide therapy.
† Died. Trypanosomiasis (?).
‡ Died. Amœbic dysentery—trypanosomiasis (?)
§ Improvement.
‖ Marked improvement.
** Marked improvement. Deserted.
†† Stationary state.

92 per cent and in addition no large mononuclear or mulberry cells were seen. By this time the visual disturbance had completely disappeared and there was a noticeable mental and physical improvement. She no longer showed any tendency toward a lethargic state and the tremors had disappeared although the deep reflexes continued to be exaggerated. Treatment was resumed after 3 weeks and 3 doses of 4.0 gm. were given at weekly intervals, so that the same amount of drug, 12.0 gm. or 245 mg. per kilo was given again but during a period of 14 instead of 9 days. No visual or other disturbances occurred and there was a continued striking clinical improvement. She appeared cheerful and happy, was able to take care of herself and answered questions intelligently, all of which contrasted sharply with her condition when first seen. A third examination of the spinal fluid 3 months after admittance contained 3.1 lymphocytes per cmm.—a practically normal count.

Etumbu № 4 had been treated with 1.5 gm. soamin and 0.2 gm. tartar emetic during a period of 22 days. He was somewhat emaciated and very anemic. Mentally apathetic. 48.5 kilos. Spinal fluid contained 142.5 lymphocytes per cmm.; large mononuclears +. He was given 3 doses of 2.0 gm. and 1 dose of 3.0 gm. at 2, 4, and 3 day intervals—a total of 9.0 gm. or 185 mg. per kilo in 9 days. Visual impairment developed 3 to 4 days after the last dose and no further treatment was given. This effect was transitory and his sight became normal within 2 weeks. A second spinal fluid examination made 4 weeks after the first showed 17.5 lymphocytes per cmm. or a decrease of 88 per cent. At this time, however, amœbic dysentery developed and although emetine treatment resulted in negative stool examinations, he died 3 weeks later. The question of a trypanosomiasis exacerbation must also be considered as a possible cause of death.

Tokamba № 8 was an old advanced case, who had been in the hospital for 9 months, during which time he had received 27 injections of 0.5 gm. soamin (13.5 gm.), and 29 injections of 0.1 gm. tartar emetic (2.7 gm.). His general state had not been improved. There was marked emaciation and weakness; anemia; greatly exaggerated deep reflexes; tremors of the tongue, hands, and feet; a typical shuffling gait and marked mental deterioration and apathy. 39 kilos. Spinal fluid contained 100 lymphocytes per cmm.; large mononuclears ++. He was given one dose of 4.0 gm. tryparsamide, followed by 8 doses of 2.0 gm. at 3 and 4 day intervals so that a total of 20.0 gm. or 513 mg. per kilo was administered in 28 days. No untoward effects were observed. A second spinal fluid examination, 39 days after the beginning of treatment, showed a markedly diminished number of cells—7.5 lymphocytes per cmm., or a decrease of 93 per cent and only 1 large mononuclear was seen. At this time, patient's physical condition was distinctly improved; he had gained weight and seemed brighter mentally but his nervous symptoms were still marked. Treatment was resumed 5 weeks later and he was given 6 weekly doses of 2.0 gm. or 286 mg. per kilo. The clinical improvement in this patient was not as striking as in the case of M'Boyo № 3 but the mental deterioration and nervous symptoms at the time he was transferred to tryparsamide treatment were of a more advanced and serious character as well as of longer duration. In addition, he had been previously treated for many months.

Engondo #7 had been under more or less constant observation for 7 years. She had been originally treated with salvarsan-copper, followed by atoxyl and tartar emetic, after which she deserted. She was readmitted to the hospital 4½ years later in a markedly advanced stage of the disease. During 2½ years, she received 63 injections of 0.5 gm. of atoxyl (31.5 gm.), 53 injections of 0.5 gm. soamin (26.5 gm.), and 114 injections of 0.1 gm. tartar emetic (11.4 gm.). Examination showed an extreme mental deterioration, typical shuffling gait, marked tremors of tongue, hands, and feet, and greatly exaggerated reflexes. She was wholly irresponsible with hallucinations and violent hysterical attacks and in addition was in a lethargic state much of the time. Thin but otherwise fair general physical condition. 45 kilos. Spinal fluid contained 572 lymphocytes per cmm. with numerous large mononuclears and mulberry cells. 4 doses of 4.0 gm. tryparsamide were given at weekly intervals, a total of 16.0 gm. or 356 mg. per kilo, in 32 days. There were no untoward effects but little mental improvement was observed. A second course of 6 weekly doses of 2.0 gm. was begun a month later and after 4 of these had been given a lumbar puncture was done (12 weeks after the beginning of tryparsamide treatment). The spinal fluid showed the markedly diminished cell count of 25 lymphocytes per cmm., a decrease of 96 per cent, and only 3 large mononuclears were seen. The patient's mental condition, however, was still very abnormal; her disposition was unchanged and she still showed periods of lethargy. Her gait, however, had materially improved, the deep reflexes were less exaggerated; there were no tremors and 3 months after the beginning of treatment, there was a gain in weight of 4 kilos. The cerebrospinal involvement of this patient was extreme and of long duration, persisting in spite of continued atoxyl and tartar emetic treatment, and she thus represents a type of case considered as hopeless of therapeutic influence. Under these circumstances, therefore, a marked diminution of the cells of the spinal fluid with a certain degree of clinical improvement may be considered as a definite effect of tryparsamide treatment.

Monololo #21, a soldier on sick leave, gave a history of having been treated for several months about a year before admittance. He was a well developed, well nourished man, with normal reflexes and no mental or nervous symptoms. Cervical adenitis; gland puncture ++. 60 kilos. Spinal fluid contained 37.5 lymphocytes per cmm. He was given 4 weekly doses of tryparsamide of 4.0 gm. each, or 267 mg. per kilo in 21 days with no untoward effects. 32 days after the administration of the first dose, a second examination of the spinal fluid showed a cell content of 17.5 lymphocytes per cmm.—a decrease of 53 per cent; 3 large mononuclear cells were seen. A second course of treatment was begun 2 weeks after the first because the decrease of the spinal fluid cells had not been as great as in most of the other cases. Because of his size and excellent physical condition, the dose was increased to 6.0 gm. and he was given 2 doses 10 days apart. 10 days after the second dose, he complained of slight visual dimness which had occurred 2 or 3 days before. He did not return for 3 weeks and was then given 4.0 gm. 12 days later, or 11 weeks after the administration of the first dose of tryparsamide, the spinal fluid contained 33 lymphocytes per cmm. with several large mononuclears, a similar finding to that seen on admittance.

The correct interpretation of the last spinal fluid examination must take into account the type and nature of the infection, but, at all events, it is possible that with a greater number of regularly spaced doses, a more favorable effect might have been obtained. With this in view, it was decided to continue the treatment with weekly doses of 3.0 gm. over a longer period of time.

K. Lukas # 27, a house servant, had been treated for a long time in various localities. He was unable to work and complained of pains in his legs. Well nourished but anemic with a general glandular enlargement, tongue tremor and greatly exaggerated deep reflexes. Mental state normal. Gland puncture ++ 48 kilos. Spinal fluid contained 327.5 lymphocytes per cmm.; large mononuclears +++; mulberry cells ++. He was given 15.0 gm. or 313 mg. per kilo in 3 weekly doses of 5.0 gm. with no untoward effects. 31 days after admittance, his spinal fluid contained 15 lymphocytes per cmm., a decrease of 95 per cent. A second course of tryparsamide, consisting of 2 doses of 2.0 gm. per week, was begun 4 weeks later and he received 8 doses, a total of 16.0 gm. in 26 days, practically the same amount of the drug as in the first course but in 26 instead of 14 days. The third spinal fluid examination made 11 weeks after admittance showed a cell content of 41.5 lymphocytes per cmm., a decrease of 87 per cent from the original count but an increase above the second, and in addition 8 to 9 large mononuclears were seen. The physical condition of this patient was excellent and therefore it was decided to begin a third course of larger doses of 4.0 gm. administered once a week for at least 5 doses. Although the second course of tryparsamide had not been sufficient to produce a continued diminution of the spinal fluid cells, he was able to return to his work.

