Observations

ON

ADMINISTRATION OF ARSENIC IN SYPHILIS.

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THE educated portion of all civilized nations is becoming more and more alive to the enormous influence which syphilis will have on the future well-being of the nation and to the increase in the dissemination of this previously world-wide disease that may follow the great war. Measures of prevention are now freely discussed in places where a short time ago the mere mention of venereal disease would have caused consternation. With this awakening there will come a demand for the sole effective means of prevention, which consist in the sterilization by treatment of infective cases, so that they no longer constitute foci for the dissemination of their disease.

It has been observed that syphilis is the most protean of diseases. Its manifestations in individual cases are as varied as humanity itself, and it is scarcely to be expected that the general practitioner will have time or opportunity thoroughly to familiarize himself with all of them. There will always be room and work for the specialist, but the general practitioner should be able to recognize the more obvious cases, which are those really dangerous to the public, and by the method introduced by Ravaut and Thibierge, and referred to here, he can treat the majority of them far more satisfactorily than most of the other ailments with which he has to deal.

One of the chief objections appears to be that raised by a London doctor in a recent letter to the *BRITISH MEDICAL JOURNAL*, in which he complained that the technical apparatus required was elaborate, expensive, and troublesome to manipulate. In the majority of clinics this is quite correct, for they still use the gravity apparatus, and dissolve the arsenic preparations in large quantities of distilled water, and have also a considerable amount of normal saline solution in the alternate tube for the purpose of indicating that the needle has penetrated the vein, and for washing out the portion of the dose below the Y tube at the completion of administration. This method of administration necessitates a special still and much sterilization each day of the apparatus used, as well as possession of the equipment itself.

Many efforts are being made to simplify the administration of the organic arsenic preparations. They have been enclosed in capsules by enterprising manufacturing chemists, in order that the dose might be swallowed or introduced into the rectum. Unfortunately the drug is too unstable for this method, and appears to lose its efficiency when so administered. To obtain therapeutic effect it is necessary to introduce it directly into the circulation or mediately by intramuscular injection.

Persistent attempts have been made, by combining the drug with various local anaesthetics, to avoid the intense pain and disability which is caused by even the blandest of the new organic arsenic preparations when injected into muscle or subcutaneous tissue. Susceptibility to pain varies so greatly that, while some individuals do not appear to suffer much, the majority complain very bitterly of the pain caused by these injections, and it is not likely that this method will become at all popular among patients; and this consideration will probably have more weight in private practice than in the army.

The view sounds reasonable and may yet be proved, that, owing to slower and more continuous absorption, the therapeutic effects of arsenic introduced into muscle tissue are greater than when introduced directly into the circulation, but in so far as therapeutic effect is indicated by the rapid involution of external syphilitic lesions, and the reversal or inhibition of the Bordet-Wassermann reaction, the intravenous method is equally effective.

The publication of a translation of Professor Thibierge's work on the treatment of syphilis¹ led us to adopt his

method of administration of concentrated solutions in this clinic, where it has now been in use for three months, and we think that a description of the technique used here and the results obtained would be of interest, more particularly to the general practitioner, who requires simplicity of administration without loss of effect.

The apparatus required is to be found in the most modest surgery, for it consists of a hypodermic syringe and two or three small basins, although, where a large number of injections have to be given, several other articles may be used to increase speed and efficiency.

We have found that, by the method about to be described, two officers and two orderlies can give from fifty to seventy intravenous injections of arsenic and the same number of intramuscular injections of mercury in less than an hour.

After trial of a number of hypodermic syringes, the one we have found most useful is a cheap two-piece glass syringe made by Maw of London. The points of special advantage are a comparatively long barrel, of moderate diameter, so that, although graduated to 2 c.cm., it will really hold nearly 4 c.cm., while its narrow diameter enables the needle to be introduced at an acute angle with the skin. The plunger fits accurately and may be entirely withdrawn. There are no metal contraptions at either top or bottom. The tapering connexion has no shoulder, and fits well, so that there is no leaking, and the needle, when in place, is firm, but can be easily removed. The needle is rather larger than the ordinary hypodermic needle and has a shorter point, so that, while a vein is easily picked up, there is less danger of a through-and-through penetration.

