FURTHER EVIDENCE OF THE VALUE OF THE COMPLEMENT FIXATION TEST IN PULMONARY TUBERCULOSIS.

BY

A. LISLE PUNCH, M.B.LOND., M.R.C.P.LOND.,

ASSISTANT PHYSICIAN, BROMPTON HOSPITAL FOR CONSUMPTION AND
DISEASES OF THE CHEST; PHYSICIAN TO OUT-PATIENTS,
ROYAL NORTHERN HOSPITAL;

AND

A. HOPE GOSSE, M.D.CANTAB., M.R.C.P.LOND.,

PHYSICIAN, BROMPTON HOSPITAL FOR CONSUMPTION AND DISEASES OF
THE CHEST; PHYSICIAN TO OUT-PATIENTS, ST. MART'S HOSPITAL.

It is now nearly twenty years since Bordet and Gengou first demonstrated the presence of antibodies capable of uniting with tubercle bacilli and fixing complement in the serums of tuberculous animals. Since then numerous attempts have been made to utilize this fact in order to obtain a reliable biological test for tuberculosis in human beings, and many different methods of performing such a test have been described. Varying results have been obtained from these methods, but by none of them do the results obtained in definite cases of pulmonary tuberculosis, 10 to 30 per cent. of which have given a negative result, appear to have been sufficiently accurate to cause the adoption of the test as a means of diagnosis for early tuberculosis.

A method of performing the test was described by one of us (A. L. P.)¹ in 1920; this test has been made use of frequently in both definite and doubtful cases for over two years by both of us. We have previously shown that a positive complement fixation test is obtained in 98 per cent. of cases with tubercle bacilli in the sputum. We have, moreover, subsequently collected evidence which suggests that this small error of 2 per cent. occurs in cases of very sudden onset and running a very rapid course, in which presumably the tubercle bacilli are so virulent and the invasion so massive that those cells of the body which are responsible for the production of the complement fixing substances are overwhelmed with toxins and unable to respond to the call made upon them. In the rare cases in which, with symptoms due to tuberculosis, the test is negative at first but later becomes positive it is reasonable to assume that a sufficiently long interval has not elapsed from the time of infection for the complement fixing substances to be developed.

We have also shown² that in a series of controls consisting of healthy persons or patients suffering from diseases other than tuberculosis the test was negative in 98.5 per cent.

Further, in a series of 50 Brompton Hospital cases with symptoms strongly resembling those of pulmonary tuberculosis, and sometimes even with apical signs, giving a negative result to the test, 49 showed no further evidence of tuberculous infection ten to twenty months later.³ The one exception was a man who was living for a year subsequent to his first examination with a brother suffering from consumption, and it is reasonable to suggest that he became infected while under observation. The test was positive at the second examination six months before tubercle bacilli were found in the sputum. In the other 49 cases the test was negative at the second as well as at the first examination.

RECENT EVIDENCE.

The subsequent history of suspicious cases which give a positive result will now be shown to give further evidence of the value of the test, in this instance in the early positive diagnosis of pulmonary tuberculosis.

For this purpose we have recently investigated 50 of our Brompton Hospital cases in which the complement fixation test was positive in 1920 or early in 1921, and in which tubercle bacilli had never been found in the sputum, as far as we were able to determine, prior to the testing of their blood. They were unselected cases, and were consecutive so far as the above condition of a previous absence of tubercle bacilli in the sputum and a positive test were concerned.

Of the 50 cases a reply was received from relatives that 8 had died. None of them died while in-patients of the hospital, so *post-mortem* evidence is not available. In 3 cases tubercle bacilli had been found in their sputa. The result of the examination of the sputa in the other 5 is not known. These 8 deaths can be compared with the 2 deaths in the 50 complement fixation negative cases previously published, both

of which showed malignant disease, at the necropsy, as the cause of death.

Of the remaining 42 cases 29 attended for re-examination, 10 failed to reply, and 3 replied but were unable to attend. No less than 13 out of these 29 cases had been proved definitely tuberculous between the first and second examinations by the finding of tubercle bacilli in their sputa; the notes of 5 of them were as follows:

Case 1.—L. E. June, 1920: Complained of cough, sputum, and loss of weight for three weeks; weight 7 st. 10 lb.; sputum streaked with blood; sputum negative three times. Complement fixation test positive. May, 1921: Streaks of blood again; weight 8 st.; sputum negative. Complement fixation test positive. September, 1921: Sputum positive; weight 9 st. 10 lb. The complement fixation test was still positive in May, 1922.

Case 2.—E. M. May, 1920: Complained of cough, sputum, slight haemoptysis; loss of weight; sputum negative. Complement fixation test positive. August, 1920: Sputum positive. May, 1922: Still cough and sputum; complement fixation test positive.

Case 3.—G. W. June, 1920: Complained of cough, sputum, and loss of weight; sputum twice negative. Complement fixation test positive. July, 1920: Sputum positive. May, 1922: Still cough and sputum. Complement fixation test still positive.

