skin dose under certain known conditions and give as large a dose of heterogeneous rays as possible. The calculation of the skin dose used in the treatment of tinea is simple and accurate, but difficulties arise when a filter is inserted. We have the Sabouraud pastille, the Kienböck strip, the Holzknecht strip, and many others by which the dose can be gauged, but most of these are intended for use without a filter. We are waiting for a simple practical unit for filtered rays.

For want of a better I have, for many years, used the Sabouraud pastille on the skin as my unit, Kienböck's strip not being very practical, as an overdose or underdose may easily be given, usually too late to remedy the error. The time factor with a Coolidge tube is fairly accurate, but even here each tube must be tested periodically by some method or other. It is better to take the reading on the skin itself, as the distance of the tube and the thickness of the filter can then be practically disregarded, although this process involves the establishment of a new unit. The main difficulty when using a Sabouraud pastille on the skin is the reading of the slight tint alteration that takes place, but this may be overcome by the use of a tintometer.

I have found from experience that the effect on the skin of an erythema dose through a filter was not the same as without a filter, a fact which, I believe, agrees with the expectations of physicists. Realizing this, would it be possible to fix a unit which would give us the danger dose through a filter? The method I adopted some years ago to gauge roughly the maximum skin dose with a filter, when treating deep-seated tumours, is as follows: A Sabouraud pastille is placed on the skin; when this registers a quarter B tint the skin has received a 10 X dose, irrespective of the distance of the tube or of the thickness of the filter. This was taken as the minimum dose, not as the erythema dose, the maximum which I have applied being a 20 X dose, again measured on the skin through 3 mm. of aluminium. The pastille in this case will read $\frac{1}{2}$ B tint. The $\frac{1}{2}$ B tint and the $\frac{1}{2}$ B dose must not be confused; they are entirely different. Penetration should not be below 9.5 Wehnelt. Caution is required by the operator in using these large doses; they should be worked up to gradually. The margin of error being small, a certain amount of proficiency in the use of the apparatus and in the reading of the pastille changes is essential.

I have given this 20 X dose through 3 mm. of aluminium as often as twice a week in desperate cases with no resulting skin changes beyond deep pigmentation. Such possibilities as late reactions must be risked when the patient's life is at stake.

Possible Dangers.

1. *Blood*.—Massive doses are said to lead to definite blood changes, the details of which cannot be gone into here. With the dual radiotherapy, not only is the total dose large owing to the extensive area of the body subjected to radiations, but the heart, when thoracic conditions are being treated, is being radiated from all sides. I believe, however, that any blood changes that occur are caused by the direct action of the rays on the blood-making tissues, such as the spleen and bone marrow, rather than on the blood corpuscles. So far no blood changes have been found.

2. *Intestines*.—Various organs are said to be influenced by radiations, amongst them the intestines. As the dual method has not yet been applied to abdominal cases this point cannot be settled. A careful watch should be kept on all patients under treatment for indications of possible damage to organs in the field of radiation. Any undesirable effect should be rectified by modification of dosage and frequency of treatment.

Results.

The first patient was treated by the dual method only on February 24th, 1921, and some time must therefore elapse before any reliable data can be expected where an effort is being made to prevent metastases, but in those cases in which the primary lesion has been treated, such as an intrathoracic growth they appear to respond very much more rapidly than with the localized method used previously.

It must always be remembered that the time is possibly approaching when the cure may prove worse than the

disease. In our efforts to destroy malignant cells we may destroy far more than we intended.

The *secondary phenomena* so far noted are of some interest. Few can tolerate the full 80 X dose, nausea and vomiting, lasting from several hours to three days, appearing shortly after treatment. If, however, the dose is halved—two opposite areas only being treated instead of four—the patients may experience a feeling of well-being, which one patient aptly compared to the effect of a glass of champagne. In one case, that of a large intrathoracic growth (the patient was a doctor), the secondary symptoms—nausea and vomiting—were very marked after even the first 40 X dose, yet others experienced no ill effects whatever, even after the full 80 X dose. These secondary phenomena are somewhat puzzling and are being investigated, as other causes besides the direct action of x rays may be responsible.

I have given but a rough description of the method, hoping that others may work on the same lines, and that at some future time interesting comparisons and conclusions may be made.

Radiologists appear to have divided themselves into two schools—those who endeavour to attain *maximum cell absorption* and those who pin their faith on *excessive penetration* at the expense of absorption. The dual method follows the cell absorption line of technique.