Method of Administration.

A burette (30 c.cm.) containing the sterile water is held upright by a stand, and is continued at the bottom by a short piece of rubber tubing, terminating in a glass nozzle and closed by a pinchcock. One of the orderlies flames the outside of an ampoule of the drug with a small alcohol lamp, files off the tapering end, runs in 2 c.cm. of water from the burette, and inserts a piece of small glass tubing with rubber connexion at one end and a few filaments of wool at the constriction near the centre, such as is supplied with the galy ampoules. The ampoule is then gently shaken. Solution is complete in a few seconds. The ampoule is placed upright in a small board which has had sufficient half-inch holes drilled in it to hold the required number of ampoules.

The officer, having picked a syringe out of a small basin of alcohol with dressing forceps, washes it in sterile saline solution, aspirates the contents of the ampoule by means of the rubber connexion to the glass tube, picks out one of several needles which are boiling in a container beside him, and adjusts it to the syringe. Meanwhile the other orderly has prepared the patient by fastening a light rubber tube round the upper arm and painting below the bend of the elbow with iodine. The patient seats himself at a narrow table on the opposite side from the officer, his arm resting on the table. The officer, steadying the skin with his left hand, introduces the needle into a vein, slightly withdraws the plunger to make certain that the needle is in the lumen of the vein, and removing the tourniquet, completes the injection. The table should be so placed that the light falls freely on it. The needle puncture is so small that no bleeding takes place and no cotton or collodion is required to seal it.

The officer, having completed the injection, washes needle and syringe, and returns the syringe to the alcohol and the needle to the boiling water. He picks out a second syringe and proceeds as before, using the syringes alternately.

It would be quite feasible, of course, for one medical man to do all this himself, but he would require several minutes to make each injection.

During the past three months 2,859 intravenous injections have been given in the above manner in this clinic. There has not been a single case of thrombosis of the vein. There have been no early reactions of an anaphylactic character such as we used to have fairly frequently when injecting large quantities of distilled water which was not above suspicion. There have been no reactions, late or early, which could be attributed to the method of administration. Owing to the small size of the needle the pain of introduction is less than where the larger needle required by the gravity apparatus is used, and much smaller veins

may be successfully entered. On three or four occasions the vein has been missed or completely penetrated, and solution has been injected into the surrounding tissue. This accident causes a good deal of pain, swelling, and disability, which, however, pass off in a few days without abscess formation or permanent induration.

A microscopic examination of blood withdrawn from the vein into the syringe containing the arsenic solution shows the blood cells apparently perfectly normal even some hours after withdrawal.

The drugs used by us have been novarsenobillon and novarsenobenzol, which have been supplied in ampoules containing 0.6 gram and 0.9 gram. The smaller doses when required have been obtained by splitting one or more of these, when dissolved, between two patients.

We have used distilled water in making the solutions, but only a very small quantity is required, and it is pointed out by Thibierge that ordinary sterilized water free from gross impurities may be used in this small amount with impunity.

Results.

It has seemed to us that the administration of arsenic in concentrated solution is more effective than when it is given diluted. Our records for July, the first month in which all the patients being discharged had had a full course of treatment by the above method, show that 141 patients were discharged from hospital as out-patients during the month with their external lesions soundly healed, and that the average duration of their stay in hospital was sixteen days, a considerably shorter period than formerly. These patients return for treatment as out-patients at weekly intervals until the full course is completed.

Distribution of Cases.

Cases with primary lesions only—71.

Average stay in hospital	...	16 days
Discharged in less than 10 days	...	16 cases
Discharged in 10 to 20 days	...	32 "
Discharged in 20 to 30 days	...	18 "
Discharged in over 30 days	...	5 "

Cases with secondary lesions—49.

Average stay in hospital	...	14 days
Discharged in less than 10 days	...	13 cases
Discharged in 10 to 20 days	...	24 "
Discharged in 20 to 30 days	...	6 "
Discharged in over 30 days	...	6 "

Cases with recurrent lesions—13.