Langomo # 34 was a "vagabond" appearing first in one district and then in another and had been treated for an unknown period of time. He was a large, strong, powerfully built man, with a slight general glandular enlargement and markedly exaggerated deep reflexes. He showed great mental deterioration and apathy but was not lethargic. Gland puncture +. Spinal fluid contained 467.5 lymphocytes per cmm.; large mononuclears +++; mulberry cells +++. 62.5 kilos. He was given 3 doses of 7.0 gm. of tryparsamide in 21 days at 13 and 8 day intervals, a total of 21.0 gm. or 336 mg. per kilo with no untoward effects of any kind. There was a very evident mental improvement, however, shown by his rational answers to questions and the disappearance of mental apathy. The second spinal fluid examination, 5 weeks after the first, showed a cell content of only 10 lymphocytes per cmm., a decrease of 98 per cent and in addition no large mononuclear or mulberry cells were seen. Unfortunately no further observations on this patient could be made, as he ran away.

The striking feature of the treatment of this group of advanced cases is the marked and rapid diminution of the cells in the spinal fluid induced by a few doses of tryparsamide. Decreases in the cell count of from 47 to 98 per cent occurred in 4 to 5 weeks with the

exception of one patient, Eali #1, who was given only 2 fortnightly doses, and here there was a decrease of 22 per cent.

The system of therapy employed in the majority of instances consisted of 3 or 4 injections of 2.0 to 7.0 gm. at various intervals ranging from 3 to 14 days. The administration of doses at weekly or 10 day intervals was well borne with two exceptions but more frequent dosage caused visual disturbances in 3 instances which for the most part were transitory. In the case of Yali #13, the decrease of the cells in the spinal fluid induced by one course of tryparsamide continued over the observation period of $7\frac{1}{2}$ weeks after cessation of treatment; regarding Langomo #34, only the early effect of one course of treatment was observable as he deserted. The second course of treatment given to M'Boyo #3 caused a further diminution in the cell count of the spinal fluid and it is probable that a similar condition existed in the case of Engondo #7. It was not possible to obtain additional lumbar punctures from the 3 patients who died, and with Tokamba #8, it was deferred until further treatment had been given. In 2 patients, Monololo #21 and K. Lukas #27, the diminished cell content of the spinal fluid was not further influenced by the second course of tryparsamide and in one instance this may be partly explained by the irregular spacing and insufficient number of doses. Further, in judging the results of the treatment of this group of patients, the type and stage of the disease and the fact that prolonged previous treatment had been given must also be taken into consideration.

The mental and physical improvement which paralleled the changes in the spinal fluid were likewise striking and it should be pointed out that they occurred in all patients with 3 exceptions in whom the treatment was stopped.

GENERAL OBSERVATIONS.

Effect upon the Blood.—The changes in the blood counts of advanced cases of trypanosomiasis treated with one or two courses of repeated doses of tryparsamide were studied in 24 patients as shown in Tables XXVI to XXVIII. The first 17 patients in these tables were previously untreated, while the last 7 had been treated before. The amount of tryparsamide given to these patients ranged from 70 to 680 mg. per kilo; in general this was given in weekly doses of 2.0 to

TABLE XXVI.

Changes in Blood Counts, Advanced Cases, Treated with Repeated Doses of Tryparsamide. (*One Course.*)
(*No Previous Treatment.*)

Case No.	Name.	Doses of tryparsamide.	Total.	Blood count before treatment.		Last blood count after treatment.	Change.	Interval between counts.
							per cent	*days*
18	Loyoko.....	3 x 3.0 gm.	9.0 gm.	R.B.C.	2,720,000	4,800,000	+ 76	82*
	60.0 kg.	in 28 days.	150 mg. per kg.	Hb.	45 %	80 %	+ 78	
				W.B.C.	7,500	8,000	+ 7	
49	Makalamba.....	9 x 1.0 gm.	9.0 gm.	R.B.C.	4,320,000	4,640,000	+ 7	47†
	52.5 kg.	in 29 days.	171 mg. per kg.	Hb.	70 %	75 %	+ 7	
				W.B.C.	11,000	10,000	− 9	
29	Fulu.....	8 x 1.0 gm.	8.0 gm.	R.B.C.	4,160,000	4,160,000	−	46‡
	25.5 kg	in 33 days.	314 mg. per kg.	Hb.	55 %	50 %	− 9	
				W.B.C.	4,500	11,000	+144	
32	N'Siola.....	4 x 4.0 gm.	16.0 gm.	R.B.C.	4,160,000	5,120,000	+ 23	73
	40.0 kg.	in 32 days.	400 mg. per kg.	Hb.	60 %	75 %	+ 25	
				W.B.C.	8,500	8,000	− 6	
35	Koloshi	4 x 5.0 gm.	20.0 gm.	R.B.C.	3,840,000	5,120,000	+ 33	45§
	44.5 kg.	in 29 days.	449 mg. per kg.	Hb.	45 %	60 %	+ 34	
				W.B.C.	5,000	8,000	+ 60	

* Filariasis.
† Syphilis; malaria.
‡ Scabies; pustular skin infection; filariasis.
§ Chronic ankylostomiasis and amœbiosis.

5.0 gm. The second blood count was made from 3 to 14 weeks after the first. The red and white cell counts and hemoglobin determination before and after treatment are also tabulated separately for convenience of comparison (Tables XXIX, XXX, XXXI).

The striking feature of the initial blood counts was the marked degree of secondary anemia. 17 patients had red cell counts of below 4 million, 6 between 4 and 4½ million, and only 1 had a normal number of red cells. The hemoglobin was likewise diminished; 14 determinations were 50 per cent or lower, 8 were between 50 and 60 per cent, and 2 were 70 per cent. There was a leukopenia of below 6,000 white cells in 12 instances, in 3 between 6 and 8 thousand, while 9 patients had counts of between 8 and 12 thousand.

The effect of tryparsamide treatment upon the red cell count is seen in Table XXIX. In only one instance (Fulu #29) was an improvement not observed, while in 23 patients, the red cells were increased from 7 to 100 per cent. In 13 patients this increase amounted to more than 20 per cent and in 10 patients from 7 to 19 per cent.

The hemoglobin changes were even more striking (Table XXX). There was an increase of 7 to 78 per cent in 23 patients and a decrease of 9 per cent in one patient (Fulu #29). 11 patients showed an increase of 40 per cent or more, while in 6 others the increase was above 20 per cent.

The white cell counts were also influenced by the tryparsamide treatment as shown in Table XXXI. There were both increases and decreases but in general there was a definite tendency toward a normal count as may be seen by comparing the 4th and 5th columns in this table.

These results are in accord with the observations on the blood picture of patients in the earlier stages of the disease treated with single or repeated doses of tryparsamide and are indicative of a favorable response to the drug.

