CLINICAL PATHOLOGY IN GENERAL PRACTICE

TESTS FOR VENEREAL DISEASE—II

BY

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The method of taking serum from a suspected syphilitic primary sore has been described in Part I (March 6, p. 575), and the finding of *Treponema pallidum* by dark-ground examination is proof of the disease. One negative finding is not conclusive evidence that the patient is not harbouring the parasite, and it may be that three or four attempts at daily intervals may be necessary for success. During this time the lesion should be protected and bathed with normal saline as opportunity serves. Should any difficulty arise it might be wise to send the patient to the pathologist.

Blood Tests for Syphilis

Blood tests for syphilis include the standard serum tests and Nelson's treponemal immobilization test. The former tests are usually reported as being negative or positive, with neat serum or dilutions thereof. The strength of a reaction (the higher the serum dilution the stronger the reaction) is no indication of the "amount" of the infection, but rather a reflection of the reaction of body tissues to the disease. Time should never be wasted in taking specimens of blood from the umbilical cord of infants. Such specimens when they arrive at the laboratory are nearly always infected, thus vitiating precipitation tests, or are anti-complementary to such a degree that they cannot be tested by a complement-fixation test.

Standard serum tests for syphilis and their modifications are legion, but all come under two headings: (1) complement fixation—for example, Wassermann tests, using standard or cardiolipin antigens; and (2) precipitation tests (including the clarification tests) such as the Kahn, Meinicke, Venereal Diseases Research Laboratory (Chamblée, U.S.A.), and Price's precipitation reaction.

Most laboratories employ a Wassermann reaction as the standard test, and a precipitation test as a check. It is important to seek the advice of the serologist concerning the relative sensitivity of the tests on which the report is based before attempting to assess the results. Fig. 1, in

FIG. 1.—Relative sensitivities of five serum tests for syphilis.

which five serum tests for syphilis are depicted, illustrates this point. There is little difference during the rising phase in the sensitivity of any of these tests. Thus in the early stages of the disease one is not likely to become positive much earlier than the others. In the static and declining phases marked differences are evident. Thus test 1 stays static for the shortest time and becomes negative before any of the others. It is followed by tests 2, 3, 4, and 5. If, therefore, a blood were tested by these five reactions at time point A, the report would read: tests 1 and 2 negative, tests 3, 4, and 5 positive. Lack of knowledge of the rela-

tive sensitivities of the various tests would make the interpretation of such a report difficult.

It must be made clear that in the absence of any clinical signs a diagnosis of syphilis should never be made on the strength of positive tests obtained with one blood specimen. When such an occasion arises, it is unwise to inform the patient that he or she is suffering from syphilis. The history and clinical condition should be reinvestigated, and the possibility of a non-treponemal reaction (so-called biological false positive) discussed with the pathologist before any action is taken.

Non-treponemal Reactors

In Britain non-treponemal reactions (approximately 0.3% of all bloods tested) are most commonly obtained with bloods from patients suffering from atypical pneumonia and bronchial infections, from antenatal patients, and from those who have been vaccinated recently for smallpox or inoculated with T.A.B.C. vaccine. It follows therefore that when standard serum tests are being performed for emigration purposes the blood specimen should be taken before vaccination or inoculation is performed. Rarer causes of non-treponemal reactions are haemolytic anaemia and some cases of lupus erythematosus. In my experience glandular fever was possibly responsible for only one non-treponemal reaction when sera from 92 patients suffering from this disease were tested. In the conditions listed above the serum may, on serial testing and in the absence of any antisyphilitic treatment, remain positive at a low titre for a relatively short time (three months) before gradually fading in strength until it becomes negative.

The real difficulty arises in the case of antenatal patients, for time is short. Here Nelson's treponemal immobilization test may be of value, but the pathologist should be consulted before asking for this investigation. The test is so complex and time-consuming that it cannot be regarded as a routine test; it must be reserved for special "problem" sera. At least 10 ml. of blood taken with aseptic precautions into a sterile container is required, and the results are reported in percentage terms of immobilization. Thus 100 to 50% immobilization is a positive reaction, 50 to 20% a doubtful reaction, and 20 to 0% a negative reaction. Because the living *Treponema pallidum* is used as an antigen the test is said to be specific, and so far few non-treponemal reactions have been substantiated. One other serum test can be used with the blood of suspected non-treponemal reactors—the Kahn universal serological reaction. The serum is tested by a series of quantitative reactions using different solutions of saline. The results are read immediately as well as after 4 and 18 hours at 4° C. Different serological patterns are thus obtained, one of which is said to be typical of a syphilitic serum.

Chronic non-treponemal reactions are more difficult to deal with because serial blood testing may consistently yield positive results for years before the test returns to negative, and this in the absence of any family or clinical history, signs, or treatment of the disease. In fact it may be almost impossible to decide whether a patient is suffering from latent syphilis or whether he is a non-treponemal reactor. In such cases the treponemal immobilization test and Kahn's universal reaction may be of help. The decision to treat or not to treat can be extremely difficult, and if confronted with such a dilemma the practitioner is strongly advised to consult a venereologist.