Average stay in hospital	...	24 days
Discharged in less than 10 days	...	1 case
Discharged in 10 to 20 days	...	8 cases
Discharged in 20 to 30 days	...	3 "
Discharged in over 30 days	...	1 case

Cases with positive Wassermann reaction, but without infective lesions on admission—8.

Average stay in hospital	...	11 days
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The records for August show that 166 syphilis cases were discharged as out-patients during the month, with an average stay in hospital of 16 days. They were distributed as follows:

Cases with primary lesions only—92.

Average stay in hospital	...	16 days
Discharged in less than 10 days	...	32 cases
Discharged in 10 to 20 days	...	40 "
Discharged in 20 to 30 days	...	12 "
Discharged in over 30 days...	...	8 "

Cases with secondary lesions—31.

Average stay in hospital	...	15 days
Discharged in less than 10 days	...	19 cases
Discharged in 10 to 20 days	...	8 "
Discharged in 20 to 30 days	...	3 "
Discharged in over 30 days...	...	1 case

Cases with recurrent lesions—35.

Average stay in hospital	...	17 days
Discharged in less than 10 days	...	19 cases
Discharged in 10 to 20 days	...	10 "
Discharged in 20 to 30 days	...	4 "
Discharged in over 30 days...	...	2 "

Cases with positive Wassermann reaction, but without infective lesions on admission—8.

Average stay in hospital	...	4 days
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The total number of patients admitted to the clinic from May 26th, 1918, to the end of August was 540, of whom 430 were diagnosed as syphilis and placed on treatment; 257 of these have not completed their routine course. Of the remainder, 35 have completed a course and are awaiting a Wassermann test. The Wassermann test result has been received in 138 cases, of which 127 are negative and 11 are positive.

Examination of the 11 cases with positive reactions on completion of course shows that 9 had generalized syphilis prior to

coming to this clinic, while of the other two, one had his primary chancre for five weeks before admission to hospital.

The Wassermann tests were made by No. 1 Canadian General Laboratory, Witley.

It has been shown that intravenous arsenic as ordinarily administered is eliminated pretty rapidly by the kidneys, so that a large part of the dose is disposed of in this way within a few hours after administration. The diuretic effect of the distilled water and saline solution introduced into the circulation along with the arsenic may have something to do with this, and it is reasonable to suppose that when the dose is given in concentrated form it is less rapidly eliminated. We have not had the means to estimate quantitatively the arsenic in the urine, and have been unable to verify this supposition.

When arsenic is administered by a gravity apparatus it is customary, in large clinics at any rate, to dissolve the doses for several patients at once, and, as the solution is run out, more is continuously added during the period of an hour or longer, according to the number of patients. It is clear that in this way some portion of the drug will be exposed to the air for a considerable time, as the tube is never allowed to entirely empty itself, and some degree of oxidation is bound to occur.

Where solution is effected in the ampoule immediately after it is opened and the contents injected within a minute or less, oxidation prior to administration must be very slight indeed. In default of support from estimation of the rapidity of arsenic excretion, it must be admitted that the number of cases is too few and the period of observation too short to establish the truth of the supposition that concentrated solutions of arsenic are more effectual than dilute, but there is sufficient evidence to show that by their use syphilitic lesions undergo very rapid involution, and that their administration in suitable dosage is perfectly safe.

ADDENDUM.

Since this paper was written, early in September, 1918, the use of the method of administration there described has been continued.

In September 111 syphilis out-patients were discharged, average stay in hospital 13.5 days; in October 139, after an average stay in hospital of 16 days; in November 97, after an average stay in hospital of 14 days.

Slightly under 1,000 intravenous injections have been given in each month, and up to date there has been no case of thrombosis or other contraindication to the use of concentrated solutions. There has been an entire absence of early anaphylactic reactions.

The course of treatment referred to in the paper is the minimum course as laid down by the War Office, and consists of 3.9 grams neosalvarsan divided into seven doses and given at weekly intervals, the first two doses being 0.45 gram and the remainder 0.6 gram. An intramuscular injection of mercury gr.1 is given each week in addition to the neosalvarsan.

