SERONEGATIVE POLYARTHRITIS

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CHAPTER 1

The Meaning of Seronegativity and Seropositivity

1.1 Historical background

Until recently medical writers were barely able to distinguish different types of chronic arthritis and observers up till the turn of the century considered them all to be variants of gout.

It is probable, however, that both Hippocrates and Soranus of Ephesus (second century A.D.) were aware of the difference between "chronic rheumatoid arthritis" and "chronic podagra". In more modern times, H. W. Fuller in 1854 (cited by Copeman 1964) provided a good description of rheumatoid arthritis, calling it "rheumatoid gout".

Further strength was added to the distinction between true gout and other forms of arthritis by Sir Alfred Garrod's discovery of an excess of uric acid in the blood of gouty subjects. Garrod in 1859 was the first to give rheumatoid arthritis its present name.

In 1857, osteoarthritis (or osteoarthrosis as it is now called) became separated from rheumatoid arthritis by Robert Adams in his *Treatise on the Rheumatic Gout.* Ankylosing spondylitis also became widely known as a separate entity at about this time, not only due to the classical reports by Bechterev and Strümpell from Germany and Marie from France, but also in the United Kingdom from the work of C. Hilton Fagge in 1877. For further historical details the reader is referred to the excellent monograph by Copeman (1964).

The next significant advance in rheumatological classification was made by Waaler in 1940, and again by Rose et al. in 1948, when rheumatoid factor, a gamma-M immunoglobulin, was discovered. This finding made possible a division of inflammatory arthritis into two main groups, i.e. those in which rheumatoid factor was present (seropositive and usually typical rheumatoid arthritis), and those in which the factor was consistently absent throughout the natural history of the disease (seronegative arthritis). It is with this second group, the seronegative arthritides, that we have been particularly concerned, and in order to study this subject in further detail it is clearly important to examine in some depth the immunological background to rheumatoid factor.

1.2 Rheumatoid factors

1.2.1 Physicochemical features of rheumatoid factors

Rheumatoid factors are antibodies mainly of the IgM class with a molecular weight of about 1,000,000 and an ultracentrifugal sedimentation coefficient of 19S (Franklin et al. 1957). These macro-gamma globulins constitute a class of proteins which contain, in addition to rheumatoid factors, many other types of antibody such as cold agglutinins, the Wassermann and heterophil antibodies, and typhoid "O" agglutinin.

The evidence for the antibody nature of rheumatoid factors has been summarised by Anderson and Buchanan (1966):

(1) Rheumatoid factors are immunoglobulins (usually IgM, sometimes IgG) which react only with IgG and with no other protein or tissue antigen.

(2) Rheumatoid factors demonstrate, with few exceptions, primary specificity for human IgG and cross-reactivity with other mammalian IgG (Butler and Vaughan 1964), which is consistent with the behaviour of classical antibody.

(3) Rheumatoid factors frequently demonstrate specific reactivity with certain genetically determined groupings (Gm Groups) (Grubb 1961; Fudenberg and Kunkel 1961) which suggests the specificity characteristic of antibodies.

(4) Rheumatoid factors have been shown by immunofluorescent techniques to be located in, and hence presumably produced by, cells capable of producing antibodies. These cells include plasma cells and germinal centre cells of lymph nodes, and also plasma cells in affected synovia and around subcutaneous nodules (Mellors et al. 1959; Mellors et al. 1961; McCormick 1963).

(5) Rheumatoid factor-like serum factors, albeit of IgG class, have been produced in animals by immunization with autologous denatured IgG incorporated in Freund's adjuvant (Milgrom and Witebsky 1960; McCluskey et al. 1962).

Although it is now reasonably clear that rheumatoid factors are antibodies to IgG, it is still not fully understood whether they are antibodies to native IgG or IgG denatured by immune complex formation or by physical aggregation. There is equally good evidence to support both the "native" (Grubb 1961; Fudenberg and Kunkel 1961) and "denatured" (Christian 1958; Edelman et al. 1958) hypotheses.

There is also controversy as to whether rheumatoid factors should be regarded as auto-antibodies or iso-antibodies (Milgrom and Witebsky 1960). However, as McCormick (1963) has pointed out, rheumatoid factors probably represent a heterogeneous collection of immunoglobulins, some behaving as auto-antibodies, some as iso-antibodies, and some as hetero-antibodies to IgG. It is also apparent that the reactant (IgG antigen) of normal human serum and other mammalian sera is complex in its antigenicity, and it is likely that different rheumatoid factors react with different parts of the IgG reactant molecules.

1.2.2 Basis for tests to demonstrate rheumatoid factors

Franklin et al. (1957) have demonstrated that rheumatoid factors in serum are in reversible complex with some of the smaller IgG molecules. The affinity of IgM rheumatoid factors for immunoglobulins of IgG class provides the basis for agglutination tests to demonstrate rheumatoid factor. Most of the test systems developed in recent years depend on the agglutination or flocculation of particles coated with IgG. Different test systems utilising the principle of agglutination are shown in Table 1.1. The particles used as indicators in these tests include human and sheep erythrocytes, bacterial cells, and synthetic particles such as latex and bentonite. The most popular systems for detecting rheumatoid factor in the United Kingdom are those in which the particles are either sheep red cells or latex.

TABLE 1.1
Tests for detecting rheumatoid agglutination (after Ziff 1957)

Test	Form of coating IgG	Type of particle	Nature of attachment between IgG and cell or particle
Sensitized sheep cell agglutination	Unaggregated rabbit IgG	Sheep cell	Antibody bond
F II tanned sheep cell agglutination	Aggregated human IgG	Tanned sheep cell	Adsorption
Bacterial agglutination	Unaggregated human IgG	Bacterial cell	Antibody bond
Sensitized human cell agglutination	Unaggregated human IgG	Human Rh+ cell	Antibody bond
Latex flocculation	Aggregated human IgG	Latex	Adsorption
Bentonite flocculation	Aggregated human IgG	Bentonite	Adsorption
F II BDB[a] human cell agglutination	Human or animal IgG	Human "O" cell	Covalent diazo bonds

[a] Bis-diazotized benzidine.

1.2.3 Nature of interaction between rheumatoid factor and sensitised particle

The nature of the interaction between rheumatoid factor and a sensitised particle to give agglutination has been outlined by Vaughan and Butler (1962). A schematic representation of the probable nature of events leading to agglutination is shown in