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THE RELATIONSHIP OF THE GONOCOCCAL COMPLEMENT FIXATION TEST TO THE DIAGNOSIS AND TREATMENT OF GONORRHEA

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DISCUSSION

DR. DAVID N. NABARRO said he had had practically no experience of the gonococcal complement fixation test in adults, but from what he had read and heard there was no doubt that it was of very considerable value in the diagnosis and cure of the disease. It was in dealing with the disease in children particularly that he had been engaged for a number of years.

Dealing first with the problem of the technique of the test, he endorsed Dr. Price's appeal that serologists should be properly trained. There was no doubt, he said, that the reaction was complicated and that the test was difficult to carry out, judging from the different results obtained at different laboratories. During the past year he had had the advantage of having tests carried out in his own laboratory and by Dr. Price or by Dr. Curtis of the Whitechapel Clinic, and in a number of cases the results obtained had not tallied. The reason might be that in his own laboratory the technique of Dr. Price had not been followed as religiously and carefully as it should have been followed. Latterly his assistant, Dr. Signy, had followed the technique of Dr. Price more closely and the results obtained had been in closer agreement than formerly with the results of Dr. Price, though they were not parallel in all cases. He wondered whether the technique of the gonococcal complement fixation test would be as difficult to carry out as was the opsonic index test, which had been carried out reliably only at St. Mary's Hospital, where it originated. If that were the case, the gonococcal complement fixation test would lose its value to a considerable extent. One difficulty concerned the antigens, but he had overcome that difficulty by obtaining the antigens from Dr. Price.
There might be other factors in the technique which needed careful elaboration, and he suggested that there should be supervision of the laboratories, for he felt that there were too many differences of detail in the application of the test by the various laboratories.

Presumably it would be agreed that the gonococcal complement fixation test was of the nature of the reaction in the agglutination test, very similar in many respects, though not identical. He recalled that in the early days of the Widal reaction many false negatives were obtained; there were undoubted cases of typhoid in which the results obtained from the test were negative. It was said at that time that there was a "delayed" reaction, and that in three or four weeks the reaction would become positive. Then it was suggested that the reaction alternated, being positive one week and negative the next week. A subsequent discovery which helped to explain those negative results was that the cases were not typhoid at all, but paratyphoid, which had not been previously recognised. Since then it was found that some undoubted cases of typhoid failed to give the agglutination reaction with the ordinary H-antigen, but did with an O-antigen. Similarly, a number of false positives were experienced. Such false results might be obtained in the gonococcal complement fixation test as the result of "group" reactions.

Discussing the possible reasons why the gonococcal complement fixation test should give negative results in cases of gonococcal infection, he said it was maintained by some people that the gonococcus in children differed from the gonococcus in adults. It might be possible to investigate that point by using different antigens for the test, employing in one case the ordinary mixed antigen, and in another case an antigen prepared solely from gonococcus cases in children. Positive results might be obtained by using a gonococcus from children.

With regard to other organisms, such as the meningococcus, the micrococcus catarrhalis, etc., it seemed from Dr. Price's remarks that they did not play a very great part in the test.

The question arose as to whether the persistence of positive results meant that there was a persistent focus of infection. In that connection he referred again to the Widal reaction; he recalled that in the early days of the
test a number of people who were known to have had typhoid, in one case thirty years previously, were subjected to the agglutination test and the results were positive, although he did not think the patients were carriers. If a positive agglutination could persist—and it might persist for a considerable time—could not a positive complement fixation reaction persist also in a case of gonorrhoea without there being an active focus of infection? If there were a persistent focus it was so well hidden that it could not be discovered by the most careful investigation, and it seemed to stretch the imagination to say that because the reaction remained positive there must be a focus of infection. He was not convinced of that, and he suggested that several years should be devoted to research, in which blood should be tested by two or three serologists, in close touch with the clinicians, to determine whether those patients who showed positive reactions showed signs of recurring or relapsed infection.

