The Clinical Significance of the Biological False Positive Serologic Reactor: A Study of 113 Cases

ALLAN KNIGHT, M.D., F.R.C.P.[C]* and R. D. WILKINSON, M.D.,
Montreal

ABSTRACT

Biological false positive serologic reactors were studied during a long-term follow-up of asymptomatic patients with chronic false positive serology for syphilitic reagin. This was done with a view to facilitating the early diagnosis of systemic disease, particularly collagen disorders, which are frequently associated with this finding in women. One hundred and thirteen cases were studied. Thirty-eight were "acute", i.e. positive for less than six months, 58 were "chronic", i.e. positive for more than six months, and the remainder still positive but followed for less than six months. Of 39 female chronic reactors, 10 were diagnosed as having collagen disease, and in six the BFP reaction preceded clinical diagnosis of the disease. Five had no apparent disease. In 19 male chronic reactors, there was no evidence of collagen disorders and five were free of any recognizable pathology. The remainder in both sexes were found to have a wide variety of systemic illnesses.

THE early diagnosis of most of the chronic systemic diseases is still elusive. However, recent reports on the follow-up of persistent biological false positive serologic reactors indicate that this approach may be of real diagnostic value, at least in so far as collagen disorders are concerned.[1-6]

It was with the early diagnosis of collagen disease in mind that the present study was inaugurated five years ago. This communication is an interim report.

Historically, the patient with a positive serological reaction for syphilitic reagin has been considered to have syphilis.[7] Not infrequently, the likelihood of syphilitic infection has been remote or its occurrence well-nigh impossible, and the presence of reactive serum was unexplained. With the discovery in 1949 of the specific *Treponema pallidum* immobilization (TPI) test by Nelson and Mayer,[8] a tool became available for the separation of those patients who had immobilizing antibodies to treponemata from those free of such antibodies.

At first, the usefulness of the negative TPI was such that the patient was relieved of the anxiety and social stigma attached to the diagnostic label of syphilis, and he was reassured accordingly. However, in the past decade, in the steps of Moore, Lutz and Mohr,[1, 2] of Johns Hopkins, who first studied these people on a long-term basis, many workers have recognized that the outlook for a high proportion of patients with proved chronically reacting false positive sera, was more serious than that of those with the more easily treated luetic infection.

The classical report of Moore and Lutz[2] on the natural history of systemic lupus erythematosus, based on the follow-up of chronic false positive reactors (BFP), revealed that nearly 50% of 148 private patients with this serological status developed some type of collagen disease.

While much has been written in the past 10 years on the serological diagnosis of syphilis and, as a by-product, on the false-positive reaction, a brief review is warranted. The diagnosis of syphilitic infection by serological study is still not completely reliable, despite many refinements on the early complement fixation test of Wassermann.[9] The screening tests used in public health laboratories, such as the Venereal Disease Research Laboratory (VDRL), Kahn, Kline, Kolmer and other tests (referred to as reagin tests), indicate a reaction between a non-specific antigen, usually cardiolipin, and "reagin", which is a non-specific antibody found in the gamma globulin fraction of the serum proteins and present in small quantities in normal individuals.

If the serum is reactive, and the clinical history and physical findings point to recent or past infection with syphilis, whether congenital or acquired, there is little doubt about the diagnosis.

If, after a careful study of the patient and his contacts, there is no evidence for or likelihood of recent or past infection with the Treponema, an investigation of the patient's serum for anti-treponemal antibodies is warranted. Serological tests must be positive repeatedly and the cerebrospinal fluid sero-reaction negative, before the TPI test is requested. It may be noted that false positives of the cerebrospinal fluid (CSF) are rare, being occasionally found in the presence of various meningitides, brain tumours and cerebrovascular accidents.

Since the TPI test is technically difficult, expensive and time-consuming, attempts have been made to find other methods of making the distinction noted above, and several are now in use,

From the Departments of Medicine and Dermatology, Royal Victoria Hospital.
*Clinical Assistant, Department of Medicine, Royal Victoria Hospital, and Lecturer in Medicine, McGill University.
†Clinical Assistant, Subdepartment of Dermatology, Royal Victoria Hospital.

