Whitechapel Course: Results of Treatment on the Wassermann Reaction

Type of Case	No. of Cases	Wassermann Reaction within a Month of End of First Course		
		Positive	Doubtful	Negative
Sero-negative primary ...	65	—	—	65 (100%)
Sero-positive primary ...	114	1 (0.87%)	1 (0.87%)	112 (98%)
Sero-positive secondary	62	2 (3.22%)	1 (1.61%)	59 (95.1%)
Total	241	3 (1.21%)	2 (0.82%)	236 (97.9%)

The treatment is most accurately judged by its effect on the secondary cases, as the whole body is in a state of syphilitic septicaemia in these patients. A negative Wassermann reaction occurred in 95 per cent. at the end of the first course. No "Wassermann relapses" have been observed.

It is now the fashion, for fear of arsenical complications, to lessen the amount of arsenic, and to rely more on bismuth, which is far below arsphenamine in efficiency. This, and the lessened use of mercury, is, I think, a backward step. A course of treatment cannot be estimated by the results of the Wassermann reaction alone; the percentage and severity of the complications must be included.

Complications with the Whitechapel Course

Type of Case	No. of Cases	Arsenical Dermatitis	Jaundice	Furpura	Per cent.
Sero-negative primary...	65	4 (6.15%)	1 (1.53%)	—	7.69
Sero-positive primary ...	114	5 (4.38%)	1 (0.87%)	2 (1.75%)	7.01
Sero-positive secondary	62	—	1 (1.61%)	—	1.61
Total	241	9 (3.73%)	3 (1.24%)	2 (0.82%)	5.8

An uneventful recovery followed all these complications. They are not confined to the period of the first course, but have occurred at any time after the beginning of treatment, and cover a period extending over two years. With this Whitechapel course we have had comparatively few complications; most of them have been mild cases of dermatitis (3.73 per cent.). Jaundice (1.24 per cent.) has given little trouble. Although 29,015 arsenical injections have been given during the past two years there have been only two fatalities. The percentage of complications has, I believe, been few because the course has only one rest of three weeks, and because the dosage remains the same each week. This decreases the liability of sudden shock to, and paralysis of, the liver. If rests are given too frequently the tissues become less accustomed to the arsenic at each rest, and have to re-establish their equilibrium and become re-educated to the drug. This, if it happens too frequently, lowers the general resistance of the body. It is a mistake, I think, to give a rest every two or three weeks, just as the body is becoming acclimatized to the drug and the spirochaete is being overcome. I should like to stress the need of a sufficiency of treatment. Two or three random injections of arsphenamine are inadequate, and destroy the patient's natural immunity.

At St. Thomas's Hospital I analysed the pregnancies of 300 syphilitic mothers before and after treatment. The figures are significant in this respect. Before treatment these 300 mothers had had 739 pregnancies, of which over 50 per cent. were unhealthy. After treatment their total number of pregnancies was 305, of which just over 9 per cent. were unhealthy. The mothers who had had under one course of injections—that is, less than 5 grams of neo-

arsphenamine—had 30 per cent. unhealthy pregnancies. Those who had received more than one course of injections had only 3.75 per cent. of unhealthy pregnancies. What a difference a few extra grams of organic arsenic made to these mothers, to their babies, and to their future!

REFERENCE

¹Anwyl-Davies, T.: *Primary Syphilis in the Female*. Oxford Medical Press, 1931.

A SENSITIVE TEST FOR THE PURITY OF AVERTIN SOLUTION

BY

H. K. ASHWORTH, M.B., Ch.B., M.R.C.S.

VISITING ANAESTHETIST, MANCHESTER ROYAL INFIRMARY, ANCOATS HOSPITAL, ETC.

It is well known that avertin solution must be freshly prepared before use, at a temperature not exceeding 40° C. The reason for this is that, if overheated, or prepared too long before use, decomposition occurs, with the formation of dibromovinyl alcohol and hydrobromic acid, together with a further decomposition of the former into dibrom-acetaldehyde, according to the following equations:

The dibromacetaldehyde so formed is highly injurious to the mucous membrane of the rectum and colon, and cases of such injury have occurred, varying in severity from a mild post-operative discomfort to necrosis and sloughing of the colon, resulting in death.¹ In their original introductory article, Shipway and Blomfield² stated that the hydrobromic acid formed in the process of decomposition of avertin solution is at once detected by the Congo-red test. The experiments to be described prove that "universal indicator" (B.D.H.) is a more sensitive and reliable agent than Congo red as a test for the purity of avertin solution. These experiments were planned and carried out by Mr. Butchers, chief pharmacist, Manchester Royal Infirmary, and his chief assistants, Dr. Bullock and Mr. Priddy. The entire credit for the interesting and important discoveries which have been made is due to them, my own part being limited to the clinical application of their valuable work.

TECHNIQUE OF NEW TEST

Universal indicator gives the following colorations:

In the presence of alkaline solutions (pH 8.0)—green	
"	neutral " (pH 7.0-7.5)—greenish-yellow
"	acid " (pH 6.5)—yellow
"	" " (pH 6.0)—orange-yellow
"	" " (pH 5.5)—orange
"	" " (pH 4.0)—red

Transfer 3 mg. of prepared avertin solution to a clean test tube, and cool. In a similar test tube place an equal volume of the distilled water used in the preparation of the avertin solution. Add two drops of universal indicator to the contents of each tube. The colour of the avertin solution should be greenish-yellow, and it should not be possible to detect any difference in the colour of the contents of the two tubes. It is essential that the two test tubes should be scrupulously clean and previously rinsed with distilled water. The pH of ordinary distilled water may vary, and the actual sample previously used for the preparation of the avertin solution should serve as the control in the test. The above test is simple and rapid: if carried out as described it does not contain any fallacies. A possible theoretical objection is that greenish-yellow is a colour liable to varying individual interpreta-

tion. A little practical experience in the use of the universal indicator will, however, soon convince anybody who is not actually colour-blind that the shade is unmistakably greenish-yellow, and quite different from the yellow or green colour obtained in the presence of acid or alkaline solutions.

