COLLAGEN DISEASE AND THE CHRONIC BIOLOGICAL FALSE POSITIVE PHENOMENON

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RECENT progress in the serological diagnosis of syphilis, and the introduction of new, specific tests for treponemal diseases, have stressed the frequency and importance of non-syphilitic reactions of the type usually known as the biological false positive phenomenon. Moreover, it has been shown that the significance of non-specific reactions is frequently serious, and that they often have a grave prognostic importance. The present paper reports the experience at a large venereal disease clinic of a London teaching hospital over a five-year period, during which patients with possible non-syphilitic reactions were subjected to detailed study and prolonged follow-up.

Standard Serological Tests for Syphilis

Serological tests for syphilis were introduced 55 years ago by Wassermann, Neisser, and Bruck (1906). Using the Bordet–Gengou phenomenon of complement fixation, they commenced a new era of diagnosis of the treponemal diseases. Wassermann (1907) used foetal syphilitic liver as the antigen, on the assumption that the treponemes in the liver provided the antigenic substance, but it was later demonstrated that the test was non-specific in the immunological sense, and that extracts from various normal animal tissues provided satisfactory antigen. Flocculation tests for syphilis were first described by Michaelis in 1907. He also used syphilitic liver as the antigen. This method did not become popular until 1917, when it was reintroduced by Meinicke. He showed that treponemes or their products were unnecessary for the test, and used an extract of healthy beef heart as his antigen. Since that date many flocculation tests have been described. The ones most commonly used are named after their originators, such as Kahn, Price, Eagle, Hinton, Kline, and the Venereal Disease Reference Laboratory (V.D.R.L.). Serological tests based on complement fixation and flocculation have become highly standardized during recent years, and a considerable degree of sensitivity and specificity has been attained. The tests differ from each other only in minor technical details, and are dependent on the same basic physicochemical and immunological processes. The antigen most commonly used today in standard serological tests for syphilis is an alcoholic lipoidal extract of some normal animal tissue, usually beef heart.

1 Received January 15, 1960.

Quarterly Journal of Medicine, New Series XXX, No. 117, January 1961.
It has been purified by many workers, and Pangborn (1941) has demonstrated that the antigenic component of the extracts is a pure chemical substance called cardiolipin, which is a phospholipid.

The antibody which is detected in the serum of syphilitic animals and in man by these non-specific antigens has been called 'reagin'. It is known to have a molecular weight similar to that of other antibodies, and to be associated with the gamma globulin fraction and, to a lesser extent, with the beta globulin fraction of the serum. Little is yet known about its immunochemistry. A great deal is known about the behaviour of reagin in the treponemal diseases, whether it be syphilis, yaws, pinta, or bejel. It has also been extensively studied both in experimental animals and in man, in both treated and untreated infections. Reagin begins to appear in the serum one week after the development of the primary chancre, and increases rapidly in titre for the next five to six weeks, usually reaching its maximum at about the time of the secondary manifestations. If the patient remains untreated it tends to become stabilized at about the same level for a period of about two years, and then, in the ensuing years, to decrease in amount. In some untreated cases it tends to disappear spontaneously, but in others it persists for the rest of life, but often at a lower level than in the earlier years (see Fig. 1). In treated patients, if treatment is started before the appearance of reagin in the serum, it may never appear, and the patient will then remain seronegative. In seropositive early syphilis reagin usually disappears within a few months of the start of treatment, usually about the sixth month. In late syphilis of all types the usual effect of treatment is to reduce the titre of reagin, but not to cause it to disappear, and the patient often remains seropositive (see Fig. 2). Unfortunately, while reagin appears in considerable quantity in the serum of animals and man infected with certain
treponemes, it, or a similar substance, is also present in minute quantities in the
serum of all normal human beings (Kahn, 1951). In most cases the quantity
is so small that it is not detected by standard serological tests, because they
are usually adjusted for sensitivity and specificity so that this effect is excluded.
In the treponematoses yaws, bejel, and pinta, each caused by an organism

![Diagram](https://academic.oup.com/qjmed/article-abstract/30/1/41/1498166/1498166)

**Fig. 2.** Usual behaviour of reagin in treated syphilitic infection in man.
(After Moore and Mohr, 1952a.)

indistinguishable from *T. pallidum*, positive serological tests are found with the
same frequency as in syphilis.