Case 4.—V. D. May, 1921: Complained of being languid; no cough; no sputum; impaired note and bronchial breathing at left apex. No crepitations heard. Complement fixation test positive. February, 1922: Still feels languid; cough and sputum present; crepitations at left apex; sputum positive. Complement fixation test positive.

Case 5.—E. C. June, 1920: Complained of cough and sputum. Complement fixation test positive. May, 1921: Has been in bed four months with pleurisy; two severe haemorrhages; sputum twice positive in sanatorium. Complement fixation test positive.

An analysis of the 16 as yet unproved cases shows that 5 were cases of pleurisy when first examined; in 3 no sputum was available; in 8 there were still symptoms, and in some further physical signs were present. But, however suspicious of pulmonary tuberculosis physical signs may be, they cannot be offered as definite evidence that the tubercle bacillus is the cause of the pathological change in the lung, as there is probably no combination of physical signs absolutely pathognomonic of pulmonary tuberculosis. In 2 cases there were no symptoms at the second examination. The notes of 5 further cases to illustrate these as yet unproved cases are as follows:

Case 6.—E. S. July, 1920: Pleurisy with effusion; weight 11 st. 2 lb.; sputum negative. Complement fixation test positive. Went to sanatorium. June, 1921: Physical signs of thickened pleura. Complement fixation test positive. November, 1921: Feels fairly fit; cough for few weeks; sweats a good deal; sputum negative. Complement fixation test positive.

Case 7.—C. H. November, 1920: Complained of haemoptysis, about 10 ounces on two occasions; no abnormal physical signs; no sputum available. Complement fixation test positive. April, 1922: Complains of feeling tired; no more haemoptysis; impaired note and crepitations at right apex; no sputum available. Complement fixation test positive.

Case 8.—E. M. R. September, 1920: Complained of tiredness and loss of weight; fine crepitations at both apices; sputum negative. Complement fixation test positive. July, 1921: Signs as before. Complement fixation test positive. May, 1922: Feels fairly well; cough and sputum present, but latter not obtained for examination. Complement fixation test positive.

Case 9.—E. N. K. July, 1920: In-patient for diagnosis; cough; sputum. May, 1921: Complement fixation test positive. February, 1922: Feels better; at light work; night sweats severe; sputum negative on fifteen occasions since first seen. Complement fixation test positive.

Case 10.—C. L. July, 1920: Cough; sputum streaked with blood; loss of weight; temperature 99.2°; crepitations at right apex. June, 1921: Feels well; no sputum. Complement fixation test negative.

It will be seen that it is difficult to state the percentage of these cases giving a positive test in conjunction with pulmonary symptoms, in which tubercle bacilli were subsequently demonstrated in their sputa, owing to the death of some and the difficulty of tracing others; but of those alive and able to attend hospital 13 out of 29, or 44.8 per cent., had tubercle bacilli in their sputum within a period of not more than two years after the test.

Discussion.

First we can say definitely that the test is positive before the tubercle bacilli can be demonstrated in the sputum.

Exactly what interval elapses between the invasion of the lung and the development of a positive test cannot be determined in human beings owing to the uncertainty of the date of infection. Since, however, pulmonary tuberculosis is as a rule a disease of gradual onset, the blood, generally speaking, reacts positively by the time symptoms are present. In a few cases in which the onset is more sudden—as, for instance, with an hæmoptysis or pleurisy without any history of previous ill health—it is necessary, when such a case gives a negative result, to repeat the test after an interval of two or three months before definitely excluding tuberculosis.

Meaning of a Positive Result.—The presence of pulmonary symptoms with a positive test must be regarded as an indication of active pulmonary tuberculosis.

Duration of a Positive Reaction after Arrest of the Disease.—How long the test remains positive after arrest of the disease it is impossible to say, as there is no method of determining accurately the exact date at which the lesion has become arrested. Two of the cases in the above series offer evidence that the test does become negative after the disease is arrested. Both these cases had been free from symptoms for about a year. One case when seen in 1920 had a pleurisy with effusion from which 10 c.cm. were aspirated. He was sent to a sanatorium, where he remained for seven weeks. He brought up a pint of blood shortly after leaving the sanatorium, and entered another sanatorium for fourteen weeks. Since then for a period of sixteen months he has felt quite fit, and is now two and a half stone heavier than when seen on his first visit to the hospital. The clinical condition agrees with the negative test in these two cases, and we regard them both as arrested cases. A temporary freedom from symptoms does not, of course, necessarily indicate complete arrest of the disease. This is well illustrated by one of the cases in which the test was positive three times over a period of twelve months. In this case the patient was at one time during this period entirely free from symptoms, but later the symptoms returned and eventually tubercle bacilli were found in her sputum. We are collecting evidence bearing on this point of the duration of a positive reaction after arrest of the disease, but it must of necessity be slow in accumulating; so far it would appear that the period may not be more than twelve months.

The Value of Early Diagnosis.—It is generally accepted that early diagnosis is the key to successful treatment. All the 50 cases here published were treated as cases of active tuberculosis of the lung or pleura. Though the results are far from satisfactory, it is possible that some of the cases have been prevented by early treatment from progressing to "open" tuberculosis.

