THE EFFECT OF ANTISYPHILITIC TREATMENT, AS GAUGED BY THE SIGMA REACTION.

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APART from their diagnostic value, the Wassermann reaction and the more recent flocculation reactions have assumed a position of importance as guides in the treatment of syphilis. It is well known that the blood and cerebro-spinal fluid may give a positive reaction long after the clinical signs of active syphilis have disappeared, and although Hess Thaysen⁴ believes that in certain cases a positive reaction does not indicate active syphilis, it is very generally held that a positive reaction in the blood or cerebro-spinal fluid is a sign of active syphilis and therefore an indication for treatment (Boas,¹ Fordyce,² Osler and McCrae³).

In view, then, of the prevailing opinion that the ultimate goal of antisiphilitic treatment is a permanent negative reaction, it was proposed to investigate how far the present methods of treatment are effective in attaining this end, or at any rate in reducing the amount of reacting substance in the blood during a certain period of observation. In order to carry out this investigation, it was clear that the blood of each patient would have to be examined at fairly frequent intervals, and that the results of the examinations would have to be quantitative and comparable with one another. In the opinion of the authors (Dreyer and Ward⁵) the Sigma reaction gives more strictly comparable results than the quantitative Wassermann reaction. Madsen,⁷ Renaux,⁷ Wyler,⁷ and Houston⁶ found the Sigma reaction quantitatively accurate. Madsen gives the result of titrating four syphilitic serums by means of the Wassermann reaction. Each serum was titrated fifty times, 200 titrations in all being carried out:

85 titrations gave	0 per cent. deviation from average.
85 " " "	±33 " " "
20 " " "	±60 " " "
10 " " "	±78 " " "

In other words, the Wassermann reaction gave an average deviation of ± 24 per cent.

At the same time 109 titrations were made on ten serums by means of the Sigma reaction, and the greatest deviation observed did not exceed ± 6 per cent.

Hirzfeld,⁷ however, found that the Sigma reaction does not give a sharp end-point, and he found it difficult to calculate the real strength of the serum. In the present investigation incomplete flocculation, of the kind observed by him, has not been a source of difficulty, the end-point of the titration being always well defined.

With regard to its sensitiveness and specificity Dreyer and Ward⁵ stated in their original communication that the Sigma reaction had in their hands yielded results that compared more than favourably with the Wassermann reaction. The support given to this claim by subsequent investigators may be judged from the following comparative tests carried out by the International Health Organization of the League of Nations.*

* At the time of writing the above the results of the last League of Nations conference at Copenhagen at the end of 1923 were not available.* At this conference 536 serums were tested simultaneously by the different methods for the diagnosis of syphilis. The Wassermann reaction yielded a greater number of positive reactions than the Sigma reaction. This result was in striking contrast to the results previously obtained by the same workers, and was investigated by Dr. Mörck. He found that the Sigma reaction had been rendered less sensitive by three details in the technique: (1) the heart extract supplied had been given too low a factor of sensitiveness; (2) the serums had been inactivated in hermetically sealed tubes (that is, under pressure) instead of in tubes with a cotton-wool stopper; (3) the tests had been incubated in a semiclosed water-bath instead of an open one. In some cases this reduced the number of units by some 500 per cent. When these details had been corrected it was still found that the cases of dementia paralytica which had been treated with malaria were more active in the complement fixation than in the flocculation system. This phenomenon is being further investigated.

TABLE I.—Diagnostic Results.

Name.	Cases of Syphilis.			Controls.		
	No.	Wassermann Reaction Positive.	Sigma Reaction Positive.	No.	Wassermann Reaction Positive.	Sigma Reaction Positive.
Dreyer <i>et al.</i> ⁶	519	Per cent. 62.0	Per cent. 69.4	203	No. 5	No. 7
Madsen ⁷ ...	627	59.3	77.7	885	0	6†
Harrison ⁷ ...	498	51.0*	57.8	244	14	20†
Hirzfeld ⁷ ...	358	54.0	50.3	61	0	0
Müller ⁷ ...	1367	68.5	60.5	340	0	0
Renaux ⁷ ...	189	55.5	74.6	100	0	2
Sachs ⁷ ...	404	54.5*	51.5	576	3	3

* Including doubtful Wassermann reactions.