**The Treponemal Immobilization Test**

In 1939 Turner, while studying natural immunity to syphilis, showed that
the serum of syphilitic animals and man contained an antibody which combined
directly with virulent *T. pallidum*. He incubated living organisms from rabbit
syphilomata with normal and syphilitic sera, and then inoculated the mixture
intradermally into rabbits' backs. When normal serum was used, typical
chancres appeared at the site of inoculation. When syphilitic serum was
employed, either there were no lesions, or the appearance of the lesion was
modified or the incubation period prolonged. These experiments indicated the
presence of an antibody in syphilitic sera that either destroyed *T. pallidum* or
interfered with its virulence. Nelson (1948), working in Turner's laboratory at
the Johns Hopkins School of Hygiene and Public Health, studied the unsolved
problem of growing *T. pallidum* on artificial media. He succeeded in keeping
the organisms alive, motile, and virulent, for five to 10 days on tissue-free
artificial media. Nelson and Mayer (1949) mixed an emulsion of motile tre-
ponemes in this medium with normal and syphilitic sera in the presence of
complement, and observed the results directly under the microscope. In the
mixture containing normal serum, treponemes, and complement, nothing
happened within 15 to 18 hours, and the organisms remained motile and virulent. When syphilitic serum, either animal or human, was used, the treponemes were immobilized and killed. Absorption experiments demonstrated that the responsible antibody was distinct from reagin. There are then at least two antibodies or antibody fractions present in the serum in syphilitic infections, and these are non-specific reagin and the treponemal immobilizing antibody. More recent work by d'Alessandro and Dardanoni (1953) in Italy and others elsewhere indicates that there may be more than two distinct antibodies or antibody fractions.

Further studies by Nelson, Zheutlin, Diesendruck, and Austin (1950) have shown that the treponemal immobilizing antibody does not occur in the serum of normal persons or of those suffering from non-treponemal diseases, but occurs uniformly in cases of syphilis and of the closely related treponematoses yaws, pinta, and bejel. It does not occur in other spirochaetal diseases such as leptospirosis, relapsing fever, rat-bite fever, or Vincent's infection. In untreated syphilitic infection its rate of appearance nearly parallels that of reagin. It is first detectable when the primary lesion is between five and 15 days old, rapidly increases in titre for the first few weeks, and reaches a peak about the second or third month of infection. Probably, though this has not yet been conclusively demonstrated, it does not spontaneously decrease in titre with the passage of years. Thus in the untreated syphilitic, from the secondary stage onwards, the specific antibody is almost always present for the duration of the patient's life, even though reagin may have disappeared spontaneously (see Fig. 3). The treponemal immobilization test is therefore a useful diagnostic procedure in patients whose serum is reagin-free, such as those with lesions possibly due to syphilis but with negative standard serological tests. It may, for example, help to differentiate between rheumatic and syphilitic aortic
Incompetence, and in the diagnosis of certain neurological disorders. In treated primary, secondary, and early latent syphilis the antibody disappears from the blood as does reagin, but at a slower rate and not usually in a parallel manner. The sera of patients, therefore, who have been treated for early syphilis are found years later to be seronegative for both tests, though they are sometimes positive for immobilizing antibody and negative for reagin. With syphilis of several years' duration, treated late in the course of the disease, the immobilizing antibody does not disappear from the serum, though sometimes reagin may do so, and the sera of such patients, when examined from one to 35 years after clinically successful treatment for late syphilis of whatever type, are between 95 and 98 per cent. positive for the treponemal immobilizing antibody (Zellman, 1954) (see Fig. 4).

It thus appears certain that the treponemal immobilization test detects an antibody that is specific for syphilis and the related treponematoses. Unfortunately the test is expensive, and depends on maintaining a large rabbit colony infected with live treponemes. It is time-consuming, dangerous to technicians, complicated, and subject to many technical pitfalls, and its application is therefore limited to large medical centres.