ESTIMATION OF DECOMPOSITION RATES

The use of universal indicator has facilitated the experiments which have been performed on the rate of decomposition of avertin solutions under varying conditions of preparation and storage. Full chemical details of these experiments have been published elsewhere,³ and the simple examples given are those from which practical conclusions may be drawn.

The preliminary experiment tabulated below shows that universal indicator is a more delicate reagent than Congo red as a test for the purity of avertin solution; and that the higher the initial temperature at which avertin solution is prepared the greater is the acceleration in the rate of decomposition.

Preliminary Experiment

Temperature	When Prepared		10 Minutes		20 Minutes		40 Minutes		60 Minutes		75 Minutes	
	U. I.	C. R.	U. I.	C. R.	U. I.	C. R.	U. I.	C. R.	U. I.	C. R.	U. I.	C. R.
38° C.	Green-yellow	Red	Green-yellow	Red	Green-yellow	Red	Green-yellow	Red	Green-yellow	Red	Green-yellow	Red
40° C.	"	"	"	"	"	"	"	"	"	"	"	"
42° C.	"	"	"	"	"	"	"	"	"	"	Yellow	"
48° C.	"	"	Orange-yellow	"	Orange-yellow	"	Orange-yellow	"	Orange-yellow	"	Orange-yellow	"

U. I. = Universal indicator.

C. R. = Congo-red test solution.

Experiment No. 2

Bearing in mind the customary clinical practice of preparing an avertin solution, and then keeping it in a vacuum flask or bottle for a variable period of time before administration, a 2.5 per cent. solution of avertin was prepared at 38° C. One portion of this solution was placed in a vacuum flask and the other portion in a bottle at room temperature. Small samples were withdrawn at intervals and tested. The constant opening of the vacuum flask caused a more rapid fall in the temperature of its contents than that which occurs in clinical practice, when the flask remains closed between the time of preparation and the time of administration of the solution. The rate of decomposition of the contents of the vacuum flask was therefore probably retarded under the existing experimental conditions.

		When Prepared	30 Minutes	1 Hour	2 Hours	3 Hours
In bottle	Congo Red	Red	Red	Red	Red	Red
	Universal Indicator	Green-yellow	Green-yellow	Yellow	Yellow	Yellow
In vacuum flask	Congo Red	Red	Red	Red	Red	Red
	Universal Indicator	Green-yellow	Yellow	Yellow	Yellow	Orange-yellow

The above experiment demonstrates that storage of avertin solution in a vacuum flask—with a consequently slower loss of initial temperature—tends to accelerate the rate of decomposition; that the avertin solution in the vacuum flask was unfit for use thirty minutes after preparation, and that in the bottle was unfit for use sixty minutes after preparation. Further, it shows that no change was detected in either solution three hours after preparation by the use of the Congo-red test.

Shipway and Blomfield² deduced, from the experiments of H. Gainsborough and J. A. Gardner, that if a solution

of fluid avertin prepared for injection is kept at a temperature of about 32°–38° C., and not exposed to light, it may be used even several days after preparation.

Experiment No. 3

One thousand mg. of avertin solution were prepared at 38° C., divided into three parts, and stored for eighteen hours. The three specimens were then tested, with the following results:

How Stored	Congo Red	Universal Indicator
1. In incubator at 32° C.	Purple	Red
2. In vacuum flask ...	Red (no change)	Red
3. At room temperature	Red (no change)	Orange

This experiment—and in particular the result of the tests on the unexposed sample stored in the vacuum flask—shows that the insensitivity of Congo red as a test reagent was responsible for fallacious results in the experiments of Gainsborough and Gardner.

Emphasis must be laid on the fact that the above experiments are simple examples taken from a large series. The accuracy of the entire series of experiments was further checked by estimation of the hydrobromic acid liberated during the process of decomposition of avertin solution: (1) by titration with N/50 caustic soda, and (2) by Volhard's method of estimating free bromide ions.³ A possible criticism of the new test is that, owing to its extreme sensitiveness, it may indicate the presence of decomposition of avertin solution in traces so minute that these could not possibly cause irritation of the intestinal mucous membrane. This criticism may be true, but my own feeling is that if one of my patients were to develop signs of irritation of the lower bowel following the administration of avertin, I should not feel that I had taken every possible preventive precaution unless the avertin solution (having been properly prepared, placed in a bottle, and administered not more than one hour after preparation) had been satisfactorily tested with universal indicator rather than with Congo red. The new test is in routine use throughout the Manchester Royal Infirmary.

CLINICAL APPLICATIONS

To summarize the practical application of these experiments to the work of the anaesthetist:

1. Universal indicator is a more sensitive and reliable reagent than Congo red as a test for the purity of avertin solution.
2. Avertin solution should never be prepared at a temperature exceeding 40° C.
3. Avertin solution should be kept in a bottle rather than in a vacuum flask during the interval between preparation and administration.
4. Avertin solution should be administered to the patient not later than one hour after preparation.

REFERENCES

- ¹ Wymer: *Schmerz Narkose-Anaesthesie*, April, 1931.
- ² Shipway and Blomfield: *Lancet*, 1929, i, 546.
- ³ Butchers, Bullock, and Priddy: *Pharmaceutical Journal*, July 29th, 1933, p. 160.