Effect upon the Weight.—The changes in weight of 28 advanced cases treated with repeated doses of tryparsamide are given in Tables XXXII and XXXIII. The 18 patients in Table XXXII are those who had had no previous treatment, while the 10 in Table XXXIII had been treated before for varying periods of time. The first 7 patients in Table XXXII were given 1 course of tryparsamide,

TABLE XXVII.

Changes in Blood Counts, Advanced Cases, Treated with Repeated Doses of Tryparsamide. (Two Courses.)
(No Previous Treatment.)

Case No.	Name.	Doses of tryparsamide. Total.	Blood count before treatment.	Last blood count after treatment.	Change.	Interval between counts.
					per cent	*days*
22	Bose.....	2 x 3.0 gm. 6.0 gm	R.B.C. 2,560,000	5,120,000	+100	85
	56.0 kg.	in 7 days.	Hb. 52 %	75 %	+ 44	
		4 x 5.0 gm. 20 "	W.B.C. 5,200	8,400	+ 61	
		in 19 days.				
		26.0 gm. 464 mg. per kg.				
26	M'Pala.....	3 x 3.0 gm. 9.0 gm.	R.B.C. 4,136,000	5,120,000	+ 24	71*
	62.0 kg	in 14 days.	Hb. 55 %	80 %	+ 45	
		4 x 5.0 gm. 20.0 "	W.B.C. 9,600	10,000	+ 4	
		in 27 days.				
		29.0 gm. 468 mg. per kg.				
6	Nembezi.....	5 x 2.0 gm. 10.0 gm.	R.B.C. 3,616,000	4,160,000	+ 15	93†
	46.0 kg.	in 27 days.	Hb. 40 %	65 %	+ 63	
		4 x 4.0 gm. 16.0 "	W.B.C. 8,500	6,600	− 22	
		in 21 days.				
		26.0 gm. 568 mg. per kg.				
14	Tono.....	4 x 2.0 gm. 8.7 gm.	R.B.C. 3,352,000	4,000,000	+ 19	81
	45.0 kg.	1 x 0.7 "	Hb. 48 %	75 %	+ 56	
		in 28 days.	W.B.C. 6,000	5,200	− 13	
		3 x 4.0 gm. 12.0 "				
		in 14 days.				
		20.7 gm. 460 mg. per kg.				

16	Masimango..... 48.0 kg.	5 x 2.0 gm. 10.0 gm. in 28 days. 3 x 4.0 gm. 12.0 " in 14 days. 22.0 gm. 458 mg. per kg.	R.B.C. 3,040,000 Hb. 50 % W.B.C. 7,500	5,040,000 70 % 9,000	+ 66 + 40 + 20	84
15	Babuli..... 57.5 kg.	5 x 2.0 gm 10.0 gm. in 28 days. 4 x 4.0 gm. 16.0 " in 21 days. 26.0 gm. 452 mg. per kg.	R.B.C. 3,840,000 Hb. 46 % W.B.C. 4,000	4,320,000 65 % 8,000	+ 13 + 41 +100	81‖
24	Miaku ..... 46.5 kg.	2 x 4.0 gm. 8.0 gm. in 7 days. 5 x 2.0 gm. 10.0 " in 29 days. 18.0 gm. 411 mg. per kg.	R.B.C. 3,104,000 Hb. 52 % W.B.C. 5,400	3,200,000 65 % 4,400	+ 3 + 25 − 18	78§
25	Madina..... 48.0 kg.	3 x 4.0 gm. 12.0 gm. in 14 days. 8 x 2.0 gm. 16.0 " in 24 days. 28.0 gm. 583 mg. per kg.	R.B.C. 3,728,000 Hb. 50 % W.B.C. 5,550	4,000,000 70% 7,800	+ 7 + 40 + 40	74*
20	Kiale..... 47.0 kg.	4 x 4.0 gm. 16.0 gm. in 21 days. 8 x 2.0 gm. 16.0 " in 24 days. 32.0 gm. 680 mg. per kg.	R.B.C. 4,000,000 Hb. 60 % W.B.C. 12,000	4,320,000 70 % 9,000	+ 8 + 17 − 25	81‡

TABLE XXVII—*Continued.*

Case No.	Name.	Doses of tryparsamide. Total.	Blood count before treatment.	Last blood count after treatment.	Change.	Interval between counts.
					per cent	*days*
17	Bwaba.....	4 x 3.0 gm. 12.0 gm.	R.B.C. 2,400,000	4,060,000	+ 69	87§
	51.5 kg.	in 21 days.	Hb. 42 %	55 %	+ 31	
		5 x 2.0 gm. 10.0 "	W.B.C. 12,000	8,000	− 33	
		in 28 days.				
		22.0 gm. 427 mg. per kg.				
10	Makengo.....	1 x 1.0 gm. 1 x 2.0 " 1 x 3.0 " } 15.0 gm. 1 x 4.0 " 1 x 5.0 "	R.B.C. 2,940,000	4,480,000	+ 52	88
	41.5 kg.		Hb. 48 %	60 %	+ 25	
			W.B.C. 10,000	7,200	− 28	
		in 24 days.				
		1 x 2.0 gm. 1 x 0.5 " } 7.5 gm. 5 x 1.0 "				
		in 30 days.				
		22.5 gm. 541 mg. per kg.				
9	Bolendo.....	5 x 2.0 gm. 10.0 gm.	R.B.C. 2,912,000	4,000,000	+ 37	88
	49.0 kg.	in 34 days.	Hb. 55 %	65 %	+ 18	
		3 x 4.0 gm. 12.0 "	W.B.C. 6,200	7,000	+ 13	
		in 18 days.				
		22.0 gm. 449 mg. per kg.				

* Malaria.
† Malaria (?).
‡ Tinea versicolor.
§ Trypanosomiasis exacerbation (?).
‖ Malaria; leg abscess.

while the remainder, 21 (Tables XXXII and XXXIII), received 2 courses averaging 1 month each and separated in most instances by an interval of 4 to 6 weeks. The observation periods range from 4 to 16 weeks.

Taking up first the weight changes in the previously untreated patients, it is seen that 14 showed a gain of from 0.5 to 8.5 kilos during 8 to 14 weeks; 2 patients showed no change—Loyoko #18, a well nourished adult, and Fulu #29, a small boy with an extensive skin infection and filariasis; and 2 others lost weight—Babula #15, who had a large leg abscess and an attack of estivo-autumnal malaria, and Bwaba #17, who probably had an exacerbation of the disease together with visual disturbances. The smaller increases of 0.5 to 1.0 kilo occurred in 7 patients, 2 of whom had malaria, 1 visual disturbances and probably an exacerbation of trypanosomiasis, and 1 chronic amœbic dysentery and ankylostomiasis, while 7 patients showed a gain of from 3.0 to 8.5 kilos.

The 10 patients in Table XXXIII were previously treated with other drugs as has already been described. 3 of them became very ill during the period of observation, lost weight, and eventually died (Eali #1, Bibaba #2, and Etumbu #4). The other 7 patients showed increases of weight of from 3.0 to 7.0 kilos except Langomo #34, who was in a good state of nutrition on admittance and gained only 0.5 kilo during 6 weeks.

The general beneficial effect of tryparsamide in advanced cases of trypanosomiasis, as indicated by increases of weight in the majority of patients, is similar to that observed after the administration of single and repeated doses in early stages of the disease. However, since the advanced cases were usually more emaciated, the improvement is relatively more pronounced.