FURTHER REPORT ON THE TREATMENT OF SLEEPING SICKNESS.

BY

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In a previous report published in the *BRITISH MEDICAL JOURNAL* of May 22nd, 1920, p. 702, by one of us (C. H. M.), attention was drawn to the treatment of sleeping sickness by combined intravenous and intrathecal injections of organic arsenical preparations (neo-kharsivan). An epitome of twelve cases thus treated was also given.

Since then the number of cases treated and under observation has increased to over 50, and the conclusions we have drawn are that this treatment shows prospects of a possible cure for, at any rate, early cases of this protean disease.

The following is a summary of the technique of the treatment, given in detail in the report previously alluded to:

An intravenous injection of an organic compound of arsenic is given, and after a period varying from one to four hours a certain quantity of blood—usually 20 c.cm.—is withdrawn. This is kept in a vessel, stood in cold water, until the serum separates completely from the formed elements of the blood. The separated serum is then injected into the cerebro-spinal cavity, an equal amount of cerebro-spinal fluid having been previously drawn off. This completes the treatment, and the patient is free to resume his normal life, subject to his reporting from time to time for re-examinations.

The principle of the treatment was based on the theory that the trypanosomes having once reached the cerebro-spinal canal were, after a certain time, immune to any medication via the blood stream; since we have adopted this routine procedure for sleeping sickness cases we have had striking examples of this fact.

The following are examples:

Case 30.

Karungaho, a man with large typical chains in the neck, admitted to hospital on June 14th, 1920. Gland puncture showed numerous trypanosomes and flariæ. On June 15th, 0.6 gram neo-kharsivan was injected intravenously; on the 17th 12 c.cm. of cerebro-spinal fluid were drawn off by lumbar puncture. The cerebro-spinal fluid on examination showed trypanosomes.

Case 33.

Wana, a man with large typical glands, was admitted on June 19th, 1920, gland puncture showed trypanosome infection. Neo-kharsivan 0.6 gram was administered intravenously on June 20th, and on the 23rd when 12 c.cm. of cerebro-spinal fluid were drawn off, prior to intrathecal medication, it was found to contain living trypanosomes.

The next case is, to our mind, more striking, and we think proves conclusively our theory.

Case 34.

Asumani, a boy with typical enlarged glands on both sides of the neck from which trypanosomes could easily be recovered, was admitted on August 31, 1920. On August 5th he received 0.6 gram of neo-kharsivan, and as his home was far away he was kept in hospital. He was given no intraspinal treatment. Towards the end of October this boy reported difficulty in walking and general debility; on examination of his cerebro-spinal fluid living trypanosomes were found, while none were discoverable in the blood or in his cervical glands. His glands were again examined at the time of writing this report (December 24th, 1920), and still nothing could be found.

(It should be noted that in none of the above cases was there any chance of reinfection.)

While there is no doubt that in healthy individuals drugs administered intravenously may find their way into the cerebro-spinal fluid,¹ we are of opinion that the choroid plexus mainly and other structures concerned in the diffusion of the plasma and the cerebro-spinal fluid, become obliterated at a clinically early stage; the result is we have two foci of disease—the blood or lymphatic stream and the cerebro-spinal cavity—and to get rid of the disease it is necessary to attend to both these foci. That the permeability of the meninges is seriously affected at an early stage of the trypanosome infection is evidenced in the living by early lymphocytosis of the cerebro-spinal fluid, and in the dead by microscopical examination of the meninges, the latter being at times the only evidence of the disease; and when such nervous alterations have occurred, blood medication, however active, will fail to influence the course of the disease.

Many authorities are agreed that the administration of a dose of salvarsan, neo-salvarsan, or atoxyl is sufficient to sterilize the blood in a surprisingly short time; the patient is thus looked upon as temporarily cured, but within a variable period of time nervous symptoms appear, and the infection goes on unchecked, the patient eventually dying. Excluding reinfections, two theories have been put forward to account for this: (a) That there are resistant forms, and (b) that certain trypanosomes are protected from the action of the medicament by their position in the organism, for example, bone marrow, central nervous system.² While the possibility of the trypanosome in forming new races cannot be doubted, and is by some considered as unlimited,³ we are more inclined to think that the second theory is the more probable, from the arguments we have set forth.

