I

THE URINARY EXCRETION OF NOVARS- SENOBILLON IN SYPHILIS AND ITS RELATION TO TOXIC EFFECTS*

By V. E. LLOYD, *M.C., M.B., B.S.*, Director of the Department for Venereal Diseases, Guy's Hospital, and N. L. LLOYD, *M.B., M.R.C.P.*,† Medical Officer to the Department for Venereal Diseases, Guy's Hospital.

PAPER NO. I

By N. L. LLOYD, *M.B., M.R.C.P.*, Medical Officer to the Department for Venereal Diseases, Guy's Hospital.

MR. PRESIDENT, LADIES AND GENTLEMEN,—I feel it is a great privilege to read a paper to this Society to-night, and I trust that the report of this work, which has been carried out in the Venereal Disease Department at Guy's Hospital will be of interest to you. We consider that certain technical details are essential in evaluating a comparatively unknown test, and for the inclusion of these details we would solicit your tolerance.

In spite of the widespread use of salvarsan and its derivatives in the last fifteen years, our knowledge of the fate of these compounds in the human body is by no means complete. That a considerable proportion of these compounds is quickly excreted, principally in the urine and fæces, is well known, although the factors concerned in regulating the rate of elimination are little understood. The inter-relationship of intensity of therapeutic effect, the rate of elimination, and the production of toxic manifestations, events which are probably closely associated, is a subject of great interest and clinical importance.

Considerable information concerning the harmful effect of these compounds on liver efficiency has accumulated during the last few years since the introduction of hepatic function tests. It has been shown repeatedly by such tests that in toxic jaundice the liver has suffered con-

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siderable damage. Gerrard,¹ using the van den Bergh reaction, has reported that latent jaundice indicative of slight hepatic inefficiency is not infrequently present in patients undergoing systematic treatment; in some of these latent cases jaundice developed within a short time. In a large series of cases tested at regular intervals by one of us this reaction demonstrated latent jaundice in a few cases, in all of whom jaundice became clinically obvious in spite of the cessation of treatment.

In exfoliative dermatitis of organic arsenical origin such tests have rarely shown any abnormality.

In considering the treatment of syphilis, the chief aim is the maximum therapeutic action that can be attained with a minimum toxicity. Any measure which would indicate, at the beginning of treatment, those patients who may be susceptible to toxic effects would be of value in deciding upon a modified scheme of dosage and intervals which may avoid future toxic complications.

It seemed to us that to be of maximum practical value such a test should possess certain additional features. The majority of patients in whom such a test is desirable are attending as out-patients. Their attendance is usually unknown to their relations or to their employers. Secrecy is of great importance, and this is not merely a matter of keeping names unrevealed, but has a wider application in that treatment and investigations should be arranged in such a way that little time is lost, and the patient is not obliged to account for some hours' deviation from his accustomed routine.

It is for these reasons among others that the existing tests have failed in their practical clinical application. The lvulose hepatic tolerance test, for example, necessitates the attendance of the patient for two hours. Further, the repeated insertion of a needle and withdrawal of blood may cause apprehension and even lead to cessation of attendance.

It is conceivable that in those who are liable to toxic effects the excretion of the arsenical preparation might be delayed. An indication of such variation of excretion could be ascertained by quantitative estimations of arsenic in the urine. Such estimations, however, even by the shortest methods, are very laborious and require the services of an expert; they are therefore inapplicable for routine use in a clinic or by a general practitioner.

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In searching for some method of investigation which might be of value in this connection, all these points were considered, and we were led to make use of a colour reaction described by Abelin² which is given in the presence of salvarsan in solutions of considerable dilution.

The research described in this paper was carried out in the hope that this reaction might be of value in determining whether, and to what degree, excretion varies, and whether abnormal excretion, if it were found, would indicate those patients who are liable to toxic effects; it was also hoped that any such indication might be given at a time which is early enough to prevent such undesirable complications.

This test has the advantages of being extremely simple, of requiring no special apparatus, of taking up little of the patients' time, and of being easily applicable to out-patients.