Untoward Effects.—The administration of single or repeated doses of tryparsamide in all types of human trypanosomiasis represented by the 77 cases treated in Léopoldville was singularly free from immediate or delayed so called toxic symptoms or reactions, such as nausea, fever, headaches, diarrhœa, renal disturbances, jaundice, petechial hemorrhages, cutaneous reactions of various types, and syncope which may occur after the administration of various arsenical agents. A continued clinical improvement was characteristic of the tryparsa-

TABLE XXVIII.

Changes in Blood Counts, Advanced Cases, Treated with Repeated Doses of Tryparsamide.
(Previous Treatment.)

Case No.	Name.	Doses of tryparsamide. Total.	Blood count before treatment.	Last blood count after treatment.	Change.	Interval between counts.
					per cent	*days*
13	Yali.....	2 x 3.0 gm. 14.0 gm.	R.B.C. 3,360,000	4,800,000	+ 43	88
	51.5 kg.	2 x 4.0 "	Hb. 45 %	75 %	+ 67	
		272 mg. per kg. in 21 days.	W.B.C. 2,300	8,000	+248	
1	Eali.....	2 x 2.0 gm. 4.0 gm.	R.B.C. 2,720,000	4,160,000	+ 49	20*
	57.0 kg.	70 mg. per kg. in 13 days.	Hb. 35 %	51 %	+ 46	
			W.B.C. 4,400	9,000	+104	
2	Bibaba.....	4 x 3.0 gm. 12.0 gm.	R.B.C. 2,480,000	3,616,000	+ 46	35*
	59.0 kg.	203 mg. per kg. in 9 days.	Hb. 48 %	55 %	+ 14	
			W.B.C. 3,500	7,000	+100	
3	M'Boyo.....	4 x 3.0 gm. 12.0 gm.	R.B.C. 2,780,000	3,680,000	+ 32	99
	49.0 kg.	in 9 days.	Hb. 35 %	60 %	+ 71	
		3 x 4.0 gm. 12.0 gm.	W.B.C. 2,700	6,000	+122	
		in 14 days.				
		24.0 gm. 490 mg. per kg.				
4	Etumbu.....	3 x 2.0 gm. 9.0 gm.	R.B.C. 2,280,000	2,480,000	+ 9	24†
	48.5 kg.	1 x 3.0 "	Hb. 34 %	40 %	+ 18	
		185 mg. per kg. in 9 days.	W.B.C. 9,500	12,580	+ 32	

21	Monololo..... 60.0 kg.	4 x 4.0 gm. 16.0 in 21 days. 2 x 6.0 gm. 20.0 gm. 2 x 4.0 " 36.0 gm. 600 mg. per kg.	R.B.C. 4,800,000 Hb. 70 % W.B.C. 8,000	5,120,000 75 % 8,000	+ 7 + 7 —	84
27	K. Lukas..... 48.0 kg.	3 x 5.0 gm. 15.0 gm. in 14 days. 8 x 2.0 gm. 16.0 gm. in 26 days. 31.0 gm. 646 mg. per kg.	R.B.C. 4,000,000 Hb. 60 % W.B.C. 4,000	4,600,000 75 % 7,000	+ 15 + 25 + 75	79

* Trypanosomiasis exacerbation (?).

† Acute amœbiosis; trypanosomiasis exacerbation (?).

mide treatment in practically every patient, with the exception of those who had complicating infections and those who presented the only untoward effect observed. This consisted in the occurrence of a visual impairment in 9 advanced cases.

TABLE XXIX.

Changes in the Red Blood Cells of Advanced Cases Treated with Repeated Doses of Tryparsamide.

Case No.	Name.	Total amount tryparsamide.	R. B. C. before treatment	Last R. B. C. after treatment.	Change.	Interval between counts.
		mg. per kg.			*per cent*	*days*
18	Loyoko	150	2,720,000	4,800,000	+ 76	82
35	Koloshi	449	3,840,000	5,120,000	+ 33	45
29	Fulu	314	4,160,000	4,160,000	—	46
32	N'Siola	400	4,160,000	5,120,000	+ 23	73
49	Makalamba	171	4,320,000	4,640,000	+ 7	47
17	Bwaba	427	2,400,000	4,060,000	+ 69	87
22	Bose	464	2,560,000	5,120,000	+100	85
9	Bolendo	449	2,912,000	4,000,000	+ 37	88
10	Makengo	541	2,940,000	4,480,000	+ 52	88
16	Masimango	458	3,040,000	5,040,000	+ 66	84
24	Miaku	411	3,104,000	3,200,000	+ 3	78
14	Tono	460	3,352,000	4,000,000	+ 19	81
6	Nembezi	568	3,616,000	4,160,000	+ 15	93
25	Madina	583	3,728,000	4,000,000	+ 7	74
15	Babuli	452	3,840,000	4,320,000	+ 13	81
20	Kiale	680	4,000,000	4,320,000	+ 8	81
26	M'Pala	468	4,136,000	5,120,000	+ 24	71
4	Etumbu	185	2,280,000	2,480,000	+ 9	24
2	Bibaba	203	2,480,000	3,616,000	+ 46	35
1	Eali	70	2,720,000	4,160,000	+ 49	20
3	M'Boyo	490	2,780,000	3,680,000	+ 32	99
13	Yali	272	3,360,000	4,800,000	+ 43	88
22	K. Lukas	646	4,000,000	4,600,000	+ 15	79
21	Monololo	600	4,800,000	5,120,000	+ 7	84

The first 5 patients were treated with 1 course of tryparsamide; the next 12 with 2 courses; the last 7 had been previously treated with other drugs.

Before discussing the significant features of this disturbance, a brief description of its occurrence in each patient will be given. The first 5 patients were known to have received previous treatment with

arsenical drugs and we suspected that one other, Miaku #24, had been treated before. All had marked involvement of the cerebrospinal system on admittance as shown clinically and by spinal fluid examination with the exception of Monololo #21.

TABLE XXX.

Changes in the Hemoglobin Content of the Blood of Advanced Cases Treated with Repeated Doses of Tryparsamide.

Case No.	Name.	Total amount tryparsamide.	Hemoglobin before treatment.	Hemoglobin after treatment.	Change.	Interval between counts.
		mg. per kg.			*per cent*	*days*
18	Loyoko	150	45	80	+78	82
35	Koloshi	449	45	60	+34	45
29	Fulu	314	55	50	− 9	46
32	N'Siola	400	60	75	+25	73
49	Makalamba	171	70	75	+ 7	47
6	Nembezi	568	40	65	+63	93
17	Bwaba	427	42	55	+31	87
15	Babuli	452	46	65	+41	81
14	Tono	460	48	75	+56	81
10	Makengo	541	48	60	+25	88
16	Masimango	458	50	70	+40	84
25	Madina	583	50	70	+40	74
22	Bose	464	52	75	+44	85
24	Miaku	411	52	65	+25	78
26	M'Pala	468	55	80	+45	71
9	Bolendo	449	55	65	+18	88
20	Kiale	680	60	70	+17	81
4	Etumbu	185	34	40	+18	24
1	Eali	70	35	51	+46	20
3	M'Boyo	490	35	60	+71	99
13	Yali	272	45	75	+67	88
2	Bibaba	203	48	55	+14	35
27	K. Lukas	646	60	75	+25	79
21	Monololo	600	70	75	+ 7	84

The first 5 patients were treated with 1 course of tryparsamide; the next 12 with 2 courses; the last 7 had been previously treated with other drugs.

Eali # 1.—Previous treatment, 0.75 gm. atoxyl. Lumbar puncture, 80 lymphocytes per cmm. Slightly exaggerated deep reflexes; mental condition normal. He was given 3 doses of 2.0 gm. in 27 days, followed after a week's interval by 2 doses of 4.0 gm. in 7 days. 2 days after the last dose, he complained of indis-

tinctness of vision of both eyes; walked unsteadily but could count fingers; treatment stopped. A month later he could count fingers with left eye but not with right; he could distinguish light with both. General condition became worse, with fever, etc. (exacerbation of trypanosomiasis?), and death occurred.