**The Biological False Positive Phenomenon**

Most of the information concerning non-specific positive reactions or the biological false positive phenomenon has come from the United States of America. Moore and Mohr (1952a) have provided evidence that the phenomenon is far more frequent than was previously supposed. In 1938 a programme of mass blood-testing for syphilis was started in the United States. In 40 of the 48 States routine blood tests for all couples before marriage and for all pregnant women were required by law. Routine tests were and are still performed on
all personnel entering the armed Services, and again on demobilization. Many industries have made a practice of demanding a blood test before employment. In most hospitals tests are performed on all new patients, and many physicians have tests carried out as a routine in their practices. As a consequence millions of Americans have had these tests performed, and each year millions more are being tested.

Moore and Mohr (1952a) further drew attention to the fact that during the Second World War, when about 16,000,000 young men were mobilized in America, epidemics of infectious diseases occurred—for example, the exanthemata of childhood, respiratory infections, malaria, infective hepatitis, and other diseases—under conditions which permitted routine and serial blood testing in a way that was not possible in civilian practice. The combination of these events provided new information as to the frequency of the biological false positive (B.F.P.) reaction in the infectious diseases. Further attention was focused on the B.F.P. phenomenon during demobilization of the United States forces. About 75,000 persons known to be seronegative on entering the Services, and with no record of infection with venereal diseases or antisyphilitic treatment, were found to be seropositive on demobilization. It was obviously impossible to follow the whole group, but investigation of a large number, whose blood was re-examined to exclude technical error, led to the conclusion that less than half probably had syphilis, and more than half were probably B.F.P. reactors. Data accumulated by Moore and Mohr (1952b) in private practice amongst a white, well educated, and prosperous population group in the east of the United States indicated that about 40 per cent. of seropositive patients were not suffering from syphilis but had the B.F.P. reaction.

The B.F.P. reaction has been divided into two types, the 'acute' and the 'chronic'. The acute B.F.P. reaction is characterized by its occurrence during or shortly after a wide variety of unrelated non-syphilitic infections and illnesses. It disappears within a few days, weeks, or months—usually not more than six months—after recovery from the precipitating illness. Some common conditions producing the acute reaction are infectious mononucleosis, infective hepatitis, measles, chicken-pox, upper respiratory infections, virus pneumonia, malaria, and recent vaccination or inoculation. It has been estimated that about 20 per cent. of the population are potential B.F.P. reactors in appropriate circumstances. Chronic B.F.P. reactions are characterized by the absence of precipitating factors which produce the acute reaction, and by the persistence of reagin in the blood for many months or years or even for a lifetime. The only infectious disease known to produce a high proportion of chronic B.F.P. reactors is leprosy, but, as leprosy is rare in Britain and the United States of America, it does not account for many of the known cases, and the clinical recognition of leprosy is not usually difficult.

Before the introduction of the treponemal immobilization (T.P.I.) test it was possible only to guess, on the results of a careful history, physical examination, and epidemiological investigation of the family and sexual contacts, whether the patient was a B.F.P. reactor or not. Zellman (1954) has shown
that the T.P.I. test is highly specific for syphilis, and studies of the test indicate that in careful hands it is highly reproducible (Sequeira and Wilkinson, 1955). Discrepancies are usually explained by technical errors, or by very low titres of antibody. It is reasonable to conclude, therefore, if repeated serological tests for syphilis are positive over a period of several months or years, and if there is no historical or clinical evidence of syphilitic infection and two T.P.I. tests are negative on separate specimens of serum, that the patient is a chronic B.F.P. reactor. The use of a variety of serological tests, both of the complement fixation and of the flocculation type, will increase the number of cases found. Disagreement between the various tests is common. The majority of reactions will be a low titre (8 units or less), but a high serological titre does not exclude the B.F.P. phenomenon. The same serological picture may be produced by syphilis, especially treated syphilis, so that it is not possible to recognize the B.F.P. phenomenon by standard serological tests alone, although its existence may be suspected by an experienced observer.