In 1911 Abelin² described a test which would show the presence of salvarsan, a test which depended on the conversion of the arsenobenzol into a diazo compound, and the subsequent linking of this body to some member of the phenol or naphthol groups such as resorcin with development of a colour. He showed³ that in patients receiving the drug the presence of salvarsan could be demonstrated in the urine five to ten minutes after injection, and that excretion continued up to about seven hours.

Escallon,⁴ following this method, found two waves of excretion, one during the first six hours and the other between twenty-five and forty hours after injection.

Kötter,⁷ on the other hand, found elimination proceeding for two or three days, and in some cases positive results were obtained seven days after injection. He also noticed two waves of excretion.

Riebes⁶ confirmed Abelin's findings for salvarsan, and found much the same with neo-salvarsan.

Leredde and Rubenstein⁸ noted elimination proceeding from five minutes to twenty-four hours as a rule. In one case no elimination could be demonstrated. Eight of their cases showed delayed elimination, and these were suffering from syphilis of the latent or tertiary stages.

Frenkel-Heiden and Navassart⁵ compared the result of the Abelin test with estimations of arsenic and found

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that arsenic was present whenever the Abelin test was positive.

Autenrieth and Taege ¹¹ have also used the test with success, and have employed it for quantitative estimations in a colorimeter of their own design.

The literature is well summed up by Beeson and Albrecht ⁹ who relate their own experience in the examination of fifty cases of syphilis. They considered the test to be specific for salvarsan and neo-salvarsan after testing other members of the benzene series. Compared with Abelin's results, they found elimination slower, though generally complete in twenty-four hours. Elimination was more prolonged in cases of tertiary syphilis and neurosyphilis. They considered the test of such importance that they agree with Leredde that absence of elimination should lead to careful examination of the patient before proceeding with further arsenical treatment. They also confirm the work of Escallon and of Riebes, who found that the rate of excretion does not always decline in a regular manner.

Kolls and Youmans ¹⁰ applied the test to blood plasma, cerebrospinal fluid, and in animal experiments, to certain body tissues and organs as well as the urine. They found that the drug disappeared with great rapidity from the blood stream, but could not determine its presence in the cerebrospinal fluid, except in dogs after massive doses. They obtained negative reactions with the fæces, although the bile frequently gave positive results.

Most authors are agreed as to the technique of the test, and although each prefers slight variations in strengths of solutions, the general outline is as follows:—

Five cubic centimetres of the fluid to be tested are placed in a test-tube and cooled in running water. To this is added 0.5 c.c. of 5 per cent. hydrochloric acid, and after a few minutes 1 c.c. of a 0.5 per cent. solution of sodium nitrite. The test-tube is allowed to remain in running cold water (some prefer ice) for ten minutes. In a second test-tube are placed 4 c.c. of a 10 per cent. solution of resorcin in water and 1 c.c. of 10 per cent. sodium hydroxide. The contents of the first test-tube are added to those of the second.

The presence of the arsenobenzol is shown by the development of a colour varying from red to reddish-brown, which appears immediately.

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It has been suggested that a more delicate end-point may be reached by allowing the diazotised urine to come gently into contact with the resorcin without mixing the two solutions. In this way a ring is formed at the juncture of the two fluids.

Using the technique already described, we made many experiments with solutions of novarsenobillon in water of varying strengths. It was found that a definite red colour developed in watery solutions of a strength of 0.005 per cent., or 1 in 20,000. In higher dilutions a colour varying from red to reddish-brown developed which was distinguishable to the naked eye in a dilution of 0.002 per cent., or 1 in 50,000. Below this the colour which developed was scarcely distinguishable from that of a control test with water. The ring modification was not successful in our hands.

We also endeavoured to increase the colour effect, and it was found that by looking through a depth of fluid of 5 cm. with transmitted light from a daylight lamp, the end-point could be further lowered to a dilution of 0.001 per cent., or 1 in 100,000.