It also appears very probable to us that, if we can obtain a case of trypanosomiasis in its early stages, one single dose of salvarsan or any other allied drug may be enough to cure once for all the patient from the infection, and this may account for those cases which have been recorded as cured, and in this category we are inclined to place two of our own cases (Case 14 and Case 28), who only received an intravenous injection, and who, up to now, are enjoying excellent health. These cases were originally kept as controls, and that is why they had no salvarsanized serum given them.

The detection of early cases is a difficult affair, except perhaps in Europeans where a history of having been bitten by a fly in a glossina-infested area, may be obtainable. Even then the assertion that the case is an early one is distinctly risky, as one cannot be sure of the presence or otherwise of the trypanosome in the cerebro-spinal fluid unless the latter is examined, and once this has been decided upon, as it should be, the salvarsanized serum can be given at the same time.

An injection into the thecal cavity, done with the usual antiseptic precautions, does not show any untoward symptoms or sequelae; we have noticed that the injection of salvarsanized serum is usually accompanied with a slight rise of temperature to 100° or 101° F., pains in the back along the spinal column—most marked in the region of the anus—vomiting, and slight diarrhoea. These symptoms disappear in a day or two, after which time the patient is discharged.

The course, therefore, of the trypanosome in the human body is, first, its passage into the blood, subsequently followed by glandular enlargement, usually in the cervical region; secondly, its passage into the central nervous system, where soon it produces lesions of the meninges, which shut it off from its parent in the blood. The curability or otherwise of the disease, therefore, depends to a great extent on how far the nervous lesions have advanced; if these are far advanced the infection ceases, so to say, to be trypanosomiasis and becomes a chronic

nervous disease, ending in death. There seems to be, though, an appreciable period of time between the passage of the trypanosomes in the cerebro-spinal fluid and the onset of nervous symptoms, and it is possible, we think, to greatly improve, and perhaps cure, the patient during this time; it is only when irremediable and irreparable damage has been done to the central nervous system that the case is hopeless.

From an analysis of cases thus treated (from these we exclude those which have been done during the last three months) it appears that the patients after the treatment start putting on weight, feel much better and are generally changed individuals. They are able to do physical work, not excluding porters' work, which, we might add, consists in the carrying of loads varying between 40 and 50 lb. for an average distance of about ten or fifteen miles. Another patient of ours, treated in April (Case 23), aged about 60, cycled in about thirty miles one morning for re-examination—a feat for him, as he stated he had been unable to ride a bicycle for at least a year before treatment.

Analysis of Cases of Sleeping Sickness treated with Neo-kharsivan, Atoxyl, or Plain Serum.

N=Neo-kharsivan; A=Atoxyl; S=Plain Serum.

Case No.	Sex.	Date of Treatment.	Drug.	No. of Re-examinations, with Date of Latest.	State of		
					Blood.	Glands.	C.S.F.
1	M.	1918. Sept. 26	N	1919. 1; Jan. 11			
2	F.	Sept. 30	N	5; Oct. 29	Neg.	None	Neg.
3	M.	Oct. 1	N	—	—	—	—
4	F.	1919. Jan. 9	N	4; June 28	Neg.	None	Neg.
5	F.	July 11	N	1; Oct. 26	—	—	—
6	Dog	—	—	—	—	—	—
7	M.	June 1	N	5; Oct. 26	Neg.	None	Neg.
8	M.	Sept. —	N	3; Nov. 28	Neg.	None	Neg.
9	M.	Sept. 26	N	1; Nov. 3	—	—	—
10	M.	Oct. 25	N	—	—	—	—
11	M.	Nov. 27	N	3; Oct. 23	Neg.	None	Neg.
12	M.	Nov. 27	N	3; Oct. 23	Neg.	None	Neg.
13	F.	Nov. 19	N	3; Nov. 3	Neg.	None	Neg.
14	M.	Nov. 29	N	3; Oct. 26	Neg.	1 gland; 2 punctures; Neg.	Neg.
15	M.	Dec. 2	N	3; Nov. 3	Neg.	None	Neg.
16	M.	1920. April 26	N	2; Oct. 26	Neg.	None	Neg.
17	M.	April 26	N	2; Oct. 26	Neg.	None	Neg.
18	F.	April 26	N	2; Oct. 28	Neg.	None	Neg.
19	F.	April 26	N	2; Nov. 3	Neg.	None	Neg.
20	M.	April 26	N	—	—	—	—
21	M.	April 27	N	—	—	—	—
22	F.	April 27	N	1; Nov. 3	Neg.	None	Neg.
23	M.	April 28	A	2; Oct. 26	Neg.	None	Neg.
24	M.	April 28	A	1; Nov. 3	Neg.	None	Neg.
25	M.	April 23	A	2; Oct. 26	Neg.	None	Neg.
26	M.	May 3	A	2; Oct. 26	Neg.	None	Neg.
27	M.	May 4	A	1; Oct. 26	Neg.	None	Neg.
28	M.	May 8	N	1; Nov. 3	Neg.	None	Neg.
29	M.	May 13	N	1; Nov. 3	Neg.	None	Neg.
30	M.	June 15	N	1; Nov. 3	Neg.	None	Neg.
31	M.	June 15	S	1; Nov. 3	Neg.	None	Neg.
32	F.	June 18	N	1; Nov. 3	Neg.	None	Neg.
33	M.	June 20	N	—	—	—	—
Under six months.							
34	M.	Sept. 5	S	No re-examinations to date.			
35	M.	Sept. 13	S				
36	M.	Sept. 14	N				
37	M.	Aug. 28	N				
38	M.	Aug. 17	N				
39	M.	Aug. 27	N				
40	M.	Oct. 4	A				
41	M.	Oct. 5	A				
42	M.	Oct. 6	A				
43	M.	—	—				
44	F.	Oct. 4	N	No re-examinations to date.			
45	M.	Sept. 29	S				
46	M.	Sept. 24	N				
47	M.	Nov. 15	A				
48	M.	Nov. 15	A				
49	M.	Nov. 15	A				
50	M.	Dec. 2	A				
51	M.	Dec. 2	A				
52	M.	Dec. 6	A				
53	M.	Dec. 6	A				
54	M.	Dec. 6	A				
55	M.	Dec. 6	A				
56	M.	Dec. 28	N				