Once the B.F.P. phenomenon has been diagnosed with certainty, the next question should be ‘What is the cause?’ In acute B.F.P. reactions the precipitating factor is frequently apparent if a careful history is taken and a detailed physical examination performed. In chronic B.F.P. reactions the cause is frequently difficult to ascertain, and extensive investigation and prolonged follow-up are required. Clinical data from a large group of chronic B.F.P. reactors studied by Moore and Mohr (19526) have shown that all the patients were white in race, that 70 per cent were female, and that the phenomenon occurred chiefly in the young. Twenty-seven per cent. of the male and 48 per cent. of the female subjects were under 25 years of age at the time of discovery. In 62 per cent. the reason for the discovery of the positive tests was stated to be routine blood testing in healthy persons. The remainder had serological tests performed for more specific medical reasons. Epidemiological studies in the majority of cases showed no evidence of syphilis in the family or sex contacts. Seventy-three per cent. of the female subjects under 25 years of age were demonstrable virgins. Antisyphilitic treatment, in contrast to its effect in syphilis, had no effect on the serological tests in chronic B.F.P. reactors. Adrenal cortical hormones were said to reverse the positive results of serological tests to negative, but the results again became positive when the hormones were withdrawn. No such effect had been observed in the cases of proven syphilis. The cerebrospinal fluid was usually normal, but an increased protein content was observed in about 12 per cent. of cases. The family history in these cases revealed an unusually high incidence of collagen vascular diseases, including systemic lupus erythematosus and rheumatoid arthritis, as well as diabetes mellitus and major allergic conditions.

Moore and Lutz (1955) reported their findings in 148 chronic B.F.P. reactors followed up over a period of six years. Ten patients had proved systemic lupus erythematosus, forty-five had ‘possible’ systemic lupus erythematosus, not yet verified, seven had rheumatoid arthritis, and five had an unusual serious illness which had not been diagnosed. Laboratory investigations showed a mild
to moderate microcytic hypochromic anaemia, especially in women; occasionally more severe anaemia occurred, and there was usually a persistently increased erythrocyte sedimentation rate. There was sometimes leucopenia, leucocytosis, or eosinophilia. Lupus erythematosus cells were usually present only in cases of clinically recognizable systemic lupus erythematosus. Disorders of the globulin fraction of the plasma proteins were a common finding, and Moore and Lutz called this abnormality 'dysgammaglobulinaemia'. It was present in about 90 per cent. of the series as measured by cephalin-flocculation, thymol-turbidity, and serum-globulin estimations. Electrophoretic patterns showed the abnormality to be in the gamma and to a lesser extent in the beta fraction of the globulin. Hypercholesterolaemia was present in 40 per cent. of the cases. Only 13 of the 148 patients investigated and followed up had no abnormality other than the B.F.P. itself. From all these facts Moore and Lutz drew the following conclusions. The chronic B.F.P. phenomenon is frequent in occurrence, and is not innocuous. It can be diagnosed by means of the T.P.I. test with only a small margin of error, probably in the region of two per cent. It is more frequent in young female patients than in male patients, and is often discovered for the first time on routine blood testing. It is frequently followed by the development of proven or possible collagen vascular disease, especially systemic lupus erythematosus. It is still more frequently associated with haematological disorders and disturbances of the serum globulin. Patients, therefore, who show the chronic B.F.P. reaction require careful observation and investigation over a period of years, and provide special opportunities for studying the natural history of collagen disease, and especially of systemic lupus erythematosus.

The Present Investigation

Patients and method of investigation. All the patients described in the present paper attended the Whitechapel Clinic of the London Hospital or were seen in consultation at the request of other physicians. Many first attended because of non-syphilitic venereal infections; some had been diagnosed as cases of latent syphilis many years earlier, and were attending for observation after treatment. A few were found to have positive serological tests for syphilis (S.T.S.) when they volunteered as blood donors, and some were referred from antenatal clinics where routine blood tests had given positive results. Others were referred from different departments of the hospital, and some by outside physicians because of the discovery of positive S.T.S.