† Three of these cases later diagnosed as syphilis.

‡ Eleven of these cases later diagnosed as syphilis.

The Sigma reaction, then, seemed to lend itself very well to the kind of investigation that was contemplated—namely, the study of the quantitative changes that took place in the blood of syphilitic patients over an extended period of time.

PREVIOUS INVESTIGATION OF THE EFFECT OF TREATMENT. AS GAUGED BY FLOCCULATION REACTIONS.

Vernes⁹ has devised two somewhat complicated methods for determining the flocculating power of the serum in cases of syphilis, the results being expressed quantitatively. He has further formulated certain rules for diagnosis and cure.¹¹ Lortat Jacob and P. Legrain¹² found Vernes's second method less sensitive than the Wassermann reaction, and the results of a comparative test by Vernes himself¹⁰ indicate that his second method is less sensitive though more specific than the Wassermann reaction. The scale used by Vernes in expressing his results is so different from that used in the Sigma reaction that it would be difficult, if not impossible, to compare his results with those obtained by workers using the Sigma reaction. Houston and others⁶ employed the Sigma reaction to study the effect of treatment in 170 cases of syphilis. They found: (1) that in general the Sigma units fell during treatment with arsenical preparations, when effective doses were used, and that a study of the results of the reaction gave considerable help in determining the effective dose and the effective interval between doses; (2) that the rate of fall in units in tertiary cases of syphilis was much slower than in primary and secondary cases; (3) that there was a certain amount of evidence that mercury, intramine, and potassium iodide have less effect than the arsenical preparations in lowering the Sigma units; (4) that a negative Sigma reaction does not necessarily mean that the case has been cured.

Stokes and Wigham⁸ observed the effect of treatment on about fifty cases of syphilis, also by means of the Sigma reaction. They found that the primary and secondary cases, when treated at regular intervals with arsenic, showed a fairly steady and continuous fall in Sigma units; but among tertiary cases they did not see one react satisfactorily during the period of observation, the curve of Sigma units in the blood showing only ups and downs.

THE PRESENT INVESTIGATION.

In the present investigation the effect of treatment upon the Sigma units in the blood of 138 cases of syphilis was observed both during courses of treatment and during varying periods following these courses. The cases were in three clinics, and while in most of the cases the ordinary routine of treatment in the clinic was not interfered with, in certain special cases, through the kindness of the directors of the clinic, changes were made.

The majority of the patients received intravenous injections of novarsenobillon (N.A.B.) at weekly intervals, and the patients were also given mercury pills (Hutchinson's pill) with instructions to take two daily. A course of injections of N.A.B. was followed in some instances by a course of intramuscular injections of mercury (1 c.cm. of

grey oil). In a few cases sulfarsenol and sodium silver novarsenobillon were used, as Harrison¹³ has stated that these preparations gave encouraging results in cases with myocardial and nervous lesions.

In certain cases in which the arsenical preparations seemed to have little or no effect on the serological reaction, injections of mercury perchloride were given intravenously. The technique of Conrad and McCann¹⁴ was followed, 1.2 to 4 c.cm. of a 1/2 per cent. solution of mercury perchloride in saline being injected. In order to prevent thrombosis of the vein, the patient's blood and the solution are mixed in the syringe before injection. They found that after from six to twenty-two injections, 64 per cent. of a series of sixty-two "Wassermann-fast" cases gave a negative Wassermann reaction. In the present series of cases it was only possible to give one injection a week, instead of twice a week as advocated by Conrad and McCann.

TECHNIQUE AND EXPERIMENTAL VARIATIONS OF THE SIGMA REACTION.

The technique described by Dreyer and Ward⁵ and supplemented⁶ was followed throughout, the results being read after an incubation period of twenty hours.

