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The Rheumatoid Factor

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Abstract

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THE RHEUMATOID FACTOR

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HISTORICAL

The observation that certain human sera had the property of agglutinating sheep erythrocytes previously sensitized with specific antibody has been made sporadically since the turn of the century. Only in 1940, however, was this property shown to belong, in the main, to sera from patients suffering from rheumatoid arthritis. In that year, Waaler,[1] working in Scandinavia, published a paper drawing attention to the phenomenon and described a serological test claimed to be useful in the diagnosis of rheumatoid arthritis. Because of the difficulties of communication in war-time, Waaler's work remained largely unknown. In 1948, Rose and his colleagues[2] in New York, unaware of Waaler's observations, "rediscovered" the phenomenon and described a diagnostic test, similar in principle to Waaler's. The observations of Waaler and of Rose and his colleagues have now been amply confirmed and the Rose Waaler test, or more usually one of the numerous modifications thereof, is used routinely as a diagnostic aid in rheumatoid arthritis.

THE ROSE WAALER TEST AND ITS DERIVATIVES

In the original test, complement is removed from the test serum by heating at 56°C. for thirty minutes. Duplicate serial dilutions of the serum are made and to one set of dilutions sheep erythrocytes, previously washed in saline, are added. This titration gives some measure of the concentration of heterophil agglutinins which are almost invariably present in human sera. To the other set of dilutions, sheep erythrocytes which have been sensitized with a sub-agglutinating dose of rabbit anti-sheep erythrocyte serum are added.*

After a period of incubation at 37°C. the titre of the test serum for non-sensitized and sensitized sheep erythrocytes is read. As an example, using serum from a healthy subject the titre for non-sensitized sheep cells might be 1 : 32 and that for sensitized sheep cells 1 : 64. In expressing the result of the test the reciprocal of the titre for sensitized cells is divided by the reciprocal of the titre for non-sensitized cells, in this instance, 64 divided by 32 = 2. The quotient is called the differential agglutination titre or D.A.T. A D.A.T. of 8 or more is generally taken to be a positive test indicating that in rheumatoid arthritis the titre of the serum for sensitized cells usually greatly exceeds the titre for non-sensitized cells. This original test is technically satisfactory, but suffers from the drawback that a "false negative" result may be obtained in a patient with rheumatoid arthritis if a high titre of heterophil agglutinins is present.

Ball[3] in 1950, proposed a modification to the original test to overcome this difficulty. In his test, the serum is first absorbed with non-sensitized cells to remove heterophil agglutinins and then titrated with sensitized cells. The result is expressed as the true titre for sensitized cells. His method is now generally preferred to the original Rose Waaler method and the test has become known as the sensitized sheep cell test, S.S.C.T. or sheep cell agglutination test, S.C.A.T.

* The dose required for sensitization is previously determined by titrating the anti-serum with sheep erythrocytes; thus, if the sheep erythrocytes are agglutinated to a titre of 1 : 1000, which would then be the aggultinating dose, erythrocytes for use in the test would be sensitized by exposing them to one-quarter or one-half of this dose, namely anti-serum diluted to 1 : 4000 or 1 : 2000.

There have been many attempts to increase the specificity and sensitivity of the S.S.C.T., but, in general, it can be said that so far as practical tests for use in a routine laboratory are concerned, any increase in sensitivity is offset by a decrease in specificity.

CLINICAL ASSOCIATIONS OF THE SENSITIZED SHEEP CELL TEST

Rheumatoid Arthritis. The test is positive in about 65 to 70 per cent of patients with adult rheumatoid arthritis. Unfortunately, from the diagnostic point of view, the incidence is considerably lower in patients in whom the duration of the disease is less than one year and in whom certain other stigmata of rheumatoid arthritis, such as the presence of radiographic erosions or of subcutaneous nodules, are absent.

Prospective studies have shown that about one-third of patients remain sero-negative throughout the course of the disease, a further third may fluctuate from positive to negative and a third remain consistently sero-positive.

Polyarthritis, other than Rheumatoid Arthritis. The incidence of positive tests in juvenile rheumatoid arthritis (Still's disease) is low, ranging from about 7 to 15 per cent. Patients with ankylosing spondylitis, Reiter's disease, rheumatic fever, psoriatic arthritis, etc. are generally sero-negative, the incidence of positivity being little greater than in the population as a whole. The incidence of sero-positivity in other members of the group of inflammatory diseases of connective tissue, (including disseminated lupus erythematosus, progressive systemic sclerosis, polyarteritis nodosa and dermatomyositis), is difficult to establish in view of the clinical overlap between these conditions and rheumatoid arthritis. Sero-positivity is most likely to occur in cases of these diseases in which polyarthritis is a prominent manifestation.

Other diseases and healthy subjects. In most reported series, the incidence of sero-positivity in diseases outwith the connective tissue group is around 4 to 5 per cent, this being no higher than in the population as a whole. There are, however, notable exceptions. Positive tests are frequently recorded during the active phase of sub-acute bacterial endocarditis. The test is also postive in about 30 per cent of patients with leprosy and in a smaller proportion of patients suffering from the rather obscure group of diseases characterised by dysgammaglobulinaemia.