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though not yet available in Canada. Among others, these include the Reiter protein complement fixation test, using a non-pathogenic strain of *T. pallidum*, and the fluorescent treponema antibody test. If these tests are reactive, it is corroborative evidence of present or past infection with treponema, including those of yaws and bejel.

If they are non-reactive, one must turn to the TPI test, which is about 98% accurate.[2] A false negative TPI test may occur very early in syphilis, when the diagnosis may be made clinically, or in early treated syphilis before a significant rise in treponemal antibodies has occurred, or very late in the disease when the level of antibodies has dropped below measurable levels. The latter occurs later in the course of infection and with less frequency than in the tests with the Reiter protein or with reagin.

If the TPI test is negative, and the presence of a false negative reaction has been ruled out, the patient is considered to be a biological false positive reactor. If the reagin tests revert to negative within six months, the patient is considered to be an acute reactor. The causes of this response are varied and include pregnancy, viral infections such as infectious mononucleosis, recent immunization procedures, bacterial pneumonias, subacute bacterial endocarditis, and more rarely other infections.

Chronic BFP reactors appear to be suitable subjects for a prospective investigation of the collagen disorders, according to the Johns Hopkins study by Moore and Mohr.[1] Here the reagin tests persist as reactive for longer than six months. This phenomenon is considered to be evidence of a disturbance in serum protein synthesis, primarily a dysgammaglobulinemia. It may be mirrored by an elevation in the erythrocyte sedimentation rate (ESR), abnormality in the flocculation tests of liver function, especially the thymol turbidity test, changes in the serum protein electrophoretic pattern, a positive latex fixation test and the presence of a positive LE cell preparation. The positive serological reaction frequently precedes the clinical syndrome which ultimately unfolds. In addition to the collagen diseases, causes of chronic biological false positive reactions include liver disease, malignancy, malaria and leprosy.

PRESENT SERIES: MATERIAL AND METHODS

This study was based on 113 clinic patients with proved BFP reactions; of these, 38 were considered acute. Nine were males ranging in age from 16 to 70 years, and 29 were females, with an age span of 11 to 73 years (Tables I and II). In the acute group the apparent etiologic factors were similar to those cited above for acute BFP reactors, but of possible significance was the finding that one patient had a transient false positive reaction following a hemorrhage due to a tooth extraction, and a second was a patient with proved sarcoidosis.

TABLE I.—SEX INCIDENCE AMONG BFP REACTORS

	Male	*Female*
Acute	9	29
Intermediate	6	11
Chronic	19	39

In the present series, 17 patients have been classified as intermediate reactors, because they are still positive to reagin tests, but have not been followed up for a six-month period. The males in this group have not demonstrated any recognizable disease as yet, nor have they shown any abnormality in routine tests which included urinalysis, hemogram, cephalin cholesterol flocculation, thymol turbidity and thymol flocculation tests, electrophoretic study of the serum proteins and examinations for LE cells. Among the female "intermediate" reactors, one patient had carcinoma of the cervix; another had a benign polyp removed from the stomach; and another had idiopathic epilepsy. Of

TABLE II.—AGE INCIDENCE AMONG BFP REACTORS

	Acute	
Years	*Male*	*Female*
10 - 20	2	4
21 - 40	2	17
41 - 60	4	2
Over 60	1	6
	Intermediate	
Years	*Male*	*Female*
10 - 20	0	0
21 - 40	3	6
41 - 60	2	2
Over 60	1	3
	Chronic	
Years	*Male*	*Female*
10 - 20	0	2
21 - 40	10	12
41 - 60	6	18
Over 60	3	7

the abnormal results of laboratory investigations, one patient had an elevated gamma globulin; one had an unexplained elevated ESR, that is above 20 mm./hr.; and a third, with no apparent disease, had abnormal sero-flocculation tests of liver function. Careful follow-up of this group of patients is planned.