The amount of experimental variation was investigated by testing portions of the same specimen of serum many times. The flocculation readings varied from day to day, but repeated themselves frequently, the mean deviation being 6.7 per cent., while the standard deviation was 9.5 per cent.

The cause of these variations was chiefly the fluctuations in temperature of the water-baths in which the inactivation of the serum and the incubation of the tests were carried out. An additional cause was the reading error of the different degrees of flocculation, and this was found to be greater in strong serums than in weak, small irregularities in the flocculation tending to occur in the high dilutions of the serum, probably owing to the small amount of protective serum-protein present.

In addition to the above, another cause of variation was noted. Two alcoholic heart extracts which had been used for a period of five months showed a sudden deterioration in the sensitiveness of their suspensions. The amount of this was determined, and the errors due to it were corrected. The sudden deterioration was probably due to the fact that these particular heart extracts had been prepared by making a more concentrated extract of the heart muscle than that described.⁶ The other heart extracts used showed no change in sensitiveness, and the stability of the heart extract which was used during the greater part of the investigation was established by an extensive series of tests. Chart 5 shows a case which was followed over a period of fifty weeks. During this period the number of Sigma units found only varied between 5.0 and 4.1. This and similar cases confirm the belief that, despite experimental variations, the unit values obtained in testing a serum from time to time are really comparable. It remains to determine the limit of the experimental variation.

It was stated above that the standard deviation found was 9.5 per cent. In a series of determinations the probable error of a single determination is about two-thirds of the standard deviation—that is, 6.3 per cent.—and the probable limit of experimental variation would be approximately 20 per cent.¹⁵ Accordingly, unless there was a 20 per cent. change in the unit value of a patient's serum, it was not considered to be a real change in the serum of that patient.

The number of Sigma units varied widely in different patients—from one unit to over two thousand units; and in order to correlate the results in different patients the changes in the Sigma units of a given patient were expressed in percentage.

EFFECT OF ARSENICAL INJECTIONS.

I. Upon Patients whose Blood gave a Negative Sigma Reaction before Treatment commenced.

In this connexion, three questions arise:

1. Can the injection of arsenical preparations in definitely non-syphilitic cases induce a positive reaction in the blood? Strickler and others¹⁶ administered one or more injections of neo-arsphenamin (neosalvarsan) to twenty-four

patients in whom there was no sign of syphilis and who all had negative Wassermann reactions prior to the injections. Fourteen of these twenty-four patients—that is, 58 per cent.—gave two or more positive Wassermann reactions after the injections. Boas and Kissmeyer,¹⁷ however, found that the injection of salvarsan or its derivatives into fifty non-syphilitic cases did not induce a single positive reaction. In the present investigation only one definitely non-syphilitic case received injections of arsenic, and the Sigma reaction remained negative.

2. Can the arsenical preparations light up a case of latent syphilis and change the reaction from negative to positive? There is a fairly widespread belief that in certain cases of suspected or latent syphilis with a negative Wassermann reaction the injection of a so-called "provocative" dose of arsenic will light up the syphilitic inflammation, and the blood of the patient will subsequently give a positive Wassermann reaction, confirming in this way the tentative diagnosis. In the light of the experience of Strickler and others,¹⁶ this "provocative" Wassermann reaction must be treated with reserve. In the present study, three cases with a history of syphilis or a history of a positive Wassermann reaction in the past, but who had a negative Sigma reaction at the time the injections began, were given several doses of N.A.B. All three cases remained negative.

3. What is the prognosis of cases of primary syphilis which give a negative Sigma reaction at the commencement of treatment and remain negative during the course of treatment? Two such cases were observed, and they remained negative subsequent to the course of treatment. So far as this limited evidence goes the prognosis is favourable, thus confirming the evidence afforded in similar cases by the Wassermann reaction. In this connexion one case (Chart 1) is of interest. The case was one of suspected primary syphilis; spirochaetes were not demonstrated, but one week after treatment commenced 1.4 Sigma units were found in the blood. This figure, though not quite high enough to warrant a definite diagnosis of syphilis, aroused further suspicion, and the treatment was continued; the number of units fell to normal and remained there. The diagnosis must remain doubtful if (according to the scale laid down by the authors of the reaction⁵) an unknown case must have at least 1.5 Sigma units in the blood to establish the diagnosis. But, of course, in such a case it is much better from the patient's point of view to be on the safe side, and treat the case as one of syphilis, rather than suspend treatment and wait to see if the reaction becomes definitely positive.