When a solution of novarsenobillon in urine was used, the urinary pigments obscured the end-point to some extent, and it could not be said with certainty that a positive result was obtained with a solution of less strength than 0.002 per cent., or 1 in 50,000, using a depth of 5 cm. By using a greater depth the colour is, of course, further intensified, but it was found that if this were done other factors came into play, and urines containing excess of normal pigments occasionally gave a reddish tinge which simulated the colour of the reaction. With a depth of 5 cm. this did not arise.

Several experiments were made in order to check certain points in the technique which I have already described. In addition, attempts were made by altering this technique, or varying the amounts or strengths of the reagents used, to intensify the colour which develops, or to render the test more sensitive as to its end-point.

It was found that the amount of sodium nitrite used was sufficient for the diazotisation of as high a concentration as might be met with in practice, and that nothing was to be gained by increasing the amount. As to the hydrochloric acid, it was only necessary to render the fluid slightly acid for diazotisation to take place. In

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practice it was found more convenient by us to use 1 c.c. of a decinormal (3.65 per cent.) solution of the acid. The colour was unaffected by this slight reduction. Reduction in strength of caustic soda resulted in a diminution of colour; increasing the strength of this solution failed to produce any advantage. With regard to the resorcin, however, it was found that the depth of colour which developed does depend on the amount of resorcin present. Several experiments were made, using varying amounts and different strengths of resorcin, as a result of which it was found advantageous to use small amounts of a high concentration, and in subsequent experiments 1 c.c. of a saturated solution of resorcin was used. This also reduces the final volume slightly and thereby increases the concentration of the colour to some extent.

Attempts were made to set up permanent colour standards with definite strengths of N.A.B. These were sealed off in ampoules, but it was found that the colours were not permanent, and that the rate of fading was unequal. A very good match was, however, made with a weak solution of potassium iodide and iodine in water, but little use was made of this in our work.

It was not found essential that the urine of patients should be tested immediately. Urines left for as long as a week or ten days gave as good a result as when tested within a short time of being voided. The urines were frequently preserved by the addition of a few drops of toluene which did not affect the test.

Previous work with the Abelin reaction on the urinary excretion of organic arsenical compounds has already indicated that well-marked positive results are met with in the urine in the first twenty-four hours after the administration of salvarsan and neo-salvarsan.

The following organic arsenical preparations of the trivalent group tested by us *in vitro* in a watery solution of a strength of 1 in 1,000 all gave well-marked positive results.

Novarsenobillon,
Metarseno-argenticum,
Metarsenobillon,
Stabilarsan,
Sodium silver salvarsan,
Kharsulphan, and
Sulfarsenol.

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Similar experiments carried out with various members of the pentavalent group of arsenicals showed that the majority gave negative results *in vitro*. A well-marked positive result was only found with one compound. Negative results were obtained with watery solutions of

Atoxyl,
Stovarsol,
Tryparsamide,
Bistovol, and
Neo-bistovol.

Acetyl-arsan, however, yields positive results in a 1 per cent. and in a 1 in 1,000 watery solution. It is not clear why acetylarsan should be the only representative of this group to yield a well-marked positive result; positive results were also obtained in the urine for several hours after the administration of 2 c.c. and 3 c.c. of this compound.

Negative results were obtained in the urine after injections of bistoval and of tryparsamide on several occasions.

Numerous experiments were made with drugs other than those of the arsenobenzol group in order to determine whether the test was specific. Since we were of the opinion that the test depends on the diazotisation of an aromatic amino group (an opinion which was confirmed by Professor C. S. Gibson of the Department of Chemistry at Guy's Hospital), particular attention was paid to non-arsenical drugs containing this radicle. Among these negative results were obtained *in vitro* with—

Acetanilide,
Antipyrine (phenazone),
Phenolphthalein,
Quinine,
Saccharine,
Pyramidon, and
Intramine.

The first six also gave negative results in the urine after a maximum parrmacopœial dose by mouth. The urine was not tested after intramine.