For the purpose of this investigation the chronic biological false positive reactor is a patient whose serum has shown positive S.T.S. in repeated tests for a minimum of one year, but in whose case there is no past history of syphilitic infection, no clinical evidence of syphilis on careful medical examination, two negative treponemal immobilization tests on different specimens of serum, and normal tests of cerebrospinal fluid. Patients whose sera showed temporary non-syphilitic reactions, that is to say, acute biological false positive reactions, which persisted for a limited period, usually less than six months,
and who were without other evidence of syphilis, were excluded from the series. A number of patients whose sera showed persistent positive reactions, about 20 in all, were also excluded because they ceased to attend during the period of follow-up, or because the complete series of investigations had not been performed. All the patients included in the series were seen personally and questioned in detail as to the medical history of themselves and their families. They were all submitted to one or more thorough physical examinations. S.T.S. were performed repeatedly on their blood sera over a minimum period of one year, and at least two T.P.I. tests and an examination of the cerebrospinal fluid were carried out. Detailed haematological studies, estimates of erythrocyte sedimentation rate, estimation of the total plasma proteins and the plasma albumin and globulin, thymol-turbidity tests, estimation of the serum cholesterol, and examinations of the peripheral blood for lupus erythematosus cells (L.E. cells), were performed at suitable intervals. The electrophoretic pattern of the plasma proteins was not investigated owing to lack of facilities. Other pathological and radiological investigations were performed in cases for which they seemed indicated. The period of follow-up varied from one to five years. Some of the patients who had been diagnosed as having latent syphilis before the T.P.I. test was available, and had been given antisyphilitic treatment, had been attending for surveillance for periods of up to 20 years. Others were seen at long intervals, but all had been observed for at least a year.

**Clinical details.** Most of the patients described came from working-class families of the lower educational group, and most lived in the east end of London. There were 54 patients, of whom 36 were women and 18 men. Of the 36 women 34 were white and two coloured; of the 18 men 15 were of European origin, two were Indians, and one Chinese. The ages ranged from 17 to 71 years. The majority (80 per cent.) of the patients, both male and female, were young, in the third and fourth decades of life.

Of the 36 women six (17 per cent.) have developed systemic lupus erythematosus, and L.E. cells have been demonstrated in the peripheral blood. One of these six patients died recently, and post-mortem examination showed changes compatible with a diagnosis of systemic lupus erythematosus. One woman had discoid lupus erythematosus with severe hypochromic anaemia, raised erythrocyte sedimentation rate, and abnormal liver-function tests, but as yet no L.E. cells have been found in her peripheral blood. Two patients have changes in the joints characteristic of moderately severe rheumatoid arthritis, but no L.E. cells have been found in their peripheral blood. The Rose-Waaler differential sheep-cell agglutination test was positive in one case and negative in the other. Two other women have developed Raynaud’s phenomenon for which no cause has as yet been found. One middle-aged patient has acquired haemolytic anaemia, which is well controlled by prednisone. Another patient has rheumatic aortic stenosis and incompetence, with electrocardiographic evidence of left bundle branch block. One patient has periodic attacks of unexplained fever and severe posterior uveitis, the cause of which is undetermined; one has a
serious undiagnosed illness which is possibly a collagen disease, and another
has had a series of psychotic episodes. Thus, of the 36 female patients, 15 (42
per cent.) have serious disabling illness, including six with proven systemic
lupus erythematosus, and one of these has died of a collagen disease. Another

Table I

Chronic B.F.P. Reactors

<table>
<thead>
<tr>
<th>Sex</th>
<th>Total</th>
<th>Systemic lupus erythematosus</th>
<th>Discoid lupus erythematosus</th>
<th>Other collagen disease</th>
<th>Possible collagen disease</th>
<th>Haematological abnormalities only</th>
<th>B.F.P. only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>36</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(16.7%)</td>
<td>(25%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Table II

Laboratory Abnormalities

<table>
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<tr>
<th>Sex</th>
<th>Total</th>
<th>L. E. cells</th>
<th>Anaemia</th>
<th>Raised erythrocyte sedimentation rate</th>
<th>Abnormal liver-function tests</th>
<th>Increased serum cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>36</td>
<td>6</td>
<td>16</td>
<td>18</td>
<td>8</td>
<td>2</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>6</td>
<td>18</td>
<td>21</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