Notes.—Case 1 died of sleeping sickness. Case 3 (the date of whose treatment is uncertain) disappeared; presumably dead. There are no records of Cases 5 and 9; ? died of sleeping sickness. Case 6 (dog) was shot. Case 10 died of sleeping sickness. Case 33 died (?CHCIs poisoning). Case 34 is under treatment; referred to in report. Case 42 died of pneumonia, October 25th, 1920. Case 43 died one day after admission; no treatment given. Case 46 was a European.

Duration of Cases up to December 31st, 1920, without any Symptoms or Microscopical Findings.

Case 2 ...	...	...	...	27 months
" 4 ...	...	...	...	Av. 24 "
" 7 ...	...	...	...	Av. 18 "
" 8 ...	...	...	...	Av. 15 "
" 9 ...	...	...	...	Av. 15 "
" 10 ...	...	...	...	14 "
Cases 11 to 15 ...	...	...	...	13 "
" 16 to 25 ...	...	...	...	8 "
" 26 to 29 ...	...	...	...	7 "
" 30 to 33 ...	...	...	...	6 "

Cases in which the Cerebro-spinal Fluid was Positive.

Case 7.	Case 39.
" 10 (since dead of sleeping sickness).	" 42 (since dead).
" 30.	" 44.
" 33 (since dead).	" 45.

Deaths and Causes.

Case 1 ...	Sleeping sickness.
" 3 ...	Disappeared; presumably dead.
" 5 ...	? Sleeping sickness (no records).
" 9 ...	Sleeping sickness.
" 10 ...	Sleeping sickness.
" 33 ...	? Delayed CHCl ₃ poisoning; marked mediastinal changes at necropsy.
" 42 ...	Pneumonia.
" 43 ...	Died on admission.

While it may be early to state positively that the present treatment promotes definite cure, we cannot help but feel optimistic in the face of the results we have obtained. Several of our cases have gone well beyond a year with one dose of treatment, and they have all invariably improved in health and no trypanosomes have been found, though they have been subjected to repeated and careful investigations.

Most of our cases have been treated with Burroughs Wellcome and Co.'s neo-kharsivan, a few cases were also treated by atoxyl, the object being to find out which is the more efficient drug. We also mean to use other drugs such as galy and also tartar emetic, and we hope to be able to publish during the next year (1921) comparative results of the various drugs used.

Experiments are also being made to see whether the results we have up to now obtained may not be due to the formation of trypanolysins or other antibodies. That the trypanosomes give rise to specific lysins was suggested by Louis Martin and Henri Darre, who attributed the fever to the massive destruction of the parasites by trypanolysis, and who showed that the blood of patients obtained at the onset of fever had a very marked trypanolytic power both *in vitro* and *in vivo*. We have therefore treated one or two well chosen cases with plain serum—that is, the serum from one of our treated cases was injected into the blood and cerebro-spinal fluid of another sleeping sickness patient; up to now it is much too early to form any opinion.