The investigation of phenacetin was, however, particularly interesting. *In vitro* no colour developed, but the urine voided up to a period of three to four hours after

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a dose of 15 grains by mouth gives an almost identical red colour with this test. This colour differs in some ways from that obtained with the arsenobenzols. It does not begin to develop for about a minute, which contrasts with the colour obtained with novarsenobillon, the latter developing immediately. The phenacetin colour also deepens fairly rapidly on standing, and in half an hour may exhibit twice the depth of colour seen at ten minutes, while in a few hours it becomes almost opaque. The colour obtained with the arsenobenzols scarcely changes at all in twelve hours, though in twenty-four hours may appear definitely darker. This observation is, we think, of great importance in view of the claim of specificity for the test which has been accepted by many other workers.

A few other drugs were tested *in vitro*, and in the urine after a maximum pharmacopœial dose by mouth. Negative results were obtained with these drugs, which included—

Aspirin,
Dial,
Medinal,
Sodium salicylate, and
Caffeine.

Atophan, tested because its use has occasionally been followed by jaundice, gave a negative result in a watery solution.

After examining the Abelin test, and subjecting it to, I think, fairly severe criticism, we became satisfied that this reaction was reliable although, as I have indicated, not absolutely specific.

It was also clear that the reaction does not indicate the presence of arsenic. Arsenic may be found in the urine many days after the Abelin reaction has ceased to show a positive result.

In general, however, the test was considered to be sufficiently reliable to justify its application to patients receiving treatment with organic arsenical compounds, and the results of our examinations in this connection will now be dealt with in the second half of the paper.

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PAPER NO. 2

By V. E. LLOYD, M.B., B.S., Director of Venereal Diseases Department, Guy's Hospital.

MR. PRESIDENT, LADIES AND GENTLEMEN,—Before proceeding with the second part of our paper, I would like to express my appreciation of the honour conferred by this Society in being allowed to present the results of our work to-night.

After the investigation of the Abelin reaction, over a period of several months, we became satisfied that this test was a reliable one and eminently suitable for use in a large clinic. We thereupon decided to apply the reaction to as many cases as possible, especially to those cases who showed any minor toxic effects at an early stage of treatment. We were careful to exclude the possibility of any patient having taken phenacetin prior to the tests. The general procedure in connection with the test was as follows: A specimen of urine was collected from each patient immediately prior to the injection of novarsenobillon; this was to make sure that the bladder was empty at the time of injection, and also to ascertain whether elimination from the previous injection had ceased. The patients were given an outfit containing three bottles, of one ounce capacity, and requested to bring back on the following day a small portion of each of the first three specimens of urine passed subsequent to the injection. This arrangement worked very well, and patients were quite keen to co-operate.

The arsenical preparation administered in the majority of these cases was novarsenobillon, injected intravenously in 10 c.c. of distilled water at weekly or fortnightly intervals.

During the last eighteen months the Abelin reaction of the modified and improved type, already described in the first part of our article, was carried out on 123 patients at various intervals after treatment.

In all, 1,330 tests were performed in the investigation of the excretion of 397 injections.

In recording results, we found that any attempt at arriving at accurate quantitative results required the use of a modern colorimeter and also accurate measurement of the total volume of urine; the latter was impracticable in out-patients.

Since it was our aim to keep the reaction as simple as

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possible, for clinical rather than laboratory use, we employed a qualitative scale to express our results.

All results were compared with a positive and a negative control by inspection in a box comparator designed by one of us (N. L. L.). This comparator held twenty test-tubes in which the final colour of the reaction was inspected by transmitted light through a depth of 5 cm.

Five simple standards were employed for the expression of results, viz. :—

	The colour given in the reaction by—	
Three plus	equal to	1 in 5,000 N.A.B. in water.
Two plus	equal to	1 in 10,000 N.A.B. in water.
One plus	equal to	1 in 20,000 to 50,000.
Plus-minus	equal to	Trace of colour.
Negative	equal to	Colour of negative control in urine.

With every batch of tests a positive control of N.A.B. 1 in 5,000 or 1 in 10,000 and a negative control of normal urine was used.

