AETIOLOGICAL RELATION OF THE STREPTOCOCCUS HAEMOLYTICUS TO THE "RHEUMATIC" DISEASES

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During the thirty-six years which have elapsed since Poynton and Paine¹ published their important studies on the relationship of streptococci to the "rheumatic" diseases, research workers in all parts of the world have been engaged in investigating this problem. Although a great deal of valuable information has been accumulated it will be generally admitted that the aetiology of the "rheumatic" diseases cannot yet be said to be settled. The efforts made to elucidate their causation have been handicapped by the fact that no universally acceptable classification of these diseases has been found.

Broadly speaking, the "rheumatic" diseases which particularly affect the joints can be divided into three main groups: (1) rheumatic fever, (2) chronic infective arthritis, and (3) osteo-arthritis. The last-named disease will not be considered further, as the lesions found in the joints are the result of degeneration and not of infection. Chronic infective arthritis is the name used to cover a wide variety of chronic arthritic conditions, some of which start acutely, secondary to an obvious septic focus, while others begin insidiously, and the fullest investigation may fail to show any convincing source of infection. The term "chronic infective arthritis" therefore includes the so-called "focal" arthritis and rheumatoid arthritis.

Though the nature of the infective agent in rheumatic fever is at present unsettled no one would deny that rheumatic fever is an infective disease. The use of the term "infective" in the subgroup chronic infective arthritis is, however, open to dispute, and this is particularly true of the cases of rheumatoid arthritis, which start insidiously. We believe that not only is the term "infective" justified, but there is a considerable mass of evidence to support the view that a close aetiological relationship exists between rheumatic fever and chronic infective arthritis. We feel that the differences in the clinical manifestations in these two diseases can be explained by changes in tissue sensitivity at different ages, and by variations in the reaction of the patient to infection, just as well as by the assumption that the clinical changes are the result of different infective agents.

Clinical Manifestations

A study of the various clinical manifestations of rheumatic fever clearly indicates how different tissues are affected at different ages. Thus in infancy and in childhood arthritic changes are slight or absent, and carditis predominates; in adolescence both heart and joint changes are often present; while in adult life carditis is rare and the joints are chiefly affected. The influence of the "soil" is recognized in other infections to be of as much importance in determining the type and extent of the clinical changes as is the virulence of the infective agent. In syphilis, for example, one person may develop general paralysis of the insane, a second luetic aortitis, and a third skin eruptions. In tuberculosis, also, no two persons react to infections of the same degree in the same way. Again, in scarlet fever and gonorrhoea less than 10 per cent. of all cases develop arthritis, and it is

certainly not the severity of the infection which determines the onset of the arthritis. If it is conceded that in these infections the clinical variations are due mainly to differences in the soil, then it is conceivable that acute and chronic rheumatic conditions, too, may represent different reactions to the same infective agent.

Haemolytic Streptococci in Causation

The wide interest which was aroused last year by the claims regarding the discovery of a virus held to be the cause of rheumatic fever has tended to obscure the great mass of evidence obtained all over the world which incriminates the haemolytic streptococcus as the chief causal agent in rheumatic fever and chronic infective arthritis. The evidence in favour of this hypothesis is based on a study of the intermediate types of arthritis which merge gradually into rheumatic fever on the one hand and into rheumatoid arthritis on the other; and on the following common factors: (1) familial relationship, (2) geographical distribution, (3) seasonal incidence, (4) initiating factors, (5) pathological similarities, and (6) immunological findings. It is unnecessary to discuss all of these, as they have been fully dealt with in a recent American publication.²

The frequency with which an attack of tonsillitis precedes the onset of acute rheumatism has been estimated by various authors at between 40 and 50 per cent. The association of upper respiratory infections with the onset of chronic infective arthritis is, in our experience, of equal frequency; of eighty cases of chronic infective arthritis seen recently in Aberdeen, thirty-six, or 45 per cent., gave a history of immediately preceding sore throat or upper respiratory infection.

Pathology and Immunology

The occurrence in chronic infective arthritis of subcutaneous nodules indistinguishable histologically from those found in acute rheumatism is a fact which cannot be dismissed lightly. Further, the histological appearances of joint tissues obtained at biopsy from cases of chronic infective arthritis show a striking resemblance to the changes found in acute rheumatism, as has been pointed out by Klinge in Germany and Timbrell Fisher in this country.

Since direct evidence of infection—namely, the cultivation of the specific agent from joint fluid or blood—is generally unsuccessful, reliance must be placed for immunological evidence on indirect measures—namely, serological reactions and sensitivity tests—for the demonstration of a relationship between the different rheumatic diseases and their association with haemolytic streptococcal infections. We investigated on these lines approximately 500 persons suffering from "rheumatic" diseases.

Anhaemolysin Estimations

Table I shows the results of a series of streptococcal anhaemolysin estimations. These were performed by the