Serological Patterns in Syphilis

Interpretation of serum-test reports depends, therefore, on the knowledge of the methods of reporting and the sensitivity of tests as well as on the behaviour of the tests during the course of the disease. Fig. 2 depicts a typical sero-

FIG. 2.—Typical serological pattern in a case of untreated latent syphilis of four years' standing, discovered on routine testing at beginning of treatment for gonorrhoea. The black rectangle indicates period of antisyphilitic treatment. P.P.R.=Price's precipitation reaction. W.R.=Wassermann reaction.

logical pattern of a patient with a positive serology tested throughout by means of the standard Wassermann reaction and Price's precipitation reaction. It will be noted that the latter returns to negative four months, earlier than the Wassermann reaction in the absence of any further treatment.

Another but more complicated serological pattern of a patient is depicted in Fig. 3. Here, in spite of treatment, two sero-relapses occurred during the course of the disease before the blood tests returned to negative.

FIG. 3.—A case of late secondary syphilis with a healed pustular rash. Two sero-relapses occurred in spite of treatment.

"Oscillatory" phenomena, mentioned in connexion with the gonococcal complement fixation test, occur also with the standard serum tests for syphilis, and Fig. 4 depicts this phase of syphilitic serology. These types of reactions usually mean that the positive result is well on its way to becoming negative.

FIG. 4.—"Oscillatory" phase in the serology in a case of early latent syphilis of less than one year's standing.

A serological relapse may be said to have occurred when a series of three consecutive rises in titre are obtained by routine tests at short intervals during the course of management of syphilis. An example of this is shown in Fig. 2. Such a pattern may precede a clinical relapse.

"Carry-over" reagin is the term given to reagin which has passed from a sero-positive mother's blood to that of her newborn infant. Usually the serum titre of the mother is higher than that of the child, but the latter's positive serum reaction rapidly returns to negative in the course of six to eight weeks. Therefore if a child born of a syphilitic mother has no signs of the disease it should not be treated merely on the strength of a positive blood reaction. Quantitative serial blood testing at fortnightly intervals will soon reveal the course of events.

In general, once a diagnosis of syphilis has been made it is necessary to perform routine blood tests at suitable intervals in order to obtain a clear appreciation of the serological pattern, which indicates the response to treatment. The timing of blood tests must be left to the clinician, but it is suggested that the blood should be tested at monthly intervals for three months after treatment; thereafter, provided the clinical condition is satisfactory and the serum tests are negative or the titres are on the down grade, at three-monthly intervals for a year, followed by six-monthly intervals for another year. If all has gone well, a final blood test one year later should be performed. Variations in this scheme must depend on the response of the patient both clinically and serologically.

Cerebrospinal Fluid in Syphilis

All cases treated for syphilis should have their cerebrospinal fluid examined at least twice before being discharged as cured. In primary and secondary syphilis the usual times are at the end of the first six months of treatment and just before final discharge. Patients who come for diagnosis at a later stage of the disease should have their cerebrospinal fluid tested before treatment is given. Tests thereafter are taken at times which will depend on the diagnosis and the clinician's assessment of the effect of treatment.

Earle Moore's Classification of Spinal Fluid Patterns in Syphilis

Group	Cell Count	Protein Content (mg., 100 ml.)	Wassermann Reaction	Lange Test
Normal	9 or less, usually 5 or less	40 or less	Negative	0000000000 to 2111000000 or 0112100000
1	10 or more, usually less than 50	40 or more, usually less than 100	"	As in normal fluid, or, e.g., 3210000000
2	10 or more, usually less than 200	40 or more, usually less than 100	Positive	Variable readings
3	10 or more, usually (except in acute syphilitic meningitis) less than 500	40-200 or more	"	First zone or "paretic" curve. 4321000000 to 5555554321

If the Wassermann reaction is negative, the total protein estimation below 30 mg. per 100 ml., the cell count less than 10 per c.mm., and the Lange colloidal gold test normal, the result can be regarded as satisfactory. Any deviation from these standards may merit a close re-examination of the patient's mental and physical condition. It has been stated, however, that minimal amounts of reagin can leak through from the blood stream into the cerebrospinal fluid (possibly through the choroid plexus) with the result that a patient with a positive blood test may have a weakly positive cerebrospinal fluid (Wassermann reaction positive with neat fluid) in the absence of any clinical signs or increase in the total protein and number of cells. The interpretation of cerebrospinal fluid reports can be extremely difficult, and Earle Moore's* classification will be found to be helpful (see Table).