At present there are 19 chronic male reactors in the group. Ten are in the age range 20-40 years; six are between 40 and 60; and three patients are in the range 60 to 75 years. Of these chronic reactors, five have no known disease although two have an abnormally rapid ESR. Two patients have chronic bacterial infections: one, chronic otitis media, and one, bronchiectasis. Two patients have cirrhosis of the liver of the Laennec type; two have had a gastrectomy for benign peptic ulcer; and two others have had malaria in the past. One of the patients with a history of malaria recently had an episode of erythema nodosum and urticaria. One man has a chronic stasis dermatitis of the legs with ulceration; another has epilepsy, and another, uncomplicated diabetes. The group contains one

TABLE III.—ABNORMALITIES FOUND IN CHRONIC REACTORS IN PRESENT SERIES

	Male	*Female*
None	3	2
Laboratory tests only	2	3
Collagen disease	0	10
Chronic liver disease	2	4
Skin disease	3	6
Malaria	2	2
Malignant tumour	0	3
Chronic infection	2	3
Gastrectomy	2	0
Other	3	6

patient with silicosis and two with chronic skin disease, diagnosed as neurodermatitis in one and seborrhea in the other. The role played by these latter conditions in the chronic BFP reaction is undetermined.

Thirty-nine female chronic reactors have been followed to date (Table III). Their ages range from 11 to 79 years, 12 being in the 20 to 40 year group and 16 in the 50 to 70 group. Ten of these patients are considered to have a type of collagen disease. In six, positive serology preceded the diagnostic signs and symptoms. Two of these are proved cases of systemic lupus erythematosus and one has discoid lupus. One patient, followed up for five years, is suspected of having systemic lupus erythematosus or possibly rheumatoid arthritis; in the past, she has had demonstrable urticaria. The laboratory tests performed on this patient reveal hypochromic anemia, abnormal liver sero-flocculation tests, an elevated alpha-$_2$ globulin, a positive latex fixation test, and an elevated ESR but a negative LE preparation. She had epilepsy as well. Another patient, 79 years of age when last seen and now dead, was diagnosed as having a "collagen disorder" some five years after the first positive serological reaction. She had macroglobulinemia with a 19 S component of 10.35% (normal 3.5%) and a total serum protein of 12.9 g. %, as well as elevated alpha-$_1$ and gamma globulins.

Three patients have rheumatoid arthritis, two in association with psoriasis. Another has had bilateral wrist swelling with destructive changes evident radiographically, but a definite diagnosis of rheumatoid arthritis has not been made. As well, this patient has pernicious anemia which has been in remission for many years. The third patient is suspected to have rheumatoid disease, with morning stiffness and swelling of the fingers, but no other evidence to support the diagnosis has been noted.

Four of the female chronic reactors have no demonstrable disease whatever, and have been followed up for five to seven years. One patient, after showing positive reagin tests for two years, has reverted to negative and remained so for three years. Of those who remain as diagnostic problems, three have had carcinoma, two of the cervix and one of the breast. Four have had chronic liver disease, and one of these has been a narcotic addict in the past; this is of interest in view of recent reports of a high incidence of BFP reactions among narcotic addicts.[10] One patient has no disease other than primary hypothyroidism; her serum beta globulin level is elevated and she will be studied with respect to autoimmune antibodies. Other diagnoses in this group of subjects include: chronic skin disorders of various types in six; chronic bacterial infection in three; malaria in two (one had a severe penicillin hypersensitivity reaction) and bronchiectasis, chronic bronchitis, chronic pyelonephritis and diabetes mellitus each in one patient. The only diagnoses made in each of four patients were cystic disease of the breast, endometriosis, pernicious anemia, and depression.

DISCUSSION

As stated earlier in this paper, definite criteria must be met before a diagnosis of biological false positive serologic reaction may be made.[11] The establishment of such criteria has been attempted with the view to carrying out a long-term follow-up of chronic biological false positive reactors, in order to achieve a better understanding of the mechanisms underlying the development of collagen vascular disease, if possible.

Such a study of the present series offers problems because the patients are all from outpatient clinics, and follow-up is rendered more difficult owing to limited co-operation and understanding on the part of this population group. Despite this difficulty, in this group a wide variety of pathological conditions in chronic reactors, and a collagen type of disorder in about 25% of the females, have been demonstrated.

Many of the other patients, who had no clearly related diagnosis but had early abnormalities in routine laboratory tests, offer a unique opportunity for long-term study. The availability in Canada of a routine test for treponemal antibodies, other than the complex TPI test, will be an aid in case-finding. The long-term approach may help to predict the development of some of these disorders.

We wish to pay special tribute to Dr. Fred Kalz, who inaugurated this study and stimulated much of the work presented here.

900 Sherbrooke St. West,
Suite 10, Montreal.

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