COMPLEMENT FIXATION IN MENINGOCOCCAL INFECTIONS AS AN AID TO DIAGNOSIS.

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WITH NOTE ON CLINICAL STANDPOINT.

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THE diagnosis of a case of meningococcal infection may, from the clinical laboratory point of view, be one of great simplicity. On the other hand, there may be very great difficulty in affording the clinician any aid, for during the septicæmic stage (or type) of the disease a clear cerebrospinal fluid without any cell increase may exist, and the cultures may be negative. Blood cultures present difficulties in private practice.

It is, I believe, probable that septicæmic and abortive types of meningococcal infection are much commoner than is supposed, and for obvious reasons such cases are less likely to be notified or enter public institutions.

With a view to rendering some assistance in such cases, the question of complement fixation tests on the blood serum has interested me, as the material from the patient can be more or less easily obtained.

Bell[1] investigated 27 cases of proved meningococcal infection in this way, and found that the serum of such persons can be expected to fix complement round about the fourth day of the disease, so that the reaction when it is developed appears early enough to be of clinical assistance. Fairly and Stewart[2] examined in this way 37 cases of cerebrospinal fever and found the blood to react in 23 cases.

I have personally investigated a series of sera and these come under three main headings:—

(1) Sera from cases of cerebrospinal fever in which meningococci have been obtained in the spinal fluid or otherwise.

(2) Sera from cases in which clinical evidence and/or cytological, etc., evidence suggested a diagnosis of meningococcal infection.

(3) Sera from cases infected with organisms other than the meningococcus.

Technique.—In general the technique used in the standard Wassermann No. 1. (Colonel Harrison),[3] was employed. The antigen was a difficulty (for typing the meningococcus is not* at present possible as the sera for this purpose are not available) and use was made of strains isolated from cases occurring locally and pooled.

A forty-eight hours' growth on blood trypagar, reinforced with ascitic serum, was washed and resuspended in normal saline, subjected to 55° C. for fifteen minutes and 0·5 per cent. phenol added. The emulsion was standardised to 250 million per 1 c.c.

A trial was made of a "residual antigen," but although more sensitive, I did not consider the results so reliable, and I am recording only those results obtained with saline suspensions. For this, I consider, I find support in one of the leaders in serological work, namely, Professor Kolmer.[4]

Table I. shows the results of complement fixation test in

TABLE I.

No.	Initial.	Complement Fixation Test.	Approximate Day of Disease Test Made.
1	R.	+ +	6th.
2	G.	+ +	8th.
3	C.	+	5th.
4	W.	+	9th.
5	Wo.	−	7th and 14th.
6	H.	+ +	11th.
7	Wh.	+ +	12th.
8	B.	+ +	14th.
9	E.	+	6th.
10	P.	+ +	16th.
11	M'D.	+	6th.
12	W. Mc.	+ +	6th.
13	D.	+ +	5th.
14	Ch.	+	10th.
15	Ho.	+	9th.
16	Br.	+ +	16th.
17	S.	Trace of fixation	Not known.
18	He.	+ +	,,
19	Wi.	+ +	,,
20	Si.	Trace of fixation	5th.

* This is *now* possible (7th January, 1932): but only for last few weeks.

20 cases in which either before or after the test, meningococci were observed in the cerebrospinal fluid.

It will be noted that eleven cases were strongly positive (++), six cases were positive (+), two cases showed a trace of fixation, and one case was definitely negative.

Table II. shows the results of the test on 14 sera from cases in which clinical evidence and/or cytological, etc., evidence suggested a diagnosis of meningococcal infection, but in which the meningococci were not demonstrated in the spinal fluid. Of these, three cases gave strong positives (++), six

TABLE II.