II. Upon Sigma-positive Primary Cases and Secondary Cases.

In the course of the investigation twenty-two such cases were observed. These cases respond more uniformly to treatment than cases in the later stages of the disease, and the following points were noted:

1. In about one-third of the cases a rise in units was found just after treatment commenced. The units then fell. This preliminary rise must be regarded as the expression of the normal evolution of the disease, which has only been partially checked by the first injections of arsenic. Chart 2 shows the curve of a case of this kind.

2. The main response in these cases was a continuous fall in the number of Sigma units during the serial injections, the fall becoming slower as the number of units approached 1 (a non-syphilitic case may show as much as 0.9 Sigma unit in the blood). Chart 3 shows a typical response to regular treatment in this stage of the disease, in this case without any well marked preliminary rise in units. The rate of fall in the number of units is of interest. In nine primary and early secondary cases, one week after each injection, the number of units had fallen on the average to half the number of units present before the injection; on the other hand, in eight late secondary cases, one week after each injection, the number of units had only fallen on the average to two-thirds the number of units present before the injection. In other words, the rate of fall is definitely slower in the late cases in this group.

3. The evidence concerning the relation of the amount of N.A.B. received and the response by the patient is suggestive but not very definite, other factors coming in to obscure the picture. Eight cases became negative after receiving an average of 6.9 grams of N.A.B. (seven of these cases remained negative up to the end of the period of observation), while fourteen cases did not become negative after receiving an average of 4.4 grams of N.A.B. However, among the cases which did not become negative, there were three which received as much N.A.B. as the cases which did become negative. In these resistant cases, however, other factors, such as irregularity of attendance, incomplete treatment, came in.

4. It had been previously noted by Stokes and Wigham⁶ that a break in the course of treatment might have a definitely prejudicial effect when treatment was resumed, the cases becoming resistant to arsenic, although previous to the break in treatment their units had been falling. In this series of cases there were four in which the Sigma units were falling steadily under treatment with N.A.B., and then there was a period of four weeks during which they received no arsenic. In two of these cases a further fall in units occurred when treatment was resumed, and one case eventually became negative. In the other two cases subsequent treatment seemed to have little effect, and indeed the units commenced to rise again after the cessation of the second series of injections with arsenic. Chart 4 shows the Sigma curve of one of these cases, and brings out very clearly the danger of breaking off the arsenical treatment of early cases before the blood gives a negative Sigma reaction. In this connexion Chart 4, showing the result of irregular and incomplete treatment, should be compared with Chart 3, where the course of treatment was regular and complete. If patients in the early stages of syphilis could be shown such charts as these it would encourage them to attend the clinic regularly for treatment. Patients in this stage of the disease are sometimes apt to regard themselves as cured when their active signs—sore, rash, etc.—have disappeared, and they attend irregularly in consequence. But if their intelligent interest in what is being done for them is aroused by charts such as these, they would be more likely to become regular attendants. The case represented by Chart 3 was shown his Sigma curve, and became keenly interested in the progress of his cure.

5. In seven cases, one injection of metallic mercury was given at the end of a course of arsenic injections, and a fall in units occurred after the mercury injection in all these cases. In four out of the seven cases the reaction became negative without further treatment. However, since in five out of the seven cases the mercury injection was given one week after the last injection of N.A.B., the fall in units cannot be ascribed entirely to the effect of the mercury. One case in the series became intolerant to arsenic when he still had 1.1 Sigma units in his blood. Six intravenous injections of mercury perchloride were given, and three weeks after the last injection his units had risen to '67. The evidence, then, as far as it goes, is in favour of the use of metallic mercury, but against the use of mercuric chloride in this stage.