Conclusions.

1. Of 56 cases treated up to now, 8 are dead. Of 6 of these we have records, and of these 6 only 3 died of sleeping sickness, the others dying of an intercurrent disease, favoured, may be, by the trypanosome infection.

2. All the remaining cases are doing well, some (21) have only been treated during the last six months and so are excluded from this paper, though included in the index of cases.

3. The drugs tried so far have been neo-kharsivan most extensively, and to a less extent atoxyl, but all that has been said in this paper refers mainly to neo-kharsivan.

4. Plain serum treatment is also being tried in a few carefully selected cases. In advanced cases we are trying direct spinal medication; so far the results are uncertain—one case treated thus died; another, under observation, in whose spinal cord 0.003 gram neo-kharsivan was introduced, seems to present a certain amount of improvement.

Finally, we wish to express our thanks to Dr. C. A. Wiggins, Principal Medical Officer of this Protectorate, for his assistance and encouragement in carrying out these investigations and for his permission to publish this report.

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THE VIRULENCE OF DIPHThERIA-LIKE ORGANISMS.

A NOTE ON THE INTRACUTANEOUS TEST.*

BY

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AND

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For testing the virulence of diphtheria-like organisms, Zingher and Soletsky¹ described a method of intracutaneous injection which was a modification of that originally described by Neisser. They advocated the method on the grounds of economy, and stated that in 60 cases it gave the same result as the subcutaneous method. These authors usually tested four strains on each pair of guinea-pigs.

We have been using a similar test for some months, and are submitting our experience of it in the hope that it may prove useful to the many public health pathologists in England who are working in the same field. The modifications we have introduced are as follows:

1. Standardization of inoculum by opacity.
2. Inclusion of a known virulent strain in each test.
3. Injection of control animal on the preceding day.
4. Administration to the unprotected animal of a "following dose" of antitoxin of such a size that the skin reactions are not obscured while the life of the guinea-pig is saved.

The technique of the test is as follows:

Two guinea-pigs are used for each test; both must be partially white.

Protecting Dose.—One animal is given 500 units of diphtheria antitoxin by intraperitoneal injection on the day preceding the test. This animal acts as a control.

Preparation of Inoculum.—The test strains and a known virulent diphtheria bacillus are grown eighteen hours on Loeffler slopes, emulsified in saline, diluted and standardized by opacity so that the suspension contains approximately fifty million organisms per cubic centimetre.

Injection of Suspensions.—White-haired portions of the guinea-pigs are depilated with calcium sulphide paste, and into corresponding skin areas of the two animals is injected 0.2 c.cm. of each suspension. The injections are strictly intradermal and at least half an inch apart. On each pair of animals we usually test eight or ten strains, including the control virulent.

Following Dose.—Four or five hours later the animal which was not given a protecting dose on the previous day receives 125 units of diphtheria antitoxin intraperitoneally.

Readings are taken for the next three days.

In the case of a virulent diphtheria bacillus the control animal shows nothing or a faint transient flush; the other animal shows a definite rose-red swelling which becomes more marked at each successive reading, and may terminate in slight necrosis. An avirulent diphtheria-like organism gives a negative result with both animals. If the test culture is contaminated with streptococci the result may be obscured by a reaction in both animals, but this does not always happen.

The advantages of the test are:

1. Economy of animals, as both survive.
2. Owing to the variability of growth shown by different strains, standardization by opacity is preferable to the use of a certain proportion of a slope culture (as in the American method).
3. Reliability. We have had the opportunity of comparing only a limited number of strains by the subcutaneous injection method; so far the agreement is satisfactory.

REFERENCE.

- ¹ Zingher and Soletsky: *Journal of Infectious Diseases*, vol. xvii, No. 3, 1915.

* From the Wellcome Physiological Research Laboratories.

MUCH is hoped in Germany from the regulation, made at the beginning of 1921, prohibiting the exploitation of Wassermann's test by persons unrecognized by the health authorities as competent to carry it out. A further precaution to secure a reliable Wassermann test is the decree that only those extracts must be used which have been tested at the Institute for Experimental Therapy, conducted by Professor Kolle at Frankfurt a. Maine.