

thought it unnecessary. The pleura was congested and the pleural cavity contained more serous fluid than natural. The lungs were dark and markedly congested. With regard to the pericardium the cavity contained more serous fluid than normal. The heart was slightly enlarged and the valves were healthy. Ante-mortem clot was present. As to the abdomen, the peritoneum was congested and spotted all over with black spots of various sizes and different shapes. There was more serous fluid than normal in the pelvic cavity. The uterus extended up close to the xiphoid cartilage of the sternum and corresponded with a uterus at full term. The peritoneum over it was congested and contained dark spots. On opening the uterus a full-term male child was removed; it was a well-developed, healthy-looking infant; the skin was healthy and without any spots or marks of any kind. The placenta, membranes, and cord were normal in size and appearance. The mesenteric glands were congested, which has been shown lately in Germany to be important from a diagnostic point of view, a view confirmed by Professor W. St. C. Symmers of Belfast. The liver was enlarged and full of blood. The gall-bladder was full of bile and the coating of the bladder was covered with dark spots. The spleen was enlarged and full of blood. The kidneys and suprarenal capsules were congested. The pancreas was congested. The stomach contained a little food with some dark grumous matter which was evidently the medicine prescribed that morning. There were dark spots over the mucous surface, which was also congested. The small and large intestines were congested and almost empty; Peyer's patches were congested and the walls of the intestines were spotted. The bladder was empty and on opening it the mucous surface was covered over the whole surface with small dark spots. As this case occurred in the earlier stage of the epidemic I regret bacteriological examinations were not made.

atoxyl were administered the parasites (*Trypanosoma Brucei*) would disappear in rats for from 16 to 25 days. A disappearance of the parasites for a similar period was also observed in guinea-pigs and rabbits. Mercury was then given and the treatment stopped. In the bigger animals this double treatment should be continued for some time.

With regard to sleeping sickness we would like to suggest as a routine treatment that one cubic centimetre of a 20 per cent. solution of atoxyl should be given daily for one week, followed by one cubic centimetre of a 1 per cent. solution of sublimate four times. This treatment should be repeated and continued for an extended period and, of course, may require occasional modification. It would perhaps be possible to give mercury in the form of pills. The theory of the action of mercury in this treatment has been discussed in a paper published in the *Annals of Tropical Medicine and Parasitology* of the Liverpool School of Tropical Medicine, Vol. I., No. 2.

It has been found that the toxic effect of atoxyl can be diminished by acetylating the atoxyl. Such an acetylated atoxyl is an antipyrine which contains arsenious acid. Acetylated atoxyl has been shown to be of use in mice by Ehrlich and in dogs by our experiments. We found, as a rule, that when atoxyl was given in a sufficient quantity to drive out the parasites (*nagana*) in dogs the host was also killed, but using acetylated atoxyl we have been more or less successful. An interesting fact, pointed out by Ehrlich, is that the parasites can get used to a drug and become resistant. It is therefore advisable to alternate various trypanocidal agents in the treatment as much as possible, that is, to give atoxyl, some other trypanosome-killing drug, and mercury; for example, atoxyl, fuchsin, or some other colouring matter by the mouth, and sublimate.

It has usually been recommended to give atoxyl in high doses at the beginning. Whether or not this is of benefit is a question, as the atoxyl apparently accumulates in the body and the toxic effect appears after a time. In laboratory experiments we have frequently noticed that even after the treatment had been stopped for a week toxic effects appeared and this could only be due to the fact that atoxyl had accumulated in the body and the arsenic had been slowly broken up. We would like to refer to one experiment; a rat was treated about nine months ago with atoxyl and is still showing toxic effects.

We think it necessary to point out that the administration of atoxyl should be given a very careful trial but that extremely high doses should be avoided as much as possible. The action of atoxyl seems to be very much on the nervous system, as neuritis is frequently caused by the administration of this drug. Blindness has also been observed after the use of atoxyl and the question therefore arises whether it would not be well to counteract somewhat the effect of atoxyl by making it less operative on the brain and nerves. This might be done by introducing radicles which are more fixed to the blood and less to the nervous system.

We think it necessary to draw attention to experiments which we have made in connexion with the reappearance of trypanosomes after treatment with atoxyl. We found that strains obtained from animals which had had relapses were sometimes much more virulent. Our *nagana* strain, used for work generally, killed a rat in from five to seven days. This strain was followed up, commencing on Jan. 14th, until May 5th by subinoculation from one rat to another; four drops of blood were always used. In none of these rats was any sudden increase of virulence noticed, but in experiments with the strain obtained from animals in which the trypanosomes had reappeared it was found that the experimental animal was killed in from three to five days. Out of 17 rats used for these experiments 11 showed a remarkable increase of virulence. Similar work done with *Trypanosoma dimorphon* showed the same increase of virulence. Our strain used to kill a rat in from 15 to 17 days and we found that in four out of six strains obtained through relapses after treatment by atoxyl the virulence obtained was from 11 to nine days. We have recently obtained through atoxyl a *Trypanosoma dimorphon* strain which kills a rat in seven days. Similar work with *Trypanosoma Gambiense* is now in progress.