III. Upon Tertiary Cases.

In the 106 tertiary cases which were investigated, the response to treatment was much slower and much less uniform than in the early cases. The following points were noted.

1. Out of the 106 cases three only became negative while under observation. The details of these cases are:

CASE I.—A case of latent syphilis which had previously received 16.2 grams of N.A.B. and nine injections of grey oil over a period of 156 weeks. At the beginning of the present treatment there were 1.7 Sigma units in the blood, and the reaction became negative after two weeks' treatment with 1.2 grams of N.A.B. Subsequent history unknown.

CASE II.—A case of angina which had previously received 16.2 grams of N.A.B. over a period of 150 weeks. At the beginning of the present treatment there were 3 Sigma units in the blood, and the reaction became negative after twenty weeks' treatment with 4.8 grams of N.A.B. Subsequently, injections of mercury perchloride were given, and the reaction was still negative at the end of a further period of nineteen weeks.

CASE III.—A case of glossitis which had previously received 6 grams of N.A.B. and six injections of grey oil over a period of

forty-three weeks. At the beginning of the present treatment there were 1.8 Sigma units in the blood, and the reaction became negative after six weeks' treatment with 5.1 grams of N.A.B. Subsequent history unknown.

It will be noticed that these three cases had all received a good deal of treatment previous to the present investigation, and they all had a low Sigma unitage at the commencement of the present treatment.

2. In three cases there was a definite rise in units during the period of observation. In two of these cases there was definite clinical evidence of increased activity of the disease. Chart 8 shows one of these cases. In the remaining case there were no symptoms or clinical signs at all during any period of the observation. The evidence thus suggests that a rise in units is associated with an increased activity of the disease.

3. The remaining cases in this group apparently responded to treatment in three ways: (1) The number of units fell steadily during the period of observation. Chart 6 is an example of this type, which may be called the "falling" type of response. (2) The number of units remained practically unchanged during the period of observation. Chart 5 is an example of this type, which may be called the "stationary" type of response. (3) The number of units fell for a variable period and then remained stationary. Chart 7 is an example of this type of response, which may be called the "plateau" type.

These differences in response to treatment are probably more apparent than real. It must be remembered that the tertiary stage of syphilis is a very long one, and that these cases came under observation at different periods, after different treatment, and were only under observation for a time (at most two years), which was short compared to the length of the tertiary stage. It is probable from the evidence obtained in this investigation that, unless there are exacerbations in the disease, the amount of reacting substance in the blood in the tertiary stage remains practically unchanged over a long period. Sometimes the amount of this substance cannot be influenced by treatment—there were a certain number of cases which remained stationary although they had had no previous treatment. In the majority of cases, however, it can be reduced, but eventually takes up a new level which is uninfluenced by further treatment. In a small proportion of cases the reaction may become negative, but the conditions under which this occurs are obscure. Probably if a continuous fall to a stable negative is to be produced with any certainty it can only be accomplished by an extensive and prolonged effort, using methods more effective than those of the present investigation.

The point at which the amount of reacting substance in the blood becomes relatively stationary varies widely, although it is rarely above 50 Sigma units, and in the majority of cases below 15 Sigma units. There appear to be several factors which influence the level at which the units tend to become stationary, and these will now be reviewed.

(i) *Novarsenobillon* (N.A.B.).—This was used in the majority of cases. Three cases showed a rise in unitage, but of the remaining 90 cases approximately two out of every three cases showed some degree of fall in unitage. It may be remarked that the 58 cases whose units fell during treatment came under observation with a higher average unitage (131 Sigma units) than the average unitage (44 Sigma units) of the 32 cases which remained stationary under treatment.

Sodium Silver Novarsenobillon (NaAgN.A.B.).—This was used in 6 cases with nervous lesions and one other case whose chart is shown—Chart 5. Here there was no change in units, although 3.2 grams were injected in all. Of the 6 cases with nervous lesions, the units were reduced in 4 cases, but 1 case remained stationary, and 1 case showed a rise in units. This result, however, may be considered more satisfactory than the result of treating cases with nervous lesions with N.A.B., where, of 9 cases, 3 only showed a fall in units and 6 remained stationary.