The Question of Latency.—The above considerations lead to the question of latency; 98.5 per cent. of our control cases gave a negative result to the test. All *post-mortem* evidence goes to show that in a certain number of these cases, variously estimated as from 10 to 97 per cent., old tuberculous foci existed. In what proportion of these old foci living tubercle bacilli would have been found we have no evidence upon which to form a definite opinion, but it may be said that they would have been found in a certain number. The explanation that we have to offer of the negative result to the test although tubercle bacilli may be present in the body is that, the formation of the complement-fixing substances being in all probability a property of the cells of the body, they are only formed when the focus which contains the bacilli is not shut off from the general circulation. In these old foci the bacilli when present may be entirely shut off from the general circulation by fibrous tissue resulting from chronic inflammatory processes, and so no complement-fixing substances are formed. We have shown that a positive reaction when the lesion is active does not mean a positive reaction ever after, as stated by others. In this lies the greater value of the test, and, taken in conjunction with the symptoms, it is an almost infallible guide to the presence or not of active tuberculosis.

We are again indebted to the lady almoner of the hospital, to whom we wish to express our gratitude for her valuable assistance in tracing the patients and asking them to attend.

REFERENCES.

- ¹ Punch, A. Lisle: *Lancet*, 1920, ii, p. 647. ² *Ibid.*, 1921, ii, p. 497.
³ Punch, A. Lisle, and Gosse, A. Hope: *BRITISH MEDICAL JOURNAL*, April 1st, 1922, p. 593.

THE PATHOLOGY OF FOETAL MACERATION.*

A STUDY OF 24 CASES.

BY

GILBERT I. STRACHAN, M.D., M.R.C.P., F.R.C.S.,

ASSISTANT TO THE PROFESSOR OF OBSTETRICS AND GYNAECOLOGY,
WELSH NATIONAL SCHOOL OF MEDICINE; RESEARCH
PATHOLOGIST, MEDICAL RESEARCH COUNCIL.

In the first 100 examples of stillbirth examined there were 24 cases of foetal maceration; it is the results of the examination of these that it is proposed to discuss in this communication. Various grades and degrees of the condition were seen, from mere laxness of the limbs to an almost pulpy state of the foetus, with the skin almost entirely denuded and the cranial bones loose inside the scalp. In passing it may be noted that, as 24 cases were macerated and 52 asphyxiated, in 76 per cent. of the first 100 cases of stillbirth the evident condition present on examination was either maceration or asphyxia.

Of the 24 cases 22 were premature, ranging from twenty-four to thirty-six weeks. This is only what one would expect from a general consideration of the subject. The two cases born at full time were only slightly macerated, and labour came on in these cases at or about the expected date. Both these latter cases were eclamptic. The associated conditions in the 24 cases were:

Maternal albuminuria	...	...	10 cases
Syphilis	...	...	6 "
Maternal eclampsia	...	...	4 "
Extensive placental infarction	...	...	4 "

External Maceration.

From these figures it appears that, in our experience, albuminuria is the condition most commonly associated with maceration of the foetus; further, syphilis was present in only 6 (25 per cent.) of the cases. Now in the cases of syphilis previously considered maceration was found present in only 6 out of 14 (43 per cent.); therefore considering both these sets of figures we come to the conclusion that maceration alone is no index of foetal syphilis and is much more likely to be associated with albuminuria.

In this series all grades of maceration were present, allowing the various stages of the process to be studied. The first change observable after the death of the foetus was solution and disappearance of the vernix caseosa; in the very slightly macerated cases vernix was present in the flexures of the groins and knees, where it had, for the time being, been shielded more than in the more exposed parts from the solvent action of the liquor amnii.

There can be little doubt that the first action of the liquor amnii on the dead foetus is to dissolve the vernix caseosa; in life it acts as a coat of armour against such action; this is aided by the fact that in life the vernix is continually being secreted and renewed by the glands of the skin, an action which, of course, stops at death. Later on the superficial layers of the skin become waterlogged and the connexion of the epidermis with the deeper layers becomes loosened, so that on rubbing, or even at the merest touch, flakes of epidermis peel off, exposing the reddened and shiny underlying corium. In time this also becomes affected, and in the more advanced cases the skin looks as though eroded in patches, the underlying tissues being exposed here and there.

These changes are most marked in the abdominal wall, scrotum, and limbs, and least on the head and scalp; indeed it is only in the most advanced examples of maceration that any desquamation at all is present in the scalp.

Internal Maceration.

Contemporaneously with these external changes the internal organs are also undergoing changes—internal maceration—which in general terms may be described as consisting of tissue lysis resulting from the uncontrolled action of enzymes on the parenchyma of the various organs, the whole process being aseptic.

In the skeletal muscles such action is recognized at the very earliest stage, even before desquamation is evident; general slackness and limpness of the body and limbs result, allowing the macerated foetus to be bent and twisted in any direction. In the brain the earliest naked-eye change consists of a brown staining of the dura mater, which is often slightly thickened and feels oedematous. The surface of the

* Part of a report on "The Etiology and Pathology of Stillbirth" to the Medical Research Council, 1922.