The gonococcal complement fixation test might be of value in many cases, such as, for example, obscure cases of arthritis; a positive reaction might help to diagnose the cause of the arthritis. But he felt that it was not of much help for diagnosis in children. Dr. Price had found it to give positive results in only one-third of the cases in Great Ormond Street; that being so, where all the smears and cultures were positive, the test was not of very great diagnostic value. Perhaps it was of more value as a test of cure; but he could not help feeling that, because a child gave a persistently positive gonococcal complement fixation test, that was not a justification for saying that the child was harbouring gonococci somewhere and should be kept away from other children, possibly for six months or more. We were not yet in a position to make dogmatic statements of that kind, and he would prefer to wait for a period of, say, five years, so that an intensive investigation could be made by serologists and clinicians, rather than to make statements which might be disproved later.

Inasmuch as his assistant, Dr. Curtis, was particularly interested in the complement fixation test on the clinical side, they were investigating cases very thoroughly with a view to determining the value of the test. He gave particulars, therefore, of six of the most recent cases which had come to his attention.
The first was a child of nine years, having a history of three weeks' discharge before he had seen her on December 17th, 1937. The culture and smears were gonococcus positive at five days. The gonococcal complement fixation test was carried out at his laboratory and by Dr. Price, and gave a negative result. At that time the discharge had occurred for a period of a month. Undoubtedly the cultures and smears were positive then. A swab was taken a week later and was negative. The child then contracted measles and had to leave the ward, receiving treatment outside. She came back on January 21st, 1938; the gonococcal complement fixation test was again negative and the smears were negative. The vaginal smears had been persistently negative since the end of December, but a positive result was first obtained from the urethra on February 7th. The complement fixation test was negative in December and January; then on February 4th, which was about two months after the commencement of the infection, Dr. Signy had obtained a negative complement fixation test and Dr. Price had obtained a positive result. On the following week the result was weakly positive, and after another week it was positive. Those results did not help a great deal in the diagnosis, because the child had negative swabs in the vagina for two months, and only after that period had the complement fixation test given a positive result. She was still under observation and treatment.

The next case concerned a child of four years, who came to the hospital on December 2nd, 1937, with doubtful gonococci in the smears, and the culture negative. After another five days the culture was positive, and Dr. Price obtained a (±) complement fixation test result a week after the onset of the disease. A week later Dr. Price obtained a negative complement fixation test result, a week later still it was positive, and a week later again it was negative. In successive weeks after that it was positive, negative, negative and positive. That record was really perplexing. The smears and cultures were positive for about eight days, and then from December 10th to January 19th the child remained negative. On January 19th she was positive again, and a week later Dr. Price obtained a positive test result.

The third case concerned a child of ten years who had had a discharge for a week before coming to the hospital,
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and then the vaginal smears were positive for four days. The next one was negative, and three days later the culture was positive. Dr. Signy obtained a $(\pm)$ result, and Dr. Price obtained a negative result. The cultures and smears had been quite negative from November 16th, 1937, to date, a period of more than three months. Dr. Price had obtained negative complement fixation test results throughout, whereas Dr. Signy had obtained $(\pm)$ results on four occasions up to the end of January. It was difficult to decide how to regard those test results, but he would rather accept the negative complement fixation test results of Dr. Price, who was the originator and the exponent of the test, than the results obtained in his own laboratory. That particular case was positive for about a week in the smears and cultures, but negative for the next three months, and the gonococcal complement fixation test results had been negative throughout.

The fourth case was a very interesting and long one. It concerned a girl of ten years, who had been assaulted and had had a discharge for four days when he had first seen her on August 21st last year. At that time there were positive gonococci in her vaginal smears, and they had remained positive almost daily until September 9th—a period of nineteen days. At the end of that period Dr. Price obtained a negative gonococcal complement fixation test result. Nevertheless, the child ran a temperature of $103.4^\circ$ on September 8th, and seemed to have a salpingitis; she suffered pains in the lower part of the abdomen. Sometimes smears were negative, and then positive a week later. The rectum was positive and the vaginal smears positive again on October 1st; they were then negative for a month, and positive again on November 5th. Since then the vagina had been negative, for a period of four months. The gonococcal complement fixation test had been carried out on about fifteen occasions and had shown consistently negative results, although the patient appeared to have had a salpingitis and had had a relapse in the vagina. The case was perplexing and also interesting because, although there was a deep-seated infection and the history was of long duration, the gonococcal complement fixation test results were negative throughout.