No.	Initial.	Clinical Diagnosis.	Any Confirmation in Cerebrospinal Fluid.	Complement Fixation Test.	Day of Disease on which Blood Tested.
1	K.	Cerebrospinal Meningitis	Scanty polymorph exudate	++	9th.
2	W.	,, ,,	Nil	+	14th.
3	Wa.	,, ,,	Polymorph exudate	++	Not known.
4	Q.	,, ,,	,, ,,	Trace of fixation	,,
5	T.	,, ,,	Lymphocytic exudate Chlorides not low	+	22nd.
6	Y.	,, ,,	Nil	Trace of fixation	Not known.
7	L.	,, ,,	A few polymorphs	+	10th.
8	H.	,, ,,	Slight polymorph exudate	++	18th.
9	C.	,, ,,	Nil	+	17th.
10	D.	,, ,,	,,	Trace of fixation	30th.
11	P.	,, ,,	Lymphocytic response Chlorides not low	+	22nd.
12	M.	,, ,,	Nil	Trace of fixation	4th.
13	R.	,, ,,	Lymphocytes 75 per cent. Chlorides not low	+	12th.
14	H(*a*)	,, ,,	Nil	Negative	Not known.

cases gave positive (+), four cases gave only a trace of fixation, and one case was negative.

In regard to sera from other sources: Fifty sera giving positive Wassermann findings were tested.

Of these, one case gave a positive (++). I did not get an opportunity to examine this case further.

Twenty-five sera from patients suffering from gonorrhœa, gave one positive (+).

Fifty sera from various sources, including three cases of tuberculous meningitis and two cases of pneumococcal meningitis were also submitted to the test. All these fifty cases were negative. That is that out of 125 sera other than

those thought to be meningococcal infections, two gave false positives, of which one was infected with an allied organism, namely, the gonococcus.

Summary.—The complement fixation method appears to offer further confirmation in cases diagnosed or thought to be meningococcal infections, but in common with all serological tests, it must not be considered apart from the clinical and other findings in each individual case. In my opinion it in no way displaces the significance of a polymorph exudate when such is present, or the value of the estimation of chlorides where a lymphocytic preponderance occurs, for the chloride figure is rarely very low in meningococcal infections in my experience.

Where no alteration in the spinal fluid can be observed, the examination of the blood serum by complement fixation tests may be a clue to the condition.

In difficult cases, if one or more of the tripod (1, polymorphs in spinal fluid, 2, not a very low chloride content, 3, positive fixation test) be found, I consider that the clinician should treat the case as a meningococcal infection.

Clinical Note by Dr Thorp.

Cases of cerebrospinal fever undoubtedly occur in which the clinical condition is suggestive, but in which the fluid obtained by lumbar puncture may give but little or no assistance in obtaining bacteriological confirmation, or perhaps the confirmation occurs too late in the disease to be of clinical value.

A further group of cases shows clinical signs of cerebrospinal fever and abort to antiserum, etc., treatment, and in these the confirmation may be missed altogether.

Further, some cases suggest a prolonged septicæmic stage and eventually involve the meninges at the base of the brain without alteration in the spinal fluid.

A need was felt for some further test and Dr Cookson took the matter up. His results from the clinician's point of view were good, positives agreeing with clinical diagnosis, and as a rule a negative was usually agreed to finally. Negatives occurred in cases admitted after very prolonged illness or late convalescence, that is, viewing such cases from a clinical diagnostic point of view.

In several cases the positive fixation test was obtained before any change could be detected in the spinal fluid.

H. A. Cookson

Dr Cookson's remarks on his findings are the important feature of this paper, but I have most wholeheartedly to state that the findings are extremely valuable to the clinician and often at an earlier stage than a subsequently confirmatory spinal fluid. This is, of course, an extremely important matter to the patient.

Details of groups of cases from the clinical aspect have already been published by me. It is now a routine procedure here to send a specimen of blood with the first spinal fluid, so that the complement fixation test may be undertaken.

REFERENCES.—[1] "Medical Research Council," *Special Report Series*, No. 50. [2] "Commonwealth of Australia," *Quarantine Service. Service Publication*, No. 9. [3] "Medical Research Council," *Special Report Series*, No. 14. [4] Professor J. A. Kolmer, *Serum Diagnosis by Complement Fixation*, p. 204.