Table III

Clinical Manifestations Occurring with the B.F.P. Phenomenon

Arthritis or arthralgia, frequently limited to the small joints of the hands
Cutaneous lesions, such as discoid lupus erythematosus
Fever, malaise, and fatigue, often episodic but frequently prolonged
Haematuria and nephritis
Haemolytic anaemia
Hypersensitivity, especially to penicillin
Neurological lesions
Ocular lesions, usually posterior uveitis
Pleurisy, pericarditis, and involvement of other serous cavities
Photosensitivity
Psychoses
Raynaud's phenomenon and cold sensitivity
Splenomegaly and sometimes associated hepatomegaly
Subcutaneous nodules

patient has discoid lupus erythematosus without evidence of systemic involve-
ment. The remaining 20 (55.5 per cent.) feel well at the present time, but four
of them have moderately severe anaemia, six persistently raised erythrocyte
sedimentation rates, one abnormal liver-function tests, and one a persistently
raised serum-cholesterol level. Thus, only eight (22 per cent.) of the 36 women
have shown no clinical or laboratory evidence of disease up to the present time.
The findings in the group of 18 men were rather different. One patient died after a long and unusual illness, and was found at post-mortem examination to have polyarteritis nodosa and chronic nephritis. Two patients have discoid lupus erythematosus, and one of these also has severe peripheral vascular disease, leading to gangrene of the fingers and toes. Two patients have changes typical of rheumatoid arthritis, and one Indian patient has skin lesions on the nose suggestive of leprosy, but this diagnosis has not been proved. One patient has haemolytic anaemia, but the diagnosis of systemic lupus erythematosus has not been proved in his case. Another patient has had severe psychotic episodes. L.E. cells have not been demonstrated in the peripheral blood of any of the men. Haematological abnormalities are few, and the erythrocyte sedimentation rate was raised in only three cases. One patient has abnormal liver-function tests, with a raised serum-cholesterol level and clinical signs of enlargement of the liver, but no symptoms.

Of the whole series, a history of sensitivity to penicillin was obtained in 11 cases (20 per cent.). Eight of these patients were women, and three were men. Four patients had had very severe reactions when penicillin was administered to them. The reactions in the cases of the other seven were of the delayed type, such as skin rashes and swelling of the face and ankles. Intradermal tests were performed in four cases, and in each case the local reaction was so violent that this method of investigation was not repeated. Most of the patients had received only one course of penicillin, but about one-quarter had received two or more courses.

Illustrative Case Histories

The following very brief case histories illustrate some of the typical problems associated with the chronic B.F.P. reaction.

Case 1. The patient is a 39-year-old woman, who was first found to have positive S.T.S. at the age of 31 when she was pregnant. She was diagnosed as having latent syphilis, and given treatment with penicillin. One year later she began to have painful and stiff hands and fingers, with slight swelling of the wrists. This condition progressed for years despite various forms of treatment. At the age of 38 she complained of lassitude, shortness of breath, and worsening of her arthritis. The haemoglobin was 60 per cent., the erythrocyte sedimentation rate considerably raised, and L.E. cells were found in the peripheral blood on several occasions. She developed systemic lupus erythematosus seven years after the discovery of the B.F.P. phenomenon.

Case 2. A woman of 21 years. The S.T.S. were found to be positive when she volunteered as a blood donor at the age of 18. Two years ago she gave birth to a normal female child after a normal pregnancy and confinement. She has never had any clinical manifestations of illness apart from marked pallor. She has a mild hypochromic anaemia which is resistant to iron, and the erythrocyte sedimentation rate is persistently raised to about 60 mm. in one hour. No L.E. cells have been found in the peripheral blood. This is a fairly typical case in which the only abnormality so far detected is in the blood.
Case 3. A 49-year-old man. At the age of 28 he developed a patch of discoid lupus erythematosus on the face, for which he was treated at various times with bismuth, gold, local carbon-dioxide snow, radium, sulphonamides, and mepacrine. When aged 43 he was given penicillin for pneumonia, and had a severe reaction. Since the age of 47 he has suffered from bouts of tiredness and lassitude, and at the age of 48 was found to be anaemic, to have an enlarged spleen, and to have positive S.T.S. The haemoglobin was 70 per cent.; the direct and indirect Coombs tests were positive; the cold agglutinin titre was 1/128, and the Donath–Landsteiner test negative. The electrophoretic pattern of the plasma proteins was normal, and no L.E. cells were found in the peripheral blood or sternal marrow. During his stay in hospital his haemoglobin level fell to 57 per cent. On treatment with cortisone his haemoglobin responded satisfactorily, and his spleen became much smaller. He has haemolytic anaemia, possibly associated with systemic lupus erythematosus, although L.E. cells have not yet been demonstrated.