TABLE XXXI.

Changes in the White Blood Cells of Advanced Cases Treated with Repeated Doses of Tryparsamide.

Case No.	Name.	Total amount tryparsamide.	W. B. C. before treatment.	Last W. B. C. after treatment.	Change.	Interval between counts.
		mg. per kg.			*per cent*	*days*
29	Fulu	314	4,500	11,000	+144	46
35	Koloshi	449	5,000	8,000	+ 60	45
18	Loyoko	150	7,500	8,000	+ 7	82
32	N'Siola	400	8,500	8,000	− 6	73
49	Makalamba	171	11,000	10,000	− 9	47
15	Babuli	452	4,000	8,000	+100	81
22	Bose	464	5,200	8,400	+ 61	85
24	Miaku	411	5,400	4,400	− 18	78
25	Madina	583	5,550	7,800	+ 40	74
14	Tono	460	6,000	5,200	− 13	81
9	Bolendo	449	6,200	7,000	+ 13	88
16	Masimango	458	7,500	9,000	+ 20	84
6	Nembezi	568	8,500	6,600	− 22	93
26	M'Pala	468	9,600	10,000	+ 4	71
10	Makengo	541	10,000	7,200	− 28	88
17	Bwaba	427	12,000	8,000	− 33	87
20	Kiale	680	12,000	9,000	− 25	81
13	Yali	272	2,300	8,000	+248	88
3	M'Boyo	490	2,700	6,000	+122	99
2	Bibaba	203	3,500	7,000	+100	35
27	K. Lukas	646	4,000	7,000	+ 75	79
1	Eali	70	4,400	9,000	+104	20
21	Monololo	600	8,000	8,000	−	84
4	Etumbu	185	9,500	12,580	+ 32	24

The first 5 patients were treated with 1 course of tryparsamide; the next 12 with with 2 courses; the last 7 had been previously treated with other drugs.

Bibaba № 2.—Previous treatment: soamin, 5 doses of 0.5 gm., and tartar emetic, 4 doses of 0.1 gm., during 43 days. Lumbar puncture 37.5 lymphocytes per cmm. Greatly exaggerated deep reflexes and mental apathy. He was given 4 doses of 3.0 gm. or 203 mg. per kilo in 9 days. 2 days after last injection, complained of

TABLE XXXII.

Weight Changes of Advanced Cases (No Previous Treatment) Treated with Repeated Doses of Tryparsamide.

Case No.	Name.	Spinal fluid before treatment.	Doses of tryparsamide.	Initial weight.	2nd week.	4th week.	6th week.	8th week.	10th week.	12th week.	14th week.	Total change.
			gm.	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*
18	Loyoko.....	17.5	3 x 3.0	60	60	63	62		61.5	60		0‡‡
49	Makalamba...	22.0	9 x 1.0	52.5	54.5	54	53	53.5				+1.0§§
9	Bolendo.....	47.5	5 x 2.0 3 x 4.0	49	51	51	53		56.5	57	57.5	+8.5
29	Fulu.....	142.5	8 x 1.0 1 x 2.0 2 x 1.0	25.5	25	25.5	25	26	25.5			0**
32	N'Siola.....	52.5	4 x 4.0	40	39.5	40	38.5	39	41			+1.0
35	Koloshi.....	285.0	4 x 5.0	44.5	44.5	45	44.5	44.5	45			+0.5††
44	N'Kusu.....	47.5	4 x 4.0 2 x 2.0	38.5	37.5	39	39	39	39.5			+1.0
22	Bose.....	15	2 x 3.0 4 x 5.0	56	55	56	56	58.5	59.5	60.5		+4.5
26	M'Pala.....	15	3 x 3.0 4 x 5.0	62	60.5	61.5	64	62	63	63		+1.0‡
6	Nembezi.....	+(?)	5 x 2.0 4 x 4.0	46	47.5	47.5	48.5		51	51	52	+6.0‖‖
14	Tono.....	20.2	4 x 2.0 1 x 0.7 3 x 4.0	45	48	47	48	49	48.5	49		+4.0
16	Masimango....	35	5 x 2.0 3 x 4.0	48	47.5	47.5	48	48	48.5	48.5		+0.5
15	Babuli.....	70	5 x 2.0 4 x 4.0	57.5	58	55	56	56.5	57	57		−0.5§

TABLE XXXII.—*Continued.*

Case No.	Name.	Spinal fluid before treatment.	Doses of tryparsamide.	Initial weight.	2nd week.	4th week.	6th week.	8th week.	10th week.	12th week.	14th week.	Total change.
			gm.	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*
24	Miaku*.....	305	2 x 4.0 5 x 2.0	46.5	47.5	46.5	†	†		47.5		+1.0‖
25	Madina.....	300	3 x 4.0 8 x 2.0	48	47.5	47.5	48	50.5	51	51		+3.0‡
20	Kiale*.....	387.5	4 x 4.0 8 x 2.0	47	48.5	50	50.5	50	51	51		+4.0***
17	Bwaba.....	450	4 x 3.0 5 x 2.0	51.5	52	49.5		47		45		−6.5‖
10	Makengo.....	247.5	1 x 1.0 1 x 2.0 1 x 3.0 1 x 4.0 1 x 5.0 1 x 2.0 1 x 0.5 5 x 1.0	41.5	43	42	41	45.5	46.5	48	49	+7.5

* Previous treatment suspected.
† In bed.
‡ Malaria.
§ Malaria; leg abscess.
‖ Trypanosomiasis exacerbation (?).
** Pustular skin infection; filariasis; scabies.
†† Chronic amœbic dysentery; ankylostomiasis.
‡‡ Filariasis.
§§ Syphilis; malaria.
‖‖ Malaria (?).
*** Tinea versicolor.

indistinctness of vision—worse in left than right eye; could distinguish light with both eyes. Condition improved during following 2 weeks so that patient could count fingers with both eyes but general condition became much worse with fever, etc. (exacerbation of trypanosomiasis?). 2 doses of 2.0 gm. were given with no increase in visual impairment but without influence upon the course of the disease and death occurred.

TABLE XXXIII.

Weight Changes of Advanced Previously Treated Cases After Repeated Doses of Tryparsamide.

Case No.	Name.	Spinal fluid before treatment.	Doses of tryparsamide.	Initial weight.	2nd week.	4th week.	6th week.	8th week.	10th week.	12th week.	14th week.	16th week.	Total change.
			gm.	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*	*kg.*
13	Yali.....	32	2 x 3.0 2 x 4.0	51.5	52.5	51.5	51	51.5	54	54	54.5		+3.0
1	Eali.....	80	2 x 2.0 1 x 2.0 2 x 4.0	57	56	58	56	55					−2.0*
2	Bibaba....	37.5	4 x 3.0 2 x 2.0	59	59		52						−7.0*
3	M'Boyo...	92.5	4 x 3.0 3 x 4.0	49	50	51	52.5		53.5		54.5	56	+7.0
4	Etumbu..	142.5	3 x 2.0 1 x 3.0	48.5	49	44							−4.5†
21	Monololo.	37.5	4 x 4.0 2 x 6.0 2 x 4.0 1 x 3.0	60	60	62	61.5	62	62	63			+3.0
27	K. Lukas.	327.5	3 x 5.0 8 x 2.0	48	47	48	50.5	50	52.5	52.5			+4.5
7	Engondo..	572.0	3 x 4.0 6 x 2.0	45							49		+4.0
8	Tokamba.	100.0	1 x 4.0 8 x 2.0 6 x 2.0	39		43	42.5				44		+5.0
34	Langomo.	467.5	3 x 7.0	62.5	62	63	63						+0.5

* Died. Trypanosomiasis exacerbation (?).

