So marked is this association with menstruation that Clifford Allbutt with great sagacity and epigrammatic terseness has said that "Every woman stands often at the gate of Graves's disease."

This functional and transient enlargement of the thyroid at the menstrual period was well known to the ancients, one of whom (Catullus) wrote, when speaking of the change in a girl's physique at the commencement of her menstrual life:

Non illam nutrix orienti luce revisens
Hesterno collum poterit circumdare filo.

M. Leopold Levi and M. Henri de Rothschild recently read a very interesting paper on the influence exercised by the thyroid body on the temperament of a person. They said that they had seen the temperament of a girl, aged 17 years, change completely in consequence of the administration of 175 cachets of thyroid substance. She became slightly thinner, and her figure assumed an appearance of lightness, her features became sharper, and her eyes showed more brilliancy and expression. A great mental change simultaneously manifested itself. Formerly she spoke little, was rather low spirited, and was always tired, drowsy, and inattentive to her work; but now she showed a kind of joyous excitement, attended by bursts of merriment and sometimes foolish laughter. She also talked a great deal, took an unwonted interest in her work, and was no longer anxious to go to bed. They remarked on the changes of temperament due to the thyroid body as seen during pregnancy and menstruation and at the menopause. It would be trespassing on very delicate ground if I ventured to suggest that this recurring thyroid enlargement during the most active functional part of her life must leave its mark on the character and the mental attributes of a woman. Taken in conjunction with the different and lesser degree of convulsion in the prefrontal lobes of the average woman as compared with the average man, it would seem to suggest that the periodic interference with normal mental stability and equanimity would furnish a strong argument to those who hold that a woman's duty and functions in life cannot ever exactly resemble those of man.

Many conjectures have been advanced to account for the effects following removal of the thyroid gland; not one of these has been accepted as conclusive or proved correct. The two most favourably considered are those which regard the symptoms as due to the deficiency of the colloid secretion. By some writers the function of this secretion is supposed to be its ability to render innocuous one or more toxic substances which tend to accumulate in the blood, by others it is thought to be necessary to metabolism generally, and especially to that of the central nervous system. This hypothesis is based mainly on clinical grounds such as I have stated, and if correct would relegate the thyroid gland to a subsidiary position, and would regard its functions as ancillary to those of the brain.

Whether this view be correct or not, it is quite certain that the thyroid plays a very important part in the mental and moral processes which constitute the basis of character, and that, if there is to be, as I firmly believe, a science of character, the further study of the thyroid and its functions must assume a still greater importance.

Before concluding, I should like briefly to recapitulate the main lines of my argument. I have endeavoured to show that while, on the one hand, the knowledge obtained from modern laboratory work can never take the place of clinical experience, and of the study of individual temperament in its relation to disease, we have, on the other hand, to avoid the mistakes into which our forerunners fell in their generalizations and classification of temperaments and the diseases associated therewith. We must, however, recognize in their generalizations an appreciation of the close connexion which undoubtedly exists between disease and temperament.

My own experience and the study of the work of others have led me to the conclusion that, so far as we can trace the connexion between temperament and disease, and between temperament and functional disorder, we must regard the disease or the disorder as the cause of temperament, and not as its effect.

That this is so is, I think, clearly evidenced by the cases I have specified, showing the permanent changes of character which are associated with diseases of the

thyroid gland, and the frontal area of the brain, and the temporary modifications of emotion and conduct which accompany functional disturbance and physiological changes.

To differ from the conclusions of Laycock is not to disparage his work, or to abate one jot the admiration for his powers which has become almost a tradition; nor would I seek to minimize the value of the industry and ingenuity of Wright and the experimental school of which he is so brilliant a leader, but I would urge in the spirit of Bacon that the wise man is he who unites to the enthusiasm of experiment the teachings of experience.

THE TREATMENT OF SLEEPING SICKNESS AND OTHER TRYPANOSOMIASSES BY THE ATOXYL AND MERCURY METHOD.

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THE researches conducted by various investigators connected with the Liverpool School of Tropical Medicine upon the treatment of sleeping sickness and other forms of trypanosomiasis have now reached such an interesting stage that it appears appropriate that some connected account should be given of these important studies in experimental therapeutics.

The first use of arsenic as a remedial agent against trypanosomes is due to the great explorer Livingstone, who found it to possess a beneficial action on animals infected with *nagana*, or tsetse-fly disease.