The next case concerned a child six years old, who was sent from University College Hospital and was positive on December 2nd, 1937. He had seen her on December
7th, when she was positive, and she had remained positive every day until December 13th. Since then she had been quite negative consistently. The result of the complement fixation test was negative on seven occasions; it did not become positive until February 8th, and it was positive on February 18th. The child was still under observation and he was watching for a relapse, but it had not occurred. The smears and cultures were positive for only a week, at the beginning of December, and since then they had all been negative.

The sixth case was a girl eight years old, who had had a discharge for ten days before he had seen her on July 6th, 1937. She was positive for a whole month in the smears, and Dr. Price had obtained a positive complement fixation test on July 28th, i.e., about a month after the commencement of the vaginal discharge. She was negative from July 30th, and was discharged from the ward at the end of August. But she had returned a fortnight later with “suspicious” organisms in the discharge, obviously gonococci. She was positive on September 18th, but since then had been persistently negative, for the whole of the five months to date. The results of the complement fixation tests were positive from July 28th to December 17th, i.e., a period of five months, although for four months of that period there was no gonococci in the discharge. In January and February the complement fixation tests were negative. There was no sign of a relapse, but he would watch the child to see whether she did relapse.

Those cases were instructive and had points of interest bearing on the complement fixation test. But it was rather risky yet to make a stand and to say that, because the complement fixation test persisted positive, certainly in children, those children were still infected and must be kept away from other children. Admittedly they must be kept under supervision and their swabs must be examined, at not too frequent intervals, in order to detect a relapse.

Colonel Harrison. The only point of any importance upon which he joined issue with Dr. Price was in regard to the significance of a persistent gonococcal complement fixation reaction. Having watched numbers of such cases for many years, taking very many specimens from them with negative results, he did not believe that the persistent reaction necessarily meant that the patient was a
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gonococcus carrier; he would, of course, test such a case three times as severely as he would a serologically negative one, but having then failed to find gonococci he would certainly not withhold permission to marry.

Colonel E. T. Burke said he did not agree with much that Dr. Nabarro had said concerning the gonococcal complement fixation test in relation to the disease in children. If the test does happen to be positive, we should not consider the patient to be cured even though repeated smears and cultures gave negative results. It seemed to him that, apart from the point that certain people might have antibodies floating about in their blood sera for a certain amount of time, a patient should not be regarded as cured until such time as the cultures and the gonococcal complement fixation test were negative.

Mr. Hamish Nicol, discussing diagnosis, asked whether, in the case of a man who had in the past suffered from gonorrhoea and had since developed arthritis, a persistently negative gonococcal complement fixation test result was definite evidence that the arthritis was not due to the gonorrhoea, and whether a persistently negative complement fixation test result was definite evidence that a salpingitis in a woman was not due to gonorrhoea. Again, if several examinations of the smears from a female gave negative results, and if the gonococcal complement fixation test results were weakly positive, and were becoming progressively weaker, could it then be concluded that the patient was cured, or must the complement fixation test results first become completely negative? He had concluded in the past that when the complement fixation test result had passed from the positive to the weakly positive, and if there were no physical signs, the patient was probably cured, and he asked if he were right in so thinking.

Major F. C. Doble said he had been a little worried when he was asked by a very eminent physician to examine a person who had two bad joints and marked hyperkeratosis blennorrhagica on the soles of the feet. It looked like a case of gonorrhoea and yet the joints had been diagnosed as rheumatic, but a blood test gave a positive indication. The complement fixation test did give tremendous moral support in dealing with such cases.