Sulfarsenol was given in 5 cases only, and although the units fell in 4 cases out of 5 the reduction was not very striking.

Mercuric Perchloride.—Intravenous injections were given to 24 cases, in all of which the number of units had been stationary for some time before this method of treatment was begun. Each patient received approximately 0.1 gram of HgCl_2 in all, spread over about ten injections. In 13 cases the number of units remained unchanged, and in 11 there was an average fall of 25 per cent. in the unitage. This result is apparently not so good as that claimed by Conrad and McCann,¹⁴ who, however, gave their injections twice instead of once a week and gave more injections than were given in this investigation.

Other Drugs.—No attempt has been made here to distinguish the effect of the mercury pills which were given at the same time as the arsenical preparations, and often between courses of arsenic. During intervals between courses of arsenic, 29 cases were given potassium iodide in 10-grain doses for an average period of six weeks; in 5 cases the number of units had risen at the end of this period, and in 24 cases the unitage remained unchanged.

(ii) **The Effect of Rest.**—In the majority of the tertiary cases observed there was a period of rest during which no treatment was given. In about 90 per cent. of the cases no change in the units was found; in the remainder there was a rise in 5 per cent. and a fall in units in 5 per cent.

(iii) **The Size of the Injection Dose of N.A.B.**—The effect of this can be studied in the following table:

TABLE II.

Dose.	Stationary Cases.			Falling Cases.		
	No. of Cases.	Percentage of Total Cases.	Average Amount of N.A.B.	No. of Cases.	Percentage of Total Cases.	Average Amount of N.A.B.
0.3 gram	2	2.2	Grams. 2.7	—	—	—
0.45 ..	10	11.4	3.8	10	11.4	9.4
0.6 ..	9	10.2	6.8	27	30.6	6.3
0.9 ..	11	12.5	4.0	19	21.6	4.7

It would appear from this table that 0.9 gram is the most effective dose of N.A.B., because of the relatively large proportion receiving this dose who showed a fall in units, despite the fact that they received on the average much less N.A.B.

(iv) **Interval between Doses.**—Fourteen cases received one injection at a time at irregular intervals, varying from three weeks to six months. These injections had no effect on the number of units. Subsequently 8 cases out of the 14 received a course of weekly injections, and 5 out of these 8 cases showed a substantial fall in units. However, in 2 cases where this fall was observed, the condition was not stable, and the units rose to the previous level after a period of rest.

(v) **Previous Treatment.**—Fifty-five out of the 106 cases had received at least one course of injections before coming under observation, and these were for the most part less responsive to treatment than those who had received no previous treatment.

4. The "provocative" effect of an injection of N.A.B. in tertiary syphilis. In a certain number of cases there had been no arsenical injection given within two months of the beginning of the observation, and in these the number of Sigma units was noted before and one week after the first injection of N.A.B. No "provocative" rise in units was observed.

RELATION BETWEEN THE NUMBER OF SIGMA UNITS AND THE ACTIVITY OF THE DISEASE.

This is a very difficult question, because it is impossible to determine clinically the exact extent of the disease—for example, the clinician cannot ascertain during life syphilitic changes going on in the aorta, although extensive disease is frequently seen *post mortem*.

However, in this connexion, certain cases with lesions of

the mouth and skin were studied. In these the exact extent of at least one lesion could be determined. It was found that although there was a tendency for cases with more extensive lesions to have a higher number of units in the blood, the number of units increased out of proportion to the visible evidences of the disease. For instance, three cases with ulcers of the mouth averaged 6.6 Sigma units, and three cases, with ulcers of the mouth probably twice as extensive, averaged 300 Sigma units. As the units seemed to increase out of proportion to the visible lesions, one must suppose that either the cases with higher units had undisclosed lesions, or that an additional and unknown factor was operative.