In general the test proved very reliable; positive results were obtained within an hour, and excretion could easily be followed up for twenty-four hours or longer. It was found in the majority of cases that after the administration of 0.45 or 0.6 gm. N.A.B. the reaction was markedly positive from two to six hours. The injection of 0.3 gm. N.A.B. yielded results slightly less intense; a few tests carried out after 0.15 gm. were negative.

Some of the urines examined were from cases who had received their treatment a considerable time previously, also many examinations were made on urine seven or fourteen days after injection; both these groups will be considered later.

The results of the Abelin reaction, after 257 injections of novarsenobillon in ninety-two male patients, will now be discussed. These tests, of which the total was about 800, included the first three consecutive specimens of urine. In many cases later consecutive specimens of urine were also tested. The first three specimens covered a period of six hours in some cases; in others as long as eighteen hours.

For comparative purposes the results in this selected group will be considered as they occur in the three periods, 0 to 6 hours, 6 to 12 hours, and 12 to 18 hours.

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During the first six-hour period, every specimen after 257 injections was tested with the following results :—

Total, 257. Positive, 203 or 79 per cent. Negative, 54 or 21 per cent.

During the six to twelve-hour period the results were :
Total 211. Positive, 113 or 53 per cent. Negative 98 or 46 per cent.

During the twelve to eighteen-hour period the results were :

Total, 153. Positive, 57 or 37 per cent. Negative, 96 or 62 per cent.

It is of interest to note that in some cases which were negative in the first six hours, elimination could be demonstrated later.

On comparison of the general results following injections early in the treatment with those later on, there appeared to be no consistent difference in the intensity or duration of excretion. The observations of Escallon,⁴ of Riebes,⁶ and of Albrecht and Beeson⁹ that elimination does not always proceed evenly, was confirmed on many occasions. The general rule, however, was a maximum in the first few hours followed by a gradual diminution in the next twelve or fifteen hours. We observed on several occasions that the apparent termination of excretion between fifteen and eighteen hours was followed by a positive phase after eighteen hours.

Tests were performed from twenty to thirty hours after the injection of novarsenobillon on thirty-nine occasions : positive results were obtained in nineteen. Analysis of these positive results reveals some difference in excretion in this period according to the stage of syphilis. In primary and secondary syphilis out of a total of eighteen injections, five positive results were obtained. Following six injections in cases of latent syphilis there were four positive results, whilst after fifteen injections in the tertiary stage, ten positive results were given.

It is clear that the prolongation of excretion beyond twenty hours is much more frequent in tertiary and latent cases ; this did not appear to be entirely dependent on the age incidence.

This observation conforms with that of Albrecht and Beeson,⁹ who noted that elimination proceeded over a longer period in latent and tertiary cases.

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Although excretion begins promptly and terminates within twenty-four hours in the majority of patients, considerable variation was noted in some cases; and some examples of regular and of irregular excretion are of interest.

TWO EXAMPLES OF NORMAL EXCRETION

Case No. 5102.—Male, age 21. Secondary syphilis. The urine was tested after four injections of 0.6 gm. N.A.B. Strong positive results were given from 2 to 4 hours, moderately positive results from 5 to 9 hours, and only a trace of colour at 14 and 15 hours. At 17 and 21 hours the results were negative.

Case No. 4639.—Male, age 40. Tertiary syphilis. The urine was tested on numerous occasions following the injection of N.A.B. Strong positive results were found from 1 to 6 hours after each injection. From 6 to 12 hours the reaction was still positive, but not well marked. On one occasion a positive result was present 28 hours after injection.

EXAMPLE OF INTERMITTENT EXCRETION

Interrupted excretion already referred to and also noted by other workers, was not uncommon; an example may be given here.

Case No. 3632.—Male, age 40. Tertiary syphilis. After 0.45 gm. N.A.B., the reaction was positive at 2 and 4 hours, negative at 17 hours, but positive again at 18½ hours. The same case, after another similar injection, gave a positive result at 3 hours, a negative result at 12 hours, and later, at 18 hours, a positive result was again present.

Several other examples of interrupted excretion occurred among these cases. Whether these constitute examples of abnormal excretion must at present be left undecided; it is of note, however, that more than half of these cases showed poor elimination on other occasions.