Dr. Mascall said that as the result of experience of some strongly positive cases, it had occurred to him some
time ago, that in a female there might be small foci of infection in the muscular coat of the uterus or the Fallopian tubes, which would not be touched by local treatment. Therefore, he had considered an attack through the blood stream, and he had discussed the matter with Dr. Price, who had suggested the use of antimony. Instead, however, he had decided to use large doses of quinine, with the result that quite a number of those strongly positive cases came down to negative, which suggested that such treatment was able to get at something which the ordinary treatment failed to reach.

Dr. D. C. Logan said that the complement fixation test, even before it was developed to its present stage, had been of considerable help in the study of a number of cases. An instance of particular interest was one which she saw many years ago at Dr. Rawlins’ Clinic. A mother and child suffering from severe discharges were thought to be “G,” but they did not respond to treatment, and the complement fixation test result was negative. Complete investigation microscopically showed the discharge to be due to diplococci—but the pneumococcus, not the gonococcus.

In one or two cases of her own, continued Dr. Logan, the complement fixation test had most interestingly confirmed diagnoses. They were cases in which she could not find cocci, and in one particularly it was three years later that she was given the history which had proved that the positive complement fixation test result had truly confirmed the clinical diagnosis. In a series of pregnancy discharge cases where routine complements were taken, no positive results were obtained for two years, and it was decided to discontinue those tests. But later, when a more refined technique was developed, the test was again applied and quite a number of positive complements were obtained, which had confirmed diagnosis.

It would be interesting to know whether there was any particular significance in the fact that positive results were reported to have been obtained after measles. Also, did the term “negative smears” mean an entirely negative clinical condition?

Dr. Nabarro said he had not studied specifically the significance of measles in relation to the positive complement fixation test, but he did not think it had any real significance; the fixation test result became positive six
weeks later, in the particular case he had mentioned. In another case a patient had returned after measles with a relapse in the vaginal smear, and the complement fixation test, which had been positive before the measles, was positive again after the measles. Another child, who was negative for some time before contracting measles, came back to the ward afterwards and was found to be negative in the vagina, but was positive in the urethra a month after measles. He did not think that any conclusion could be reached on the basis of those cases.

Dr. Price, commenting on Dr. Osmond's criticism of the expression "weakly positive" and his use of the word "doubtful," suggested that the latter was likely to perplex the clinician and offered no practical help. Whilst one weakly positive reaction (+) in the absence of any other evidence was not diagnostic, if the test were repeated on another specimen of the serum from the same patient and a (+) reaction was again obtained, then he held, rightly or wrongly, that this was definite evidence of the presence of gonococcal antibody.

He could not agree that the objections to the test were so serious as Dr. Nabarro had indicated. It was, however, very important that the test should be undertaken by pathologists who were properly trained in serology, not by those who learnt the technique from text-book descriptions.

There had been insufficient work to enable us to form a definite opinion as to the value of this test in the diagnosis and treatment of vulvo-vaginitis of children, but it would seem that the test should be used as a routine procedure.

Dr. Osmond also replied to the discussion. After a tribute to Dr. Price, who, after all, had done the work, he said he would not give way with regard to the use of the word "doubtful." It seemed to him that a test which did not give a proportion of doubtful results would be a wrong one. By that he meant that if the blood of a patient were tested on the day the disease was contracted, the result would obviously be negative; but after a month or two the result of the test would almost certainly be positive. If the blood were tested every day for the first three months there must be one or more days on which the test results were just turning over from the negative to the positive, and on those days the results
could be described as "doubtful." Similarly, in a case of well-established gonorrhoea the blood test would give a positive result; as the result of adequate treatment, the blood would gradually become negative and the patient would be cured. If the blood were tested every day from the time it was positive until it became negative, there must be a number of days when the test result would be "doubtful," i.e., when it was just turning over from the positive to the negative. All the serologists at the international conferences had agreed that there were only three possible interpretations of a test, i.e., positive, negative and doubtful; they had agreed that there must be a proportion of "doubtful" results, though not necessarily a large proportion.

In reply to Dr. Nabarro, he said he did not think the C.D.T. was of very much use in vaginitis, for one would expect to obtain a negative. If it became positive, perhaps the trouble had spread to the cervix and possibly to the tubes.