† Died. Amœbic dysentery; trypanosomiasis exacerbation (?).

M'Boyo № 3.—Previous treatment: soamin, 4 doses of 0.5 gm., and tartar emetic, 2 doses of 0.1 gm., in 26 days. Lumbar puncture 92.5 lymphocytes per cmm.; large mononuclears +++. Mental deterioration, apathy, and lethargy; marked nervous symptoms. She was given 4 doses of 3.0 gm. or 245 mg. per kilo in 9 days. 2 to 3 days after last dose, she complained of dimness of vision in both eyes and she walked unsteadily; there was complete recovery in 18 days.

Treatment was resumed after 3 weeks' intermission with 3 weekly doses of 4.0 gm. so that the same total amount of tryparsamide was given but in 14 instead of 9 days. There were no subsequent disturbances. Ophthalmoscopic examination 2 months after the last dose of tryparsamide was negative except for a slight reduction in size of the optic discs.

Etumbu № 4.—Previous treatment: soamin, 3 doses of 0.5 gm., and tartar emetic, 2 doses of 0.1 gm. in 22 days. Lumbar puncture 142.5 lymphocytes per cmm.; large mononuclears +. Mental apathy. He was given 3 doses of 2.0 gm. and 1 dose of 3.0 gm. or 185 mg. per kilo in 9 days. 3 to 4 days after the last dose he complained of indistinctness of vision of both eyes and treatment was stopped; the sight became normal in about 2 weeks.

Monololo № 21.—Previous treatment unknown. Lumbar puncture 37.5 lymphocytes per cmm. No mental or nervous symptoms. He was given 4 weekly doses of 4.0 gm. or 267 mg. per kilo in 21 days with no reaction of any sort. Treatment was resumed 2 weeks later and 2 doses of 6.0 gm. were given 10 days apart. A week later he complained of slight indistinctness of vision of both eyes. At his next visit, 11 days later, vision of left eye was normal and a week later vision of both eyes was normal.

Subsequent treatment with 2 doses of 4.0 gm. and 1 dose of 3.0 gm. in 19 days caused no visual disturbance whatever.

Miaku № 24.—Previous treatment suspected. Lumbar puncture 305 lymphocytes per cmm.; large mononuclears ++; mulberry cells++. Mentally apathetic, beginning lethargy (?). Marked nervous symptoms. He was given 2 weekly doses of 4.0 gm. or 172 mg. per kilo in 7 days. Complained of indistinctness of vision of both eyes and intense headache a week later. Could count fingers and gait was normal. Treatment stopped. 2 days later, vision of left eye normal; right eye slightly improved. 3 weeks later, patient became very ill with fever, etc. (exacerbation of trypanosomiasis?), and he was given 5 weekly doses of 2.0 gm. with marked clinical improvement and no increase of the residual visual impairment of the right eye.

At the end of this course of tryparsamide, vision of the left eye was normal. With the right eye he could distinguish light but vision was poor. Ophthalmoscopic examination of both eye grounds showed a pale retina with clearly defined, somewhat pale optic discs but otherwise no abnormality.

Bwaba № 17.—No previous treatment. Lumbar puncture 450 lymphocytes per cmm.; large mononuclears ++; mulberry cells ++. Mental deterioration; marked nervous symptoms. He was given 4 weekly doses of 3.0 gm. or 233 mg. per kilo in 21 days. On the last day of treatment, he complained of conjunctivitis

of the right eye with pericorneal injection and pustular discharge; no urethral discharge. Condition responded promptly to local treatment. A week later, complained of right eye being "bad" and in 2 days there was marked visual impairment of both eyes; could count fingers and see to walk.

During the following month, vision of both eyes improved slightly. Treatment with weekly doses of 2.0 gm. was resumed after the appearance of a brawny indurated swelling of the left leg and foot (trypanosomiasis?) and no intensification of visual symptoms was observed.

2 months after the onset of visual impairment, ophthalmoscopic examination of both eyes showed an anemic retina with a flattened white optic disc, the vessels of which were sharply outlined and distinctly seen. Size of disc apparently enlarged. Vision of left eye poor—of right, slight; could see to walk.

Makengo # 10.—No previous treatment. Lumbar puncture 247.5 lymphocytes per cmm.; large mononuclears ++; mulberry cells ++. Dull mental condition, slight lethargy, marked nervous symptoms. He was given increasing doses of tryparsamide from 1.0 to 5.0 gm., a total of 15.0 gm. or 361 mg. per kilo in 24 days. 5 days after the last dose, he complained of visual dimness of right eye; could not count fingers with this eye. Vision of left eye unimpaired. During the following month, the sight improved considerably. He could see objects but stated that there was a "shadow" over them. Treatment was resumed with small doses (2.0, 0.5, and 1.0 gm.) with no increase in visual symptoms. A month later, there was a slight visual dimness of the right eye which was gradually decreasing and the left eye was normal. Ophthalmoscopic examination of both eye grounds showed a pale optic disc, the vessels of which were distinctly visible, and a pale retina with small vessels.

Bandu # 54.—No previous treatment. Good general physical condition; 71 kilos. Marked edema of both legs from knee to toes. No mental or nervous symptoms. Lumbar puncture 117 lymphocytes per cmm.; large mononuclears +; 3 mulberry cells seen. He was treated at weekly intervals with 5.0 and 6.0 gm. and 4 doses of 2.0 gm., a total of 19.0 gm. or 290 mg. per kilo in 26 days. 3 days after the last dose there was slight unsteadiness and dimness of vision of both eyes; no edema except over instep of both feet; urine examinations negative. 2 weeks later, vision of both eyes was normal; ophthalmoscopic examination showed normal retinæ and slightly enlarged, pale discs. The pronounced edema of both legs had entirely disappeared by this time and a lumbar puncture 8 weeks after admittance showed a normal spinal fluid.

These observations may be summarized as follows: There were 17 instances of visual impairment of which 6 were slight, 7 were moderate, and 4 of marked degree. In 10, recovery was complete and 3 showed moderate and 4 slight improvement.

From an analysis of the above cases, certain factors in regard to the occurrence of visual impairment should be pointed out. First, all

were advanced cases, with marked alteration of the spinal fluid except 2, Monololo #21 and Bibaba #2. No visual disturbance of any kind occurred in patients in the early stages of the disease or in the beginning of the advanced period, irrespective of the system of therapy employed.

Next, 4 of the 9 patients were being treated with atoxyl and tartar emetic at the time the administration of tryparsamide was begun, while a fifth patient, and we suspected a sixth, had had previous arsenical treatment. To what extent previous treatment may contribute to the production of visual impairment is uncertain but that such a drug as atoxyl for instance may participate in this reaction is not improbable.

In the third place, there was no instance of sudden complete blindness but the condition was one of visual dimness of various grades or of inability to see distinctly; in every instance, there was either complete recovery or improvement of some degree. It is of interest to note that a marked and moderate impairment of 2 patients which was similar in degree to that observed in others was entirely transitory.