DELAY IN EXCRETION

Delayed excretion was noted in several cases, although in some this was not consistent; some of these cases showed a normal rate of excretion after other injections. Here is an example of gross delay.

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Case No. 2747. Male, age 54. Tertiary syphilis. After injection of 0.45 gm. N.A.B. all tests were negative up to 37 hours; weakly positive tests were found at 43 and 48 hours. Tests were carried on up to 81 hours after injection, but no further excretion could be detected.

On another occasion, after 0.45 gm. N.A.B. no excretion could be detected until 15 hours later; a test 7 days later was also positive.

TOTAL ABSENCE OF EXCRETION IN THE FIRST TWENTY-FOUR HOURS

Entirely negative results in the first twenty-four hours were noted by Leredde and Rubenstein,⁸ and similar negative results have been noted in a few cases in our series, of which two examples may be given.

Case No. 4201.—Male, age 21. Primary syphilis. After 0.6 gm. N.A.B. all specimens of urine were tested up to 22 hours with negative results.

Case No. 3353. Male, age 29. Primary syphilis. After 0.6 gm. N.A.B. all specimens of urine were tested up to 21 hours with negative results.

Possibly excretion might have been detected in these two cases if they had been followed for a longer period.

The elimination of inorganic arsenic in the urine after the injection of organic arsenical compounds has been determined by many workers, and considerable variation in the amount of arsenic excreted has been reported, notably by Fordyce, Rosen and Myers.¹² Total absence of arsenic in the urine has been reported in a few cases.

In a few of our cases the urine voided at short intervals after injection was examined. Ten specimens were collected fifteen minutes after injection; of these, five were positive. Of eleven specimens collected thirty minutes after injection, eight were positive.

You will recall that with the reaction as applied to our series of cases, we carried out tests on the first three consecutive specimens of urine of each patient following treatment. The periods of time elapsing between the injection and the various specimens of urine so varied that we have been able to test the excretion on urine voided at all hours from the first to the twenty-fourth. Consideration of the results indicates that if excretion be normal, a well-marked positive result should invariably

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be present in urine held for at least three hours after injection of 0.6 gm. N.A.B.

Conversely, a negative reaction at three hours definitely indicates poor excretion.

Positive results seven days after injection have been few in our cases, but we have been led to suspect that such prolongation of elimination indicates an abnormally slow excretion.

All the information in this paper applies to the excretion in male cases only. The number of female cases examined so far has been few, but there are indications that the average rate of excretion is slower than in the male.

EXCRETION IN CASES WITH TOXIC MANIFESTATIONS

It soon became apparent during the course of our investigation that there was some close association between inefficient urinary elimination of novarsenobillon and toxic effects.

Some support for a probable association of these two factors has previously been found by Fordyce, Rosen and Myers¹² during their estimations of the urinary excretion of arsenic following the administration of salvarsan and neo-salvarsan. Experiments in animals also strongly suggests a direct relationship. The toxicity to rats of numerous organic arsenical compounds of the trivalent and pentavalent groups was shown, by Voegtlin and Thompson,¹³ to vary inversely with the rate of excretion of arsenic in the urine and fæces.

During our investigations minor toxic effects occurred in sixteen cases; in twelve of these excretion was found to be poor. In one case, with repeated minor toxic reactions, no elimination could be detected up to fifteen hours after the injection which precipitated one of these attacks. In another patient who suffered from minor toxic effects following his fourth and fifth injections, the rate of excretion tested some weeks later was normal after five consecutive injections, but after the next injection the excretion was poor. This patient developed jaundice within three weeks, and will be referred to later.

The occurrence of delayed jaundice following treatment with organic arsenical preparations is well known to you as a late toxic effect.

The estimation of hepatic efficiency in jaundiced

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patients has shown that considerable damage may take place in the liver. These hepatic function tests, notably the van den Bergh reaction, carried out on patients undergoing treatment who appear in good health, not infrequently reveal some inefficiency of liver function. It may therefore be surmised that in some cases of this type the excretory power of the liver to deal with arsenobenzol compounds will become less efficient as treatment progresses.