It was our intention not to publish the results of this work until we had satisfied ourselves that *Trypanosoma Gambiense* behaves in a similar way, but since it is intended to commence atoxyl treatment on a large scale in Uganda we feel that a warning in this direction should be given.

These observations emphasise the necessity for careful

THE TREATMENT OF TRYPANOSOMIASIS.¹

By A. NIERENSTEIN, PH.D.,

OF THE LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

THE therapeutics of the present time for trypanosomiasis can be divided into the following.

A. *Arsenic compounds*.—1. Arsenious acid. 2. Fowler's solution.

B. *Colours*.—1. Colouring matters belonging to the diazo group, Ehrlich's trypanred and Mesnil's afrodol blue and afrodol violet. 2. Colouring matters belonging to the triphenyl-methan group, Ehrlich's malachite green and fuchsin.

C. *Atoxyl*, which being an organic compound of aniline and arsenious acid cannot be considered as merely "an arsenic compound," an expression recently used in the lay press.

The introduction of an acid radicle into an amido nucleus generally changes its basic character and of course, on the other hand, lessens the acidity. The combined effect of aniline and arsenic is therefore the resultant of these two factors: amido group and arsenious acid. We have been able to demonstrate experimentally that either the amount of aniline generally given in the form of atoxyl or the arsenious acid contained in that drug when administered alone will kill an animal within a few hours after the injection.

D. *Combined treatment*.—1. Combination of arsenious or acid atoxyl with colouring matters, as trypanred suggested by Thomas and Breinl, Laveran and Mesnil, and others. 2. Atoxyl and strychnine—van Campenhout. 3. Atoxyl and sublimate. The last-named treatment has recently been worked out in the Liverpool School of Tropical Medicine and the results obtained on rats are very promising.

We who have been working in the Liverpool School of Tropical Medicine found that in infected rats (*Trypanosoma Brucei*), one part of which were treated with atoxyl alone and the remainder with atoxyl followed by mercury, the first lot generally had relapses in from 16 to 25 days, while a great number of the animals treated with atoxyl and mercury are still alive, some after a period of nine months. These results are certainly encouraging. In our treatment we used, at the beginning, to give high doses of atoxyl in order to drive out the parasites entirely and it was found that if sufficient

¹ A paper read before the Society of Tropical Medicine and Hygiene on July 10th, 1907.

selection of "fly free" sites for the separation camps and for some provision by which treated natives may be kept under observation for considerable periods.

The atoxyl and mercury treatment lately used in our laboratories gives, when compared with atoxyl, fairly permanent results and if an atoxyl treatment should be undertaken in Uganda it would be advisable to start at once with this combined treatment, even if the reliability of this double treatment has so far not been fully established.

Summarising, we would like to suggest in the treatment of sleeping sickness: a fresh 20 per cent. solution of atoxyl, warmed up to 40°, to be administered in small doses to commence with and the doses to be gradually increased, not, if possible, passing the limit of one cubic centimetre of a 20 per cent. solution. The atoxyl to be followed as soon as possible by mercury in the form of sublimate and, in addition, some other trypanocide to be given; we would specially recommend fuchsin. We have lately tried a large number of colouring matters, both Ehrlich's and Mesnil and Nicolle's, and have come to the conclusion that fuchsin is the most promising. In addition to this, as was insisted upon by Thomas and Breinl, the general strength of the patient must be sustained in every way possible.

Liverpool.

CEREBRAL HYPERÆMIA AS A FACTOR IN THE THERAPEUTIC ACTION OF LUMBAR PUNCTURE.

(ILLUSTRATED BY A CASE OF TETANY.)

By FRANK C. EVE, M.D. CANTAB., M.R.C.P. LOND.,
PHYSICIAN TO THE ROYAL INFIRMARY AND TO THE VICTORIA HOSPITAL
FOR CHILDREN, HULL.