In this study the findings of one case with inflammation of the mouth and fauces is of particular interest. This patient (Chart 8) had three courses of treatment, during which he improved clinically and his Sigma units fell steadily. He did not attend the clinic between the courses of treatment, and when he did return his condition was definitely worse clinically and his units had risen. The third cycle was marked by the formation of a gumma during a six months' absence from the clinic. His units had risen then from 3 to 225. When treatment was recommenced and the gumma broke down into an open ulceration, the units dropped to 71.

THE RELATION OF CLINICAL IMPROVEMENT TO SEROLOGICAL IMPROVEMENT.

Although a detailed study of this kind was beyond the scope of this investigation, certain general observations were made. Table III summarizes 75 cases. It does not include either the latent or the early cases.

TABLE III.—Relation of Clinical and Serological Improvement.

Sigma Units.	Definite Improvement.		Doubtful Improvement.		Stationary.		Worse.	
	No. of Cases.	Percentage of Total Cases.	No. of Cases.	Percentage of Total Cases.	No. of Cases.	Percentage of Total Cases.	No. of Cases.	Percentage of Total Cases.
Falling ...	33	43.0	9	11.8	3	4.0	0	0
Stationary ...	12	15.8	7	9.2	8	10.5	1	1.3
Rising ...	0	0	0	0	0	0	2	2.7

This table shows that clinical improvement was far more frequent in cases which showed a fall in units than in cases which did not. Also, in cases which became worse clinically, the units either rose or remained stationary.

SUMMARY AND CONCLUSIONS.

In summarizing the results of this investigation it may be said that—

1. As regards technique:

By means of the Sigma reaction it was possible to estimate with a high degree of accuracy the amount of reacting substance in the serum of cases of syphilis, the probable error of any single determination being about 6 per cent. The evidence for this is based on the result of many tests on the same specimen of serum on different occasions, and many tests on the serum of certain patients at different times.

Evidence of the same type confirms the claim that properly prepared heart extracts are stable in regard to sensitiveness.

2. As regards the effect of treatment on the number of Sigma units in the blood in the early stages:

In the early cases of syphilis which gave a positive reaction at the beginning of the observation, one-third showed an abortive rise at the commencement of treatment. In these cases after the rise was over, and in the remaining two-thirds of the cases each arsenical injection produced an average fall of 42 per cent. in the number of units present before that injection.

Cases which attended regularly and had a full course of treatment showed in general a steady fall in units to a stable negative reaction, but cases which attended regularly and had an incomplete course of treatment were liable to become resistant to arsenic, the number of units often remaining stationary when treatment was resumed.

3. As regards the effect of treatment in the tertiary stage:

Only 3 out of 106 cases became negative; at the beginning of observation these cases had a low number of units, and had received much previous treatment. Of the remaining cases the units fell in about one-fifth of the cases, fell and then remained unchanged in one-third of the cases, and remained unchanged throughout in one-third.

In 3 cases a rise of units was observed, and in 2 of these cases the rise was associated with a visible increased activity of the disease.

It is probable that in the majority of tertiary cases the Sigma units fall to a certain level as a result of treatment and that it is difficult to cause a further fall in units. This level is usually between 2 and 15 Sigma units.

The most effective dose of N.A.B. was 0.9 gram. No substantial effect was observed in the number of units, if the injections of N.A.B. were given at intervals of three weeks or longer.

Intravenous injections of mercuric perchloride were given to 24 stationary cases, and produced a fall in units in about 50 per cent. of these, but no case became negative.

About 90 per cent. of cases showed no change in their unitage during rest or during oral treatment following courses of N.A.B. The remaining 10 per cent. showed a rise and fall of units in equal proportions.

The number of units in the blood corresponds to a certain degree with the visible extent of the activity of the disease. In 43 per cent. of cases a fall of units was associated with clinical improvement, but in 15.6 per cent. the units remained unchanged although there was improvement clinically.

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CARCINOMA OF THE RECTUM COMPLICATED BY PREGNANCY.