Deficient elimination of inorganic arsenic during salvarsan jaundice has been noted by Fordyce, Rosen, and Myers.¹² Also O'Donovan¹⁴ has reported a deficient elimination of trinitrotoluene in patients suffering from jaundice from the toxic action of this compound. The latter found that in munition workers continually absorbing trinitrotoluene the excretion of a chromogen derivative in the urine was normal in healthy workers, but disappeared from the urine with the onset of toxic jaundice.

Dale¹⁵ suggested that the cessation of the steady excretion of this chromogen in the apparently healthy munition worker should be regarded as a danger signal.

During our investigations five cases of salvarsan jaundice and six cases of exfoliative dermatitis were tested whilst suffering from these complications; in no case could any elimination of novarsenobillon be demonstrated.

In the series of cases under investigation, severe toxic jaundice occurred in five cases, jaundice of slight degree was noted in two additional patients. In none of the severe cases had elimination been consistently good with the Abelin test. Of the two cases of slight jaundice, elimination had been found good in one and poor in one.

Five cases of toxic jaundice will now be considered in detail.

Case No. 939.—Male, age 40. Tabes. The Abelin test was done on the urine after five consecutive injections of 0.6 N.A.B. The results showed poor elimination on two occasions, and very poor on three occasions. Four months after the first test severe jaundice developed.

Case No. 4729.—Male, age 40. Tabes. Tests after ten injections showed good excretion on six occasions, fair excretion on two occasions, and poor excretion once. After two of these injections elimination was still pro-

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ceeding on the seventh day. Severe jaundice ensued twenty weeks after the first indifferent test.

Case No. 4557.—Male, age 38. Tabes. Three tests in the first course of treatment showed excretion to be good or fair. During the second course three consecutive tests showed good excretion in the first two, but the last revealed extremely poor excretion. Three weeks later severe jaundice developed; this was four months after the first unsatisfactory test.

Case No. 2503.—Male, age 24. Primary syphilis. Three tests were done during the second course of treatment. The results were poor on two occasions, and fair on one occasion. Severe jaundice developed four months after the first poor result.

Case No. 4693.—Male, age 51. Tertiary syphilis. Tested once only during the second course. No excretion could be detected until twenty-four hours later, when the result was weakly positive. Six weeks later jaundice of slight degree occurred.

A few cases of other major toxic effects were encountered in this series.

EXFOLIATIVE DERMATITIS

Case No. 4739.—Male, age 24. Primary syphilis. Out of seven consecutive tests excretion was satisfactory only once. Three tests showed complete absence of excretion up to twenty-four hours after injection. Treatment was suspended on this account after the eighth injection, but six weeks later exfoliative dermatitis developed; this was fifteen weeks after the first unsatisfactory test.

Purpura hæmorrhagica, a rare toxic complication, was noted in one case.

Case No. 3883.—Male, age 30. Secondary syphilis. Two tests were done which showed moderate excretion once and very poor excretion once. Four months later, during a further course of injections, generalised purpura hæmorrhagica developed.

A Herxheimer reaction was noted in one case; the excretion tested after the next injection was of normal type.

Out of our original 123 cases who had been adequately tested, 67 men were followed up and closely observed for a period of six months or longer; 34 of these cases had been classified as poor excretors, and 33 classified as good excretors. Analysis of these cases showed that in the

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group of 34 in whom excretion was known to be unsatisfactory, toxic effects of major or minor degree were noted in 17, viz., 50 per cent.

Major toxic effects, chiefly jaundice, developed in 7 cases of this group, viz., 20.5 per cent; minor toxic effects were noted in 10 cases, 29 per cent. Among the 33 cases classified as good excretors, there were no major toxic complications; minor toxic effects occurred in 4 cases only. These results are very striking.

This is as far as our research has proceeded up to date, and we are now faced with many interesting problems arising out of the results.