Finally as regards tryparsamide itself, it should be pointed out that no single dose of even 7.0 gm., given in this instance to a very advanced case (Langomo #34), produced untoward effects of any kind. In one patient with a markedly abnormal spinal fluid, 2 doses of 4.0 gm. separated by an interval of a week, were followed by visual disturbances but in the others more than 2 doses were given. Attention should also be drawn to the fact that in several patients administration of considerable amounts of the drug, both before and after the occurrence of visual impairment, did not reproduce this effect or if any residual symptoms were present at the time of retreatment they were not increased by further drug administration. For example, M'Boyo #3, who had completely recovered from the disturbance which followed the first course of 12.0 gm., was afterwards given exactly the same amount of drug, 3 doses of 4.0 gm. over a slightly longer period of time, with no visual reaction whatever, and Makengo #10 who had partially recovered was given a second course of treatment of smaller doses with no increase of visual impairment.

The size of the dose together with the interval of time between doses are undoubtedly crucial factors and of the two the spacing of the doses

is probably the more important. Bibaba #2, M'Boyo #3, and Etumbu #4 were given 4 doses of 2.0 and 3.0 gm. at 2 and 3 day intervals; all of these patients developed a considerable degree of visual impairment but it was entirely transitory with M'Boyo #3 and Etumbu #4, while Bibaba #2 showed a moderate improvement. These cases illustrate the danger of too frequent dosage. The case of Makengo #10 is somewhat analogous. He was given ascending doses of from 1.0 to 5.0 gm. in 24 days with no untoward effects until a few days after the last dose. Undoubtedly with this type of treatment, the larger doses were given too closely together and it is probable that if the last dose of 5.0 gm. had been omitted no visual symptoms would have occurred. On the other hand, 3 other patients who were given weekly doses of 3.0 and 4.0 gm. developed visual impairment, Eali #1, Miaku #24, and Bwaba #17. In contrast with these cases, it should be recalled that other advanced patients who were given similar or larger weekly doses showed no resultant visual symptoms. For instance, Koloshi #35 was given 4 doses of 5.0 gm. in 29 days; K. Lukas #27, 3 doses of 5.0 gm. in 14 days; and Langomo #34, 3 doses of 7.0 gm. in 21 days, as shown in Tables XXIV to XXVI. It seems not unlikely, therefore, that the individual pathological condition of the optic structures in advanced cases is the principal predisposing factor in the occurrence of this untoward effect.

DISCUSSION.

The purpose of the work reported in this paper was the obtaining of certain fundamental facts in regard to the action of tryparsamide in human trypanosomiasis since experimental toxicologic and therapeutic investigations with the drug had indicated its possible use in the treatment of patients suffering from this disease. The observations of 77 patients in early and advanced stages of trypanosomiasis caused by *Tr. gambiense* and treated with tryparsamide formed the basis for this study. The patients came from various parts of the Belgian Congo and most of them had not received previous treatment.

It was realized that objective information on the action of single doses must precede the use of several doses and, further, that the effect of a few doses must be studied before one could devise a logical system of repeated dose therapy. Consequently the work was conducted

along the general lines suggested by these principles. The first observations were concerned with determining the trypanocidal action of various sized doses of tryparsamide by microscopic examinations of centrifuged blood and lymph gland juice and included both the time of occurrence of this action and its duration in relation to the time of treatment. From a series of some 90 examinations after the treatment of patients in all stages of the disease with doses ranging from 0.3 to 7.0 gm. or 4.7 to 112 mg. per kilo of body weight, administered intravenously in most instances, it was found that tryparsamide was an active trypanocidal agent since its administration was consistently followed by negative examinations for trypanosomes in the superficial lymph glands and blood within 24 hours. The smaller doses up to 50 mg. per kilo of body weight produced negative lymph gland and blood examinations within 15 hours in the majority of cases and this number was increased after larger doses of 54 to 112 mg. per kilo. In certain patients, no trypanosomes were found in the blood as early as $3\frac{1}{2}$ hours after treatment but, in general, doses of 2.0, 3.0, and 4.0 gm. produced a peripheral sterilization in from 6 to 12 hours.

The duration of peripheral sterilization induced by single doses of tryparsamide was next studied in patients in the first period of the disease or as indicated by a slight increase in the number of cells of the cerebrospinal fluid, in the beginning of the advanced period. Without taking into account differences in the severity or type of the infections in individual patients, it was found that the duration of peripheral sterilization varied from 17 to 58 days in the 12 patients who had been given single doses of 0.5 to 5.0 gm. or from 17 to 83 mg. per kilo of body weight. On the other hand, no peripheral relapse was detected during observation periods of from 40 to 111 days in the 9 patients who had been treated with single doses of 0.5 to 3.0 gm. or from 9 to 68 mg. per kilo. It appears, therefore, that within the limits of dosage of from 0.5 to 5.0 gm., peripheral sterilization in relapsed patients endures on an average of from 3 to 6 weeks; but since there was one relapse 17 days after treatment, it seemed advisable in planning a system of repeated doses to begin with intervals of 1 and 2 weeks until the results of larger series of single dose administrations should be available for consideration.

The effects of intramuscular administration upon the duration of peripheral sterilization is significant. 4 patients were treated by this route with single doses of from 37 to 57 mg. per kilo; the immediate effect upon the trypanosomes in lymph glands and blood was similar to that observed after the intravenous route but on the whole the duration of this action was definitely more prolonged as seen by the average time of relapse, 7 weeks after treatment. In 3 patients, there was practically no local reaction while the tenderness and induration which occurred in one instance was probably due to a passing mild infection. While no subcutaneous injections were given, a slight amount of drug solution escaped into the tissues surrounding the vein in a few instances, but no irritation or discomfort of any sort arose, and in a few hours complete absorption had taken place.

The spinal fluid of early cases treated with single doses of tryparsamide was examined because of the possibility that the disease might progress and involve the central nervous system during the period of blood and lymph gland sterilization. A lumbar puncture was made on an average of 5 weeks after treatment in 14 patients with initial normal or slightly abnormal spinal fluids who had been given single doses ranging from 0.5 to 3.0 gm. or 9.0 to 68.0 mg. per kilo. In every instance, except one, the second cell count continued to be normal or was decreased to within or toward normal limits; in one patient, the result was uncertain because of blood contamination of the first specimen of spinal fluid. No trypanosomes, however, could be found in the lymph gland juice, centrifuged blood, or centrifuged spinal fluid of this patient.

The general physical reaction of patients in the first period of the disease treated with single doses was prompt and satisfactory. In 2 or 3 days after treatment, the subjective symptoms disappeared and the pulse rate and temperature became normal; within a month the blood count was materially improved, the patient had gained weight and the cervical lymph glands were small and indurated. Interruptions of this favorable course of events occurred in those patients who harbored other infections or who ultimately had a trypanosomal relapse but in general a definite and usually a marked beneficial effect was observed. In addition, no untoward reactions of any kind

were observed in these patients, either of an immediate occurrence or of a more delayed appearance.

The use of repeated doses of tryparsamide was based upon the action of single doses, and a number of previously untreated patients as well as those who had suffered a relapse after single doses were given from 4 to 7 doses of 2.0 to 5.0 gm. at weekly or fortnightly intervals. Only the initial observations are at present available. The preliminary effect as regards negative trypanosome examinations of lymph glands and blood and general clinical improvement indicated by the disappearance of subjective symptoms, pulse and temperature curves, blood counts, gain in strength, and increase in weight occurred in both groups of patients. Microscopic examinations of lymph gland juice and centrifuged blood made from time to time during the course of treatment were uniformly negative.

Obviously no predictions of the ultimate therapeutic results in these patients can be made, and while it is not unlikely that future experience may show that a more prolonged system of therapy is necessary, it seemed advisable in the beginning to determine the effect of a relatively small number of doses.