Case 4 is that of a 33-year-old married woman, who was first found to have positive S.T.S. after the birth of a still-born child five years previously. At that time her liver and spleen were noted to be palpable, and she had changes in the hands suggestive of rheumatoid arthritis. Two years later she again became pregnant, but miscarried, and became temporarily psychotic. She recovered, and six months later developed a pleural effusion. The haemoglobin was 43 per cent., and the erythrocyte sedimentation rate 58 mm. in one hour. There was also albuminuria. L.E. cells were found in the peripheral blood two years ago. Since then she has had a small maintenance dose of cortisone, and is moderately well. Systemic lupus erythematosus was diagnosed three years after the discovery of positive S.T.S.

Case 5. A 25-year-old male patient. He was discovered to have positive S.T.S. four years ago on routine blood testing, when he was suffering from non-specific urethritis. A right nephrectomy had been performed at the age of 18 years for renal tuberculosis. He had suffered from severe urticaria since childhood, and for the past five years had had mild arthritis of the hands, wrists, and ankles. One year ago he developed pain and swelling of the elbows, and increased pain and stiffness of the hands and wrists. The changes in the joints suggested rheumatoid arthritis. The erythrocyte sedimentation rate has been persistently raised, but no L.E. cells have been found in the peripheral blood.

Case 6 is that of a 27-year-old woman. When aged 19 she developed puffiness of the face, hands, and feet. When 21 and 22 years old she had severe attacks of uveitis. At this time her liver and spleen were found to be palpable. The following year she had a miscarriage at three months, and her S.T.S. were found to be positive. Shortly afterwards she complained of further blurring of vision, paraesthesiae in the legs, and weakness. At the age of 25 she developed Raynaud's phenomenon, and 'liver' palms were conspicuous. L.E. cells were found in the peripheral blood on several occasions. She is now a complete invalid with paralysis of the lower limbs.

The six cases described illustrate the fact that the manifestations of disease in patients with the chronic biological false positive phenomenon usually occur in episodes and tend to be chronic. They also demonstrate the diversity of the clinical manifestations, the difficulty of early diagnosis, and the variability of the course. Patients may remain symptomless for many years or even a life-
time, or may have a rapid, eventful, downhill course which progresses to severe invalidism or to death.

Discussion

It has not been possible to estimate the incidence of persistent non-syphilitic reactions in the sera of patients attending this venereal disease clinic in London, owing to the high defaulter rate. It appears, however, that the incidence is sufficiently high to warrant very careful investigation of all patients with positive serological tests for syphilis before a diagnosis of latent syphilis is made and antisyphilitic treatment given. At the present time the majority of cases of syphilis when discovered present the features of latent syphilis, and the problem of differential diagnosis is of great importance to those undertaking the care and treatment of such patients. At the present time the treponemal immobilization (T.P.I.) test provides the only certain method of differentiation between latent syphilis and the biological false positive (B.F.P.) phenomenon. Whether the recent advances in serology, which have provided such diagnostic aids as the Reiter’s protein complement fixation test and the treponemal Wassermann reaction, will produce a new method which can displace the complicated T.P.I. test, is a matter for the future, and much work remains to be done in assessing new serological reactions.

The high incidence of penicillin sensitivity in the present group of patients makes it even more important that an accurate diagnosis between latent syphilis and the B.F.P. reaction is made before antisyphilitic treatment with penicillin is given to patients who are found to have positive serological tests. There is some evidence to suggest that penicillin may be harmful to chronic B.F.P. reactors, apart from the dangers of acute serious reactions during treatment. In the present series the onset of symptoms in at least two cases can be dated from the use of penicillin injections given in the belief that the correct diagnosis was latent syphilis. Further study of the mechanism of penicillin sensitivity and of the formation of antibodies following penicillin administration may help to clarify its importance in the chronic B.F.P. phenomenon.