TWO CASES TREATED BY EXCISION.*

BY

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DURING the past three years I have had the uncommon experience of operating upon two patients for the removal of carcinoma of the rectum during the period of gestation.

CASE I.

Mrs. B., aged 27, was admitted to Mercer's Hospital on January 4th, 1922. She had one child, aged 12 months, and stated that during the past five months she had had pain when the bowels moved; the pain had been much worse recently and sometimes she lost a quantity of blood; her weight had declined considerably.

A ring-like stricture of the rectum was found about the level of the cervix uteri; it was extremely painful, but with care the index finger could be passed through its lumen. The sensation given to the examining finger was that of a malignant growth. Upon bimanual examination of the pelvis the growth appeared to be freely movable, but the disconcerting fact was discovered that the uterus corresponded, in size and consistency, to a pregnancy of between three and four months' duration. No proctoscopic examination was made, as the parts were extremely tender and the diagnosis was obvious. The facts were fully explained to the patient and to her husband, and radical operation was decided upon.

Owing to the difficulty of clearing the bowels it was decided to perform a preliminary colostomy. On January 10th an incision, about four and a half inches long, was made through the left rectus muscle, at the junction of the middle and outer thirds, the pelvis and abdominal cavity were manually explored to exclude secondary growths, and a permanent colostomy opening was made, taking care to leave plenty of colon below the point of fixation. The protruding knuckle of gut was opened and trimmed before the patient left the operation table. Three weeks later, when she felt and looked much stronger, the coccyx and last segment of the sacrum were removed and the entire rectum and anus, together with the sphincters and the greater part of the levatores ani, were excised in one piece. The cut end of the pelvic colon was then closed by suture, invaginated, and fixed extraperitoneally. The wound was closed in two layers, a drainage tube being inserted rather posterior to the site of the original anal opening. There was very little loss of blood and no shock. The drainage tube was removed on the third day, sutures were removed on the eighth day, and the patient was allowed up on the twentieth day after operation. The pathologist's report was: "Columnar-celled carcinoma of the rectum."

The pregnancy progressed along normal lines, and in the following June the patient entered the Rotunda Hospital. I am much indebted to Dr. J. Quinn, one of the assistants to the Master of the Rotunda, for the following particulars:

"Mrs. B., aged 27, was delivered, on June 28th, 1922, of a healthy male child, 18 in. long and 6½ lb. in weight. Labour lasted sixteen hours, placental stage thirty-five minutes. No instruments were used. There was a very slight laceration of the perineum, which was repaired immediately by one stitch. The chief feature of the case was the absolutely normal manner in which labour progressed and terminated."

Shortly afterwards Mrs. B. and her family went to live in England, and I have lost sight of her.

The second case was diagnosed accurately and sent to me by Dr. B. H. Farrell of Castlecomer on January 14th, 1924.

CASE II.

Mrs. K., aged 38, had had nine living children, and on the date mentioned thought that she was three months pregnant. For the past seven months she had been very constipated, and an increasing amount of mucus and blood had come from the bowel, until the discharge was almost continuous. She had very little pain, and did not think that she had lost much weight, but was very depressed. On examination a friable fungating mass was felt surrounding the lumen of the rectum just above the level of the cervix uteri. Bimanual examination revealed a three months' pregnancy and almost certain involvement of the cervix, as the growth and cervix appeared to move together. At first I refused radical operation, and a colostomy did not appear necessary; but the absolutely miserable and hopeless condition of the patient made me alter my opinion, and I told her that I would, if necessary, remove the rectum and uterus.

I wrote a very full account of the risks and of the almost hopeless prognosis to Dr. Farrell, so that he might explain matters to the patient's husband, who gave me a free hand to do anything which might relieve her wretched condition.

On January 22nd, assisted by the house-surgeon, Dr. Mervyn Abrahamson, I opened the abdomen in the middle line below the umbilicus, examined the liver and iliac glands, etc.; then, having tilted the table into the full Trendelenburg position, I drew the uterus out of the pelvis and found, to my great relief, that it

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