It has commonly been assumed that any benefit which may result from lumbar puncture is due solely to relief of intracranial tension. And when (as usually happens) the tension is not measured at the time of puncture, this is the natural assumption. During the past few years I have always measured¹ the intracranial tension during a lumbar puncture, and have been led to the provisional conclusion that relief of tension should be given therapeutic credit only in cases where the hypertension is considerable; and that where the pressure is normal or slightly raised the benefit which sometimes results from lumbar puncture should be ascribed to other causes. These causes may well be manifold, but I would like to advocate the predominant claims of one factor which, so far as I know, has not received attention. And that factor is the marked passive *hyperæmia* of the cerebro-spinal vessels which must inevitably result from the removal of any considerable quantity of cerebro-spinal fluid. For, owing to the uncollapsible bony envelope of the central nervous system and to the inextensibility of its nervous and liquid contents, it follows that for every ounce of cerebro-spinal fluid removed an exactly equal quantity of blood will be added to the contents of the cerebro-spinal vessels. In other words, an equivalent *hyperæmia* will be produced. And if, as is frequently the case, an ounce or an ounce and a half of fluid is withdrawn, the consequent engorgement of the vessels must be very considerable. For if at the end of the puncture the pressure is zero, it means that the venous pressure has pushed out cerebro-spinal fluid until the veins are distended to their natural limits. To regard this *hyperæmia* in another light, it is reasonable to suppose that the addition by lumbar puncture of one and a half ounces of blood to that normally contained in the blood-vessels of the brain and cord might almost double their normal blood quantum, though I do not know the exact amount of this. The brunt of the engorgement produced by puncture would certainly fall on the thin cerebral veins. How far the *hyperæmia* would affect the venous twigs and capillaries, and hence diminish the resistance and increase the blood-flow, could scarcely be decided except by experiments.

Illustrative Case of Tetany treated by Lumbar Puncture.

This case is recorded partly because it illustrates the above thesis that the therapeutic value of lumbar puncture is largely and sometimes solely due to the *hyperæmia* produced,

and partly because I believe it to be a new treatment for a rebellious case of tetany which had resisted all other ordinary remedies.

The patient was a healthy boy, aged four years, who betrayed a neurotic constitution by nocturnal enuresis and by his capricious moods and his often anxious and fretful expression. The morbid excitability of his nerves was shown by the contraction of the circumoral muscles in response to mechanical stimulation of the seventh nerve by a penholder. The onset was acute and idiopathic a fortnight before admission, the mother noticing first a limp and then painful contractures of the hands and feet.

On admission walking was impossible owing to the contraction of the calf muscles, which drew up the heels two inches from the ground. The flexors of the forearms were also firmly contracted, producing flexion of the extended fingers and marked adduction of the thumbs. In other respects, including reflexes, appetite, and sleep, the child was healthy.

Treatment for 12 days consisted of tonics with open air (balcony) day and night. Then five days of aperients and vermifuges in response to a history of worms eight weeks previously. Next 11 days of energetic sedative treatment with chloral and bromide. The case had now a duration of six weeks with a month of hospital treatment without the slightest improvement, and there was the fear of the condition lapsing into chronicity. Encouraged by former success² in a few other refractory subacute cerebral conditions, I stopped all other treatment and tried the withdrawal of an ounce of cerebro-spinal fluid by lumbar puncture under chloroform. The pressure was normal (200 millimetres of water). Next day the child was more rigid, but from that time onwards improvement was rapid and complete. In three days the fingers could be voluntarily extended and in 12 days he could walk, but even after three weeks one heel would not quite touch the ground. The child was sent for a fortnight to the seaside and when finally inspected seven weeks after the puncture there was nothing to be made out except a scarcely noticeable tendency to adduction of the thumbs.

It will be noticed that in this case care was taken to eliminate the effects of bed and hospital environment. It will also be noted that ordinary remedies were ineffectual and that the contracture was in a stationary condition. The case convinced me therefore as strongly as any single therapeutic observation could, that the withdrawal of an ounce of cerebro-spinal fluid was responsible for the cure of this child. And since the pressure was normal, it seemed legitimate to conclude that it was the *hyperæmia* which had favourably affected the nutrition of the disordered nervous tissues in somewhat the same favourable manner as it has been shown by Bier³ and others to act in more accessible regions of the body.

In view of the almost harmless nature of lumbar puncture under suitable conditions, it seems justifiable to try it in a variety of acute or subacute cerebral affections which have resisted other treatment or are tending to become chronic. But until its indications are better understood lumbar puncture could scarcely be advocated until other remedies had failed.

Hull.

Medical Societies.

THE SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

Piroplasma Canis.—*Exhibition of Specimens.*—*Life Cycle of the Parasite of Sleeping Sickness.*—*Parasitic Protozoa observed in Africa.*—*Treatment of Trypanosomiasis.*

A MEETING of this society was held on July 10th, Sir PATRICK MANSON, the President, being in the chair.

Dr. J. W. W. STEPHENS of the Liverpool School of Tropical Medicine showed specimens prepared by Captain

² Ibid.

³ The *hyperæmia* of lumbar puncture would not be quite analogous to that of Bier's method, which in the case of the head would be produced by a ligature round the neck. Presumably this would produce engorgement of the cerebral veins when sufficient cerebro-spinal fluid had been gradually expelled, but it would be accompanied by increased cerebro-spinal pressure and a diminished blood flow owing to the embarrassment of the venous return.

¹ With my cerebro-spinal manometer. See THE LANCET, April 22nd, 1905, p. 1607.