These amounts are for the ordinary otherwise healthy man only, and are modified as considered necessary, when full doses are contraindicated. Even if the Wassermann test is negative at the end of such a course, as it usually is, it is realized that this is an insufficient amount of early intensive treatment, and since the termination of active hostilities all except the early primary cases receive more. All the men are advised to carry on taking mercury by the mouth, and to have another Bordet-Wassermann test, and further advice at the end of three to six months.

One of the difficulties experienced by the clinic has been that of ensuring the attendance of soldiers discharged as out-patients for the remainder of their hospital treatment. Many of them are from units stationed in camps at a distance from the hospital, and the necessary transport was not available in sufficient quantity. To overcome this a system has been arranged whereby an officer and staff with their equipment, which is carried in a small box, visit the two outlying camps on one half-day, in each, a week. Out-patients are paraded in one of the huts to receive treatment.

The largest number treated in one half-day so far is 100, but with a better system of organizing parades beforehand this number could easily be increased. Where any large number of cases are reporting for treatment in this manner another officer familiar with the disease should be in attendance for the purpose of examining certain of the

men prior to their receiving treatment. Urine tests when required should be carried out beforehand.

Some such system of peripatetic clinics might well be utilized by the public health authorities when they deal with the control of syphilis among the civilian population, although in this country there are probably few places not within reach of one of the larger towns, where it is presumed treatment clinics already exist.

REFERENCE.

¹ *Syphilis and the Army*. London, 1917. University of London Press. (6s. net.)

ON THE AGGLUTINATIVE AND OPSONIC ACTION

OF CERTAIN CHEMICAL SUBSTANCES ON THE RED BLOOD CORPUSCLES, THE RELATION BETWEEN THIS ARTIFICIAL AGGLUTINATION AND AGGLUTINATION BY SERUM, AND THE BEARING OF THESE OBSERVATIONS ON THE AGGLUTINATION AND PHAGOCYTOSIS OF PATHOGENIC ORGANISMS.

BY

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IN THE BRITISH MEDICAL JOURNAL of December 8th, 1917, I drew attention to the association that exists between the haemagglutinative and the opsonic actions of a foreign serum on washed red blood cells in animals and in the human subject. Although the agglutination of the individual red cells, *inter se*, seems frequently to be a preliminary step in the ingestion of these cells by leucocytes, a mutual adhesiveness between red cells and leucocytes is also necessary before actual ingestion can occur. The process of haemagglutination is thus one phase in a larger erythro-leucocyte reaction by which the phagocytosis of red blood cells is brought about.

Not only does the opsonization (or preparation of red cells for ingestion by leucocytes) depend on preliminary action by a serum agglutinative to the particular red cells to be ingested, not only does the number of red cells ingested vary quantitatively with the haemagglutinative capacity of the serum used, but actual ingestion does not occur unless a mutual adhesiveness between phagocytes and red cells is also present.

A careful analysis of this process of so-called haemagglutination under controlled conditions will probably throw further light on an allied problem—namely, the conditions under which pathogenic organisms are prepared for ingestion by phagocytes, and to what extent, if any, previous agglutination by humoral agency is a necessary step in the phagocytosis of bacteria and other organisms. It is on these grounds that the haemagglutinin reaction becomes so important.

The Leucotoxicity of Certain Serums.

IN THE BRITISH MEDICAL JOURNAL of December 8th, 1917, I referred to the fact that a serum may be haemagglutinative to the red cells and yet be toxic to the leucocytes in any given specimen of blood. Under these conditions ingestion does not occur.

This leucotoxic action can be demonstrated by incubating a drop of the whole blood in a closed cell with the foreign serum. If the serum be toxic the leucocytes do not emigrate from the clot on to the slide, or any cells that do leave the clot fail to adhere to the slide and undergo cytotoxicity. No ingestion of red cells takes place. Thus, in order to obtain successful phagocytosis of red cells the erythro-leucocyte-serum combination must be favourable.