The treatment of advanced cases of trypanosomiasis must take into account not only the invasion of the cerebrospinal axis by the infecting organism and the resultant injuries but also the chronicity of the disease, its tendency toward exacerbation and the debilitated physical state of many patients. With these facts in view, some system of repeated dose therapy appears obligatory and the treatment with tryparsamide, therefore, based upon the action of single doses, consisted in the administration of several doses ranging from 1.0 to to 7.0 gm. at intervals of from 3 to 14 days. 28 patients who presented a wide variety of nervous and mental symptoms and whose spinal fluid showed an increased cell content of from 15 to 572 lymphocytes per cmm., together with large mononuclears and mulberry cells in most instances, were under observation for a sufficient length of time after treatment to permit of subsequent lumbar punctures as well as other clinical examination. The cell content of the spinal fluid was used as a criterion of the degree of cerebrospinal involvement as well as a therapeutic guide and also as an index of the effect of treatment.

The immediate sterilizing action of tryparsamide was noted in those patients whose lymph gland examination was positive on admittance; trypanosomes were not found in 7 patients who were being treated with atoxyl and tartar emetic at the time of transfer to tryparsamide therapy. Repeated microscopic examinations of lymph gland juice and centrifuged blood made during the period of observation were negative in all patients. In general, the physical status of the patients was materially benefited as was shown by the return of the pulse and temperature to normal limits, the prompt disappearance of the subjective symptoms and by improved blood counts and gains in weight. The improvement in habits and personal appearance of several patients was also noticeable. The early termination of treatment in 3 patients was followed by a clinical exacerbation of the disease and ensuing death; in one of the 3 there was a complicating acute amœbic dysentery. The nervous and mental symptoms which were present in many instances were greatly improved or completely eliminated except in 2 very advanced patients with marked mental deterioration who had been treated with other drugs for long periods of time and in whom the change was slight.

The effect of tryparsamide upon advanced trypanosomiasis as illustrated by this group of patients is further evidenced by the marked and rapid diminution of the cells of the spinal fluid. In general, 3 or 4 weekly doses of 3.0, 4.0, or 5.0 gm. produced decreases of from 57 to 98 per cent in an average of 5 weeks. In 5 patients whose treatment was limited to one such course, the cell content continued to decrease in 4 instances as shown by a practically normal third examination made 9 to 12 weeks after admittance, while in 1 patient, there was no further decrease. 16 patients who were given second courses of treatment showed a continued decrease of cells; 3 showed practically no change from the count made after the first course of treatment; in one, there was a slight increase in cells and in another, after 3 irregularly spaced doses, the cells had returned to practically the original count. In this limited number of cases, it was apparently more difficult to accomplish a further decrease of the spinal fluid cell content by a second course of treatment than it was to produce the initial and marked diminution by the first course, but at any rate, in these 5 instances, the active progression of the disease was apparently

arrested. Considering the pathological conditions of cerebrospinal trypanosomiasis, it seems not unlikely that a longer first course of treatment than that employed in most of these patients would give more satisfactory results. Regarding the effect produced by more frequent smaller doses as contrasted with larger doses separated by longer intervals of time, it appears that the use of semi-weekly doses of 2.0 gm. for instance had apparently no advantage over a weekly dose of 3.0 or 4.0 gm.

Finally, we wish to consider the only untoward effect encountered during the course of this work. Dimness of vision of various degrees occurred in 9 advanced cases, 5 of whom had received previous arsenical treatment. It should be pointed out that there was no instance of visual disturbance of any kind in the early cases or in the first stages of the cerebrospinal period of the disease or after any single dose of tryparsamide. The largest dose given in our cases was 7.0 gm. In the majority of instances, this effect was entirely transitory and in the others various degrees of improvement took place. 3 patients who were given too frequent an administration of medium sized doses showed considerable degrees of impairment and of these 2 recovered completely; of 3 other patients with about the same degree of impairment one showed slight improvement, another moderate improvement and the third complete recovery, while in the remaining 3 a less marked visual disability was transitory. It would seem from a study of these cases that too frequent administration of medium and large doses to patients suffering from very advanced trypanosomiasis is one factor that contributed to this condition. It is significant to note in this connection that resumption of treatment with smaller or more widely spaced doses was not followed by a return of the condition or by an intensification of residual symptoms. In addition, the time of occurrence of this untoward effect, 2 to 7 days after treatment, together with the nature of the pathological injury to the optic structures in cerebrospinal trypanosomiasis and the fact that improvement of some degree always occurred, suggests that the cause of the visual impairment is related to the processes of resolution and healing of the lesion already present rather than to a direct toxic action upon the nerve itself. The ophthalmoscopic examination of several patients who had partially or completely

recovered from this condition also lends support to this view. The experimental work with tryparsamide showed that apparently the drug possesses the power of tissue penetrability to a marked degree since a characteristic feature of the treatment of rabbit trypanosomiasis was the rapidity and completeness with which extensive cutaneous and subcutaneous lesions regressed and healed. Individual variations in the extent or degree of lesions is the probable explanation of the fact that several patients with as markedly altered spinal fluids and as pronounced nervous and mental symptoms developed no visual disturbances whatever after similar treatment.

From the facts at our disposal, it would appear that the occasional occurrence of visual disturbances, which may perhaps be avoided by a slightly different system of dose repetition, does not at present constitute an objection to the use of the drug. The impression which one has after treating advanced cases with tryparsamide is that a suitable interval between doses of a certain size is probably the most important factor in preventing the occurrence of untoward visual effects. Doses of 3.0 gm. or over should preferably not be given oftener than once a week, and since longer intervals between doses have been followed by clinical improvement and marked decreases in the cells of the spinal fluid, further use of a system of wider spaced repeated doses may show similar beneficial therapeutic effects without concomitant visual disturbances.

SUMMARY.

The present study of the action of tryparsamide in human trypanosomiasis concludes a series of chemical and biological investigations in a particular problem of chemotherapy and thus represents the final step in a logical method of approach to such a problem. It has been shown that tryparsamide, the sodium salt of *N*-phenylglycineamide-*p*-arsonic acid, possesses a marked trypanocidal activity in human trypanosomiasis caused by *Tr. gambiense*. Single doses of from 0.5 to 5.0 gm. produced a peripheral sterilization of lymph glands and blood in an average of 6 to 12 hours. The duration of the peripheral sterilization following single doses of 17 to 83 mg. per kilo ranged from 17 to 58 days in patients who ultimately showed a return of trypanosomes to the peripheral blood. In a number of patients, however,

treated with single doses of 9 to 68 mg. per kilo, no such relapse was detected during an observation period of from 40 to 111 days. The drug is extremely soluble in water and may be administered intramuscularly as well as intravenously. The immediate trypanocidal action after intramuscular administration was as rapid as that following the intravenous route while the duration of peripheral sterilization was appreciably longer.

Relatively few repeated doses produced in advanced cases a marked and rapid diminution of the cells of the spinal fluid and were associated with definite improvement of mental and nervous symptoms. The occurrence of visual disturbances in certain advanced cases was the only untoward effect detected during the course of the work, and was apparently related to a too frequent administration of the drug. The condition was transitory in the majority of instances and resumption of treatment was not followed by a recurrence of this symptom.

The general beneficial effect of the drug was a noticeable feature of its action in both early and advanced cases as shown by the disappearance of subjective symptoms, by the return of the pulse and temperature to normal limits, by the pronounced improvement of the blood picture, and by well marked gains in weight.

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