About 5 per cent of apparently healthy individuals are sero-positive, but a higher figure is reported in the relatives of patients suffering from sero-positive rheumatoid arthritis. This latter observation has been advanced in support of there being a genetic factor in the pathogenesis of rheumatoid arthritis, but could equally be accounted for by an environmental factor.

THE NATURE OF THE FACTOR RESPONSIBLE FOR AGGLUTINATION OF SENSITIZED SHEEP ERYTHROCYTES

Rheumatoid factor (R.F.) has now been characterised by physicochemical methods. The factor has been shown to be a high molecular weight globulin belonging to the immunoglobulin M (IgM) class. It is most frequently detected in serum, but may also be present in synovial fluid and in other serous effusions in patients with rheumatoid arthritis. Using immuno-chemical methods, R.F. has been demonstrated in plasma cells in synovial membrane and in lymph nodes. It has many of the characteristics of an antibody and forms complexes with globulins of the immuno-globulin G (IgG) class, provided that the IgG has been denatured by physical or chemical means or, in the case of antibody IgG, combined with its specific antigen. On the basis of animal experiments, Glynn, Holborow and Johnson[4] in 1957, suggested that R.F. reacted with sites on the gammaglobulin molecule which only became revealed when the molecule was denatured.

When the globulins in the serum of a patient with sero-positive rheumatoid arthritis are separated by ultra-centrifugation, precipitation will only rarely occur when the IgG and IgM fractions are recombined. If, however, the IgG fraction is heated at 60°C. for ten minutes, and is then added to the IgM fraction (which contains rheumatoid factor), precipitation occurs. On the basis of this experiment, it has been suggested that rheumatoid factor is not only an antibody but an auto-antibody. There is, however, no clear-cut evidence that rheumatoid factor combines with native gammaglobulin *in vivo*.

The ability of rheumatoid factor to precipitate with denatured IgG forms the basis of the

latex fixation test (L.F.T.). Latex particles coated with denatured human IgG are clumped by serum containing R.F. The L.F.T. is simple to do and is more sensitive than the S.S.C.T. but is, however, less specific for rheumatoid arthritis.

POSSIBLE PATHOGENIC SIGNIFICANCE OF THE RHEUMATOID FACTOR

There is now a considerable body of opinion which favours the view that rheumatoid arthritis is an auto-immune disease. This is not the place to discuss the merits and demerits of such a hypothesis but rather to examine the possible role of R.F. in the pathogenesis of the disease.

It seems reasonable to suppose that R.F. is produced by the immune system in response to stimulation by the presence in tissues of mildly altered IgG. There is evidence that IgG is present in the synovial lesion and it has been suggested that its presence indicates an immune reaction, possibly of fundamental importance, occurring in the synovium. If such a reaction should be demonstrated in the future, it is likely that it will be shown to be of the cell-mediated or delayed hypersensitivity type, for it is with this type of immune reaction that the histological appearances in the synovial membrane are most compatible.

The suggestion that R.F. is not responsible for the synovial lesion in rheumatoid disease is borne out by a number of observations. In 1959, Vaughan and Harris[5] transfused high-titre rheumatoid serum to other patients with the disease and failed to promote exacerbation of symptoms. Also, rheumatoid factor has been shown, sometimes in high titre, in unaffected relatives of patients with rheumatoid arthritis and, from time to time, in the sera of apparently healthy subjects. Histologically, it is impossible to distinguish between sero-positive and sero-negative arthritis. An arthritis, very similar to rheumatoid arthritis, occurs in patients suffering from hypogammaglobulinaemia but no R.F. is found in the sera of these patients. Duthie, Brown, Knox and Thompson,[6] in a study of the prognosis of rheumatoid arthritis, showed that patients who were consistently sero-positive fared worse than their sero-negative fellows. It can be suggested from this that in patients with continuing active disease, the stimulus to the production of R.F. by the primary synovial lesion is constantly present.

Although in the main, the evidence is that R.F. is an indicator, rather than mediator, of the primary lesion, there is one manifestation of rheumatoid disease which could be caused by circulating R.F. It has been shown in experimental animals that injection of complexes of R.F. and denatured IgG into the mesenteric vessels may be followed by deposition of complexes in the terminal vessels, thus producing a vasculitis. It seems possible that a similar mechanism might account for the vascular lesions seen in some patients with rheumatoid arthritis, particularly as it is common to find a very high titre of R.F. in such patients.

Finally, although our knowledge of the pathogenic significance of R.F. is incomplete, two observations may give a lead to the aetiology of rheumatoid arthritis. The first, already mentioned, is the high incidence of R.F. in a few diseases of known infective aetiology and the second is the demonstration of Abruzzo and Christian[7] that an "R.F.-like" substance may be detected in the serum of animals hyperimmunised with dead bacteria.

These observations, taken with the obvious compatability of the clinical features and course of rheumatoid arthritis with a chronic infectious illness, have re-awakened interest in the search for an exogenous living antigen in the synovial membrane. Over the past few years a number of centres have reported isolation of a variety of infective agents from rheumatoid tissues. Although none of these agents has been causally implicated in the disease, there is now enough circumstantial evidence to extend this type of investigation. Should it eventually be established that rheumatoid arthritis is caused by a virus, mycoplasma or bacterium (or any combination of the three!) then hopes of a "cure" would be revived and those who find it difficult to believe that individuals turn against themselves — at least without some outside stimulus — would be satisfied.

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