Later observers, including Bruce, Lingard, Laveran and Mesnil, Thomas and Breinl, and others, found that arsenic administered in various inorganic forms possessed a marked influence upon trypanosomes of different species in the blood stream of infected animals. All these observers noticed, however, that as a general rule the protective effect of inorganic forms of arsenic was only temporary, and that, in the end, the parasites reappeared in spite of steadily-increasing doses of the drug. Finally, the animals died either of the disease or through arsenical poisoning due to pushing the drug.

Thomas and Breinl¹ then instituted a search amongst arsenical compounds for a drug which would still retain its effect upon trypanosomes, but would not be so toxic to the animal under treatment. After a number of preparations had been tested with negative results, the body known commercially as atoxyl was found to possess marked toxic action on trypanosomes, with much diminished effect on mammals.

A long series of experiments were then carried out at the Runcorn Laboratories on animals experimentally infected by various trypanosomes, and it was found that when animals very severely infected were thoroughly and persistently treated with atoxyl a very marked improvement immediately followed. The parasites underwent degeneration, and entirely disappeared from the blood in a few hours. The animals gained in weight, lost their symptoms, and appeared to be healthy. In some of them these effects were permanent; in others—and these the majority—if the treatment were stopped, the parasites reappeared in the peripheral circulation after a varying period, or even if the drug were given continuously the parasites eventually reappeared after a longer interval of freedom, and increased in numbers until the animal died. Thomas and Breinl were much impressed by the favourable results obtained with atoxyl, and advised that the drug should be given in as high doses and as continuously as possible in cases of human trypanosomiasis.

As a result of the work of these observers, the Liverpool School of Tropical Medicine has ever since consistently advised that this drug should be given a most careful trial in the treatment of sleeping sickness, and to this end has sent out, free of charge, large quantities of this hitherto somewhat expensive drug to medical men and missionaries in West Africa, who have signified their desire to give the remedy a trial.

Since the introduction of atoxyl for the treatment of trypanosomiasis a large number of observers have tested it, and all are now united in giving it the premier position, as a trypanocide.

The results of most observers upon the treatment of sleeping sickness by atoxyl alone completely confirm the results stated above as having been obtained by Thomas and Breinl in the experimental trypanosomiasis of animals. Thus, cases have been described which were apparently permanently benefited and might be described as cured, but in a great many of them recurrences were observed, and finally the infection became persistent, the trypanosomes becoming atoxyl-fast and being apparently no longer affected by the drug.

Quite recently a second distinct advance has been made in the experimental therapeutics of trypanosomiasis, and again by workers of the Liverpool School. This consists in treating infected animals, from which the trypanosomes have primarily been driven out of the blood by the use of atoxyl, by a second drug, so as to prevent the recurrences which so often follow atoxyl treatment alone.

The general principle underlying the combined method of treatment by two successive and quite different drugs is that when an infective organism, such as a protozoon, shows two distinct phases in its life-history, then these two phases ought to be attacked by separate drugs, and it is not only possible but probable that a drug which affects the first will not affect the second, and vice versa.

The application of this bio-chemical principle, which has led to success in the prevention of recurrences in trypanosomiasis, may be very wide in experimental therapeutics, especially in protozoon diseases where different phases in the life-history occur in nearly all cases. The two drugs necessary to attack two successive stages of the parasite will certainly not always be found to be an arsenical compound and a mercurial compound; but it is established as a principle that given a parasite has two successive phases, A and B, then the problem of experimental therapeutics is to find two remedial agents, *a* and *b*, of which *a* kills phase A and *b* kills phase B, and then to apply the remedies *a* and *b* in succession, killing off phase A as completely as possible with remedy *a*, and then attacking phase B with remedy *b*, and continuing this rotation until the animal is free of infection.

The research on the combined treatment was commenced in the Bio-chemical Laboratory of the University of Liverpool by B. Moore, Nierenstein, and Todd in October, 1906, and a preliminary report published in March, 1907,² followed by a fuller account in May, 1907;³ the work is now being continued on large animals in the Runcorn Laboratory, and, as far as cases are available, upon human trypanosomiasis.

At the time of the commencement of this research, a second phase in the life cycle of the trypanosome was not known with certainty to exist, but since then the life-history has been more completely investigated by J. E. Salvin-Moore and Breinl, and these observers have clearly shown the existence of such a phase.

The existence of this other phase was suspected by Moore, Nierenstein, and Todd, from the regular way in which, after the trypanosomes had been completely driven out of the peripheral blood by atoxyl, recurrence again took place, although the investigation of organs and tissues other than the blood had failed to demonstrate anywhere a storage of the ordinary phase of trypanosome.