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Group 3 is a "paretic formula" and is usually obtained with the cerebrospinal fluid of all untreated cases of paralytic dementia. This pattern can occur with other clinical forms of neurosyphilis, or even with asymptomatic neurosyphilis. When this happens the report should carry a warning to the clinician that unless the patient is treated adequately there is a grave risk that he may develop paresis. It should be realized that the cerebrospinal fluid can be normal in untreated neurosyphilis, especially in tabes dorsalis (20%) or in vascular neurosyphilis. In interpreting the results of the examination of cerebrospinal fluids, it is a good working rule to remember that the degree (or absence) of active inflammation in the nervous system (usually the meninges) is measurable by the cell count and protein content. If either or both remain high after treatment for neurosyphilis the patient should be treated again. On the other hand, if the cells and protein content recede to and remain normal, this is evidence of improvement of the inflammatory condition even if the Wassermann reaction and Lange test remain static. However, the findings in the cerebrospinal fluid of some cases of neurosyphilis (especially tabes) can show improvement in both cell count and protein, even in the absence of any treatment.

In cerebrospinal syphilis, therefore, the pathological report must be appraised with the following facts in mind: (1) the Wassermann reaction is used to exclude or confirm syphilis as the cause of an inflammatory condition; (2) the cell count and protein estimation are used as measures of the inflammation; and (3) the Lange colloidal gold reaction detects changes in the globulin/albumin ratio of the cerebrospinal fluid which occur not only in neurosyphilis but also in other infections of the central nervous system. In neurosyphilis three well-defined types of reactions are usually described—namely, the paretic curve 5555432100, the tabetic 0014321000, and the meningal 0001234320.

Lymphogranuloma Inguinale (Lymphogranuloma venereum)

Lymphogranuloma inguinale is a disease due to a virus, in the diagnosis of which the laboratory can render considerable help. Of the two tests employed, the Frei skin test is the more important. The antigen (0.1 ml.) is injected intradermally in the forearm so that a weal is raised. In positive reactions an inflammatory infiltration or nodule measuring 6 mm. in diameter with a surrounding zone of erythema is present within 48–72 hours. The antigen used is a standardized culture of infected yolk of chick embryo, whilst the control test is made with material from uninfected yolks. The other test is a complement-fixation reaction, and a titre of 1 in 16 or more obtained with the serum of patients who have a positive Frei reaction is strong evidence of infection. Standard serum tests should always be performed to exclude a coexisting syphilitic infection.

Granuloma Inguinale

Granuloma inguinale is a rare disease in this country, and the diagnosis is permissible only when Donovan bodies are found in the smears or when pathognomonic cells are demonstrated by biopsy. If the practitioner suspects that a patient may be suffering from this condition it is suggested that a venereologist should be consulted.

Addenda

Before leaving the subject of tests in venereal diseases one other investigation should be mentioned—namely, that of vaginitis due to the parasite *Trichomonas vaginalis*. This relatively common and distressing condition, so prone to relapse, often coexists with gonorrhoea. The discharge should be inoculated into Stuart's transport medium and delivered to the laboratory as soon as possible. Smear preparations have not proved to be satisfactory in my hands and therefore are not recommended.

Finally, it must be pointed out that the importance of routine blood tests for all antenatal patients should not be overlooked. A recent investigation carried out in London showed that out of a total of 6,809 antenatal patients 44

(0.64%) were found to have positive Wassermann reactions. There should be little objection to this procedure, as serological tests for venereal diseases can be carried out with the same specimen as that used for Rh grouping.

Next article on Clinical Pathology.—"Tests of Thyroid Function," by Dr. Russell Fraser.

Reports of Societies

LOCAL MEDICAL SOCIETIES

Liverpool Medical Institution

Speaking at a symposium on mitral disease held on February 11 at the Liverpool Medical Institution, Mr. F. Ronald Edwards said that the danger of recurrent rheumatic fever after valvotomy for mitral stenosis had been exaggerated. However, if any considerable mitral regurgitation was present before operation valvotomy appeared to be of little value. Mild aortic stenosis and regurgitation did not contraindicate mitral valvotomy unless the regurgitation was causing lowering of the systemic diastolic pressure. Neither was auricular fibrillation a contraindication to operation, although these cases had a higher mortality. Valvotomy in pregnancy should be undertaken only if the previous obstetrical history indicated it, and then it should be done early. The other contributors to the symposium were Dr. Ronald Ellis, on the medical aspects, and Dr. R. J. Keating, who spoke on radiological diagnosis.

Preparations and Appliances

ST. GEORGE'S MODIFICATION OF SIMS'S VAGINAL SPECULUM

Mr. IAN A. DONALDSON, first assistant, Department of Obstetrics and Gynaecology, St. George's Hospital, writes: A disadvantage of the standard Sims's duckbill vaginal speculum is the relatively short blade, which makes demonstration of the cervix in some patients difficult. The sister of the gynaecological ward at St. George's Hospital designed a modified speculum which has been made by Messrs. Charles F. Thackray Ltd., who have supplied the following technical information about the new speculum.

The whole instrument is shaped from thin material to reduce the total weight, and the overall dimensions of the two blades are: larger blade, 4½ in. (12 cm.) long and 1½ in. (3 cm.) wide; smaller blade, 4½ in. (10.8 cm.) long and 1¼ in. (2.9 cm.) wide. Varying sizes of the modified speculum have been made. The

longer and narrower blades and the marked decrease in weight make them far more convenient to use. The accompanying illustration of the largest examples of the specula shows the difference in dimensions.