The mechanism by which the successful phagocytosis of bacteria is brought about very probably depends on a right combination of analogous factors.

The Erythro-leucocyte-serum Reaction is not Wholly a Specific Reaction.

HAVING thus seen that the phagocytosis of red cells by leucocytes depends on a delicately balanced humoral cellular reaction which affects serum, red cells, and leucocytes, we now proceed to inquire whether this erythro-leucocyte-serum reaction is specific—that is to say,

whether, in order to bring about the ingestion of the red cells in any given case, the serum which induces the preliminary haemagglutination must be native to the leucocytes, or whether any foreign serum which agglutinates red cells will have an equal opsonic effect. In other words, to what extent can we vary the different factors concerned in the reaction?

While undoubtedly the best result is obtained by employing a native sero-leucocyte combination acting on foreign red cells, experiment shows that it is not absolutely necessary for ingestion that the serum and the leucocytes should be provided by the same individual. In some cases a serum may produce agglutination of the red cells, but fail to bring about ingestion by foreign leucocytes.

The three factors concerned in erythro-phagocytosis may be present but not in right combination or in right proportion. In other cases the very marked specific nature of the reaction suggests that the haemagglutinins have actually been shed into the serum by the leucocytes.

Provided that the foreign serum is not toxic to the leucocytes, then any serum which agglutinates the red cells may prepare them for ingestion up to a certain point, but for complete ingestion on a rapid and large scale, in which almost every leucocyte contains a number of red cells, a further stage of the erythro-leucocyte reaction, or an agglutination of the red cells to the leucocytes, must also be present. This is shown by the following experiments:

1. C. J. B. washed red cells previously agglutinated by a foreign serum, and subsequently washed free of that serum in normal saline, were then incubated with C. J. B. whole blood. Under these conditions slight ingestion of the red cells so treated by C. J. B. native leucocytes occasionally took place.
2. Sheep's washed red cells which had undergone a preliminary agglutination by a non-toxic foreign serum were ingested by C. J. B. leucocytes in larger numbers than sheep's red cells not so previously agglutinated.

The Condition of the Red Cells Influences Ingestion:

The Leucotoxicity of Broken up Red Cells.

While the sero-leucocyte combination has a great influence on the phagocytosis of red cells, the condition of the red cells themselves is also very important. Erythrocytes seem to be more resistant to the phagocytic action of their own native leucocytes than to leucocytes from another individual.

The leucocytes of some individuals seem to have a greater capacity for ingesting sheep's washed red cells than the leucocytes of other persons. Certain animal erythrocytes—for instance, sheep's red cells—are more easily and rapidly ingested by human leucocytes than foreign human erythrocytes from another individual.

The relative capacity of resistance to ingestion by the red cells of different human individuals also varies under different conditions. Thus my own (C. J. B.) red cells, previously washed with normal saline, were ground up in a mortar, a suspension of these disintegrated red cells was made in normal saline. The centrifuged sediment was found to consist of broken up portions of red cells which still retained their haemoglobin constituent. This corpuscular debris formed a yellowish-grey deposit when centrifuged, and on this bottom layer an upper layer of still intact red cells rested if the trituration had not been too complete.

A drop of this suspension of red cell debris in saline was then incubated in a closed cell with two drops of whole C. J. B. blood. The following striking effect was observed. After incubation the floor of the cell was found coated with the red cell debris. This adhered very closely to the glass and was not removed by a gentle stream of saline. This red cell debris also had a marked toxic effect on the leucocytes. Very little emigration of leucocytes from the clot took place in the areas occupied by the debris, while in other free areas a few leucocytes which did emigrate and adhere to the slide showed disintegration changes and gave no iodophil reaction. Thus while whole red cells are not toxic to native leucocytes, broken up red cells are highly toxic to those cells.

But if, instead of employing native red cells, broken up foreign red cells from another individual are incubated with the same C. J. B. whole blood, then the toxic effect on the leucocytes is much less and considerable emigration may occur. This is the case even if the blood serum of the individual supplying the red cells is agglutinative to the red cells of the person supplying the leucocytes.