The majority of patients in the present study were young women. Nevertheless, the incidence of the chronic B.F.P. reaction among male patients was higher than in other reported series. This is probably due to the fact that a much larger number of male patients were subjected to routine blood testing, the ratio of male to female new patients attending the clinic being of the order of five to one. The occurrence of systemic lupus erythematosus and other severe illnesses was, however, considerably higher among the female patients, and so was the appearance of haematological abnormalities. It appears, therefore, that the chronic B.F.P. phenomenon indicates disease with a more serious prognosis in women, although it is not without significance in men.

The evidence confirms the observation of Moore and Mohr (1952) that the chronic B.F.P. reaction is one of the manifestations of collagen disease, and that the phenomenon may occur months, and even years, before the appearance of clinical manifestations. The underlying abnormality is probably an alteration
in the serum globulin, affecting principally the gamma fraction. It is also probable that this deviation of the globulin from normal accounts for the increased sedimentation rate, the abnormal results of turbidity and flocculation tests, the B.F.P. phenomenon itself, and the development of the L.E. cell phenomenon. Laboratory investigations have shown that a consistent sequence of abnormalities tends to develop in these cases. The B.F.P. phenomenon usually appears first, and is followed by an increase in the erythrocyte sedimentation rate and the thymol-turbidity test. Later there is an increase in the serum globulin, and much later, in some cases, L.E. cells are found in the peripheral blood. Manifestations of disease, when symptoms do develop, tend to occur in episodes and to be unpredictable. The symptoms may be mild, as in cases presenting arthritis of the hands or Raynaud's phenomenon, or they may be severe and run a rapid course to complete invalidism or even death. A proportion of the patients appear to continue in good health for long periods with no abnormality detectable apart from the B.F.P. reaction itself. From the evidence presented here it would appear reasonable to conclude that the finding of positive serological tests for syphilis in a patient with no other signs of syphilis no longer justifies a presumptive diagnosis of syphilis and the giving of antisypililitic treatment 'just to be on the safe side'. Patients with positive serological tests for syphilis require detailed investigation including a thorough physical examination, not only for signs of syphilis but also for signs of other systemic diseases. The serological tests should be repeated at suitable intervals, and quantitative tests performed with either the complement fixation or the flocculation test. If the positive serological tests persist without signs of syphilis, the T.P.I. test should be performed. Ideally two such tests should be performed on separate specimens of serum. An examination of the cerebrospinal fluid should also be performed. In experienced hands the T.P.I. test is sufficiently reliable for a final diagnosis of the presence or absence of syphilis to be based on its results. Once the diagnosis of a chronic B.F.P. reaction has been established, periodic observation of the patient for evidence of systemic disease and repeated laboratory tests should be carried out, so that possible prophylactic measures and early treatment of the underlying disease can be considered.

I should like to thank Mr. Ambrose King for permission to record this series of patients, and the physicians and surgeons of the London Hospital for referring some of them. The treponemal immobilization tests were performed by Dr. A. E. Wilkinson, and I should like to express my thanks to him for his advice and help. I am indebted to Professor Clifford Wilson for his valuable suggestions.

Summary

1. A series of 54 patients, 36 women and 18 men, attending a large venereal disease clinic in London, were discovered to have persistent non-syphilitic reactions to standard serological tests for syphilis. During observation six women developed systemic lupus erythematosus, and one man developed polyarteritis nodosa.
2. Two patients in the series have died recently, one woman from systemic lupus erythematosus and one man from polyarteritis nodosa. Post-mortem examination confirmed the diagnosis in both cases.

3. The clinical and laboratory findings in cases of the chronic biological false positive reaction are discussed, and short histories of six typical cases are described.

4. A high incidence of sensitivity to penicillin is reported among these patients. The importance of the diagnosis between latent syphilis and the chronic biological false positive reaction is stressed.

5. The diseases of which the chronic biological false positive phenomenon is a manifestation appear to have a more serious prognosis in women than in men. The presence of such a reaction is an indication for detailed clinical investigation and prolonged follow-up in both sexes.

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