On these grounds, these observers determined to first drive out the parasite from the peripheral blood by atoxyl, and then when the blood was free to treat by other drugs, paying no attention to whether these drugs had any effect upon the usual phase of the trypanosome or not.

Accordingly a series of experiments was commenced, in which rats infected experimentally with *Trypanosoma brucei* were used on account of the rapidity of action of this type of trypanosome. After driving out the trypanosome with atoxyl, the salts of the different heavy metals were given; salts of silver, lead, copper, and antimony respectively were employed without any marked results, but when mercury was used in the form of the bichloride a distinct beneficial result was at once obtained. While the entire series of controlled rats treated with atoxyl alone succumbed, nearly 70 per cent. of the rats given the double treatment survived, never showing any recurrence of trypanosomes, and of the remaining 30 per cent. only 8 per cent. showed recurrences of trypanosomes.

It may be emphasized that the mercury salt alone has not the slightest effect upon the ordinary phase of the trypanosome as seen in the peripheral circulation. This

appears to demonstrate clearly that the two drugs act upon two quite distinct phases.

Similar results are at present being obtained with other classes of animals, and indications of like results with the more slowly acting *Trypanosoma gambiense* of sleeping sickness.

The two drugs are likewise being employed in the treatment of sleeping sickness in man, and the results so far obtained are distinctly encouraging.

In their longer paper,⁴ Moore, Nierenstein and Todd also devote a section to the chemical and physical properties of atoxyl, and show that this is not, as it was originally described, an anilide of metarsenious acid, but is an exceedingly stable chemical substance with the arsenical radicle directly attached to the benzene ring. It was shown that the aqueous solution is strongly dissociated electrolytically, giving in consequence an apparently low molecular weight by the freezing-point method, and possessing a high electrical conductivity. Except on standing in aqueous solution, it is a most stable compound, and neither aniline nor arsenic are easily detachable from its molecule by chemical means.

Its toxic properties are neither those of arsenic nor of aniline even when pushed to excess, and its therapeutic action is rapid; from this and its high conductivity, showing high dissociation, the conclusion was drawn that its activity must be ascribed, not to free inorganic ions or to free aniline, but to a complex organic ion containing both the arsenical and aniline radicles.

Ehrlich,⁵ in a paper published a few weeks earlier, stated that atoxyl was the sodium salt of p-amido-phenyl-arsenic acid, with four molecules of water crystallization; the analyses of Moore, Nierenstein and Todd yield the formula $(\text{NH}_2)(\text{C}_6\text{H}_4)\text{AsO}_3\text{NaOH}\cdot 3\text{H}_2\text{O}$, and they had independently come to the conclusion that the arsenic radicle was united directly to the ring. Since then Ehrlich and Betheim⁶ have published the details of their chemical work, showing that the arsenic radicle is in the para position to the NH_2 group.

To Fournau⁷ is due the credit of showing that, chemically, atoxyl is not a new preparation, having been synthesized as long ago as 1865 by Bechamp⁸ in the early days of synthesis of aniline colour, fuchsin being produced in abundance at the same time. Bechamp supposed that he had in hand an anilide of ortho-arsenic acid. Fournau supports this view, and the body is described as an anilide, but this from the evidence given by Moore, Nierenstein and Todd, and by Ehrlich and Betheim, is probably an error.

The importance of these new discoveries in the treatment of trypanosomiasis, especially for tropical climates, can scarcely be over-estimated. They may result not only in the saving of millions of human lives, but may make vast tracts of country, now uninhabitable by civilized man on account of the ravages of animal pests, inhabitable and capable of cultivation. India alone loses over a million pounds annually through cattle lost by *surra*, and the loss of horses in the late South African war from tsetse-fly disease is within the recollection of every one.

But the new principle underlying the combined method, that where an invading organism shows more than one phase, then treatment should be studied and adopted to each stage in order to effect complete destruction of the parasite, is an advance in experimental therapeutics which may soon find application in diseases nearer home.

Here there is an illustration of the value of experimental therapeutics which ought to stimulate the study of that subject, and induce us to foster its growth by the establishment of research positions and research laboratories in the subject.

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THE late Mr. John Venables, of Birkenhead, who died on May 25th, left £200 each to Birkenhead Borough Hospital, and the Birkenhead and Wirral Children's Hospital.