All our investigations with the Abelin test upon patients have been conducted on urinary excretion only. You are aware that a considerable proportion of the arsenic from arsenobenzol compounds is excreted *viâ* the alimentary canal. The proportion varies with the different compounds utilised; with salvarsan 80 per cent. of the arsenic excreted in the first twenty-four hours is eliminated by the alimentary canal; with neo-salvarsan the percentage is 33, and with compounds of the penta-valent group, *e.g.*, stovarsol, the percentage is as low as 5.

It is probable that there is a variation among individual patients; after the administration of the same preparation in identical amounts, one patient may excrete less in the urine and more in the fæces than another patient; such variation has been noted in animals.

In our work, as far as it has gone, we have not taken into account any possible variations of excretion *viâ* the alimentary canal; but this is possibly a factor of some importance, for in some of our cases in whom excretion in the urine had been satisfactory after several consecutive injections and then failed, it is possible that excretion may, at this point, have been chiefly by the alimentary canal instead of in the urine.

Since the Abelin test is clearly not a test for arsenic, we are almost completely in the dark as to how closely elimination, as shown by this reaction, is related to the excretion of arsenic. If novarsenobillon is excreted unchanged in the urine, then a positive Abelin test is an indication of arsenic excretion; however, it is probable that only a small proportion of this compound is eliminated in an unaltered condition. According to Sieburg¹⁶ after the administration of salvarsan, only a small

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quantity is excreted unchanged ; he reported the presence of pentavalent organic arsenical compounds and inorganic arsenites in the urine.

Most probably the end products of the benzol radicle are excreted in the urine in combination with sulphuric and glycuronic acids in a similar manner to the conjugation of many members of the phenol group.

It is conceivable that the benzol radicle of a salvarsan compound may be separated off and be excreted rapidly, leaving the arsenic deposited in the tissues. If this be so, then excretion as shown by the Abelin reaction is of little value in providing data concerning the fate of the arsenic.

However, the correlation of delayed toxic effects and inefficient urinary excretion in our cases suggests that the Abelin test DOES throw some light on the fate of both the benzol radicle and the arsenic.

The intimate relation between the occurrence of toxic jaundice and indifferent excretion in our cases, as shown by the Abelin reaction, which I would here remind you is a test for the aromatic amino radicle of a salvarsan compound and not a test for arsenic, raises the suspicion, which must have occurred to many of you, that at least some cases of salvarsan jaundice may be due to the action of the aromatic amino radicle in the salvarsan compounds rather than to the arsenic itself.

The production of a similar type of toxic jaundice by chemical compounds containing a benzol radicle but no arsenic, is well illustrated by the numerous examples of jaundice occurring among munition workers during the Great War from the absorption of trinitrotoluene (T.N.T.). Also toxic jaundice and even acute yellow atrophy of the liver are reported to have followed the oral administration of atophan,¹⁷ a compound which contains no arsenic. It is of particular interest here to note that jaundice is an exceptional result of poisoning by inorganic arsenic ; also that chemical analysis of liver tissue from fatal cases of salvarsan jaundice has not revealed any undue accumulation of arsenic.

The relation between the rate of excretion of novarsenobillon and its therapeutic effect is of great interest and importance. Animal experiments have demonstrated that the most rapidly excreted arsenical compounds tend to be the least effective, probably on account of the brief period during which they act. Those compounds which

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are excreted slowly are more effective, but also possess a greater toxicity.

When identical doses of novarsenobillon are given to patients of the same age and in the same stage of syphilis, the rate of excretion is by no means identical, as we have shown. Whether the therapeutic result is more favourable in those patients who excrete slowly is at present unknown.

It has frequently been stated that patients who have experienced a severe toxic reaction in the early stage of syphilis are less liable to have serological relapses than those whose toleration for arsenical preparations has been good and whose excretion has presumably been normal.

These are all points which we hope will provide a discussion to-night, and that some additional light will be thrown on these interesting problems.

In conclusion I wish to thank all the Medical Officers of the Venereal Diseases Department at Guy's Hospital for their interest and co-operation during this work ; and to you, Mr. President, and fellow members, I am most grateful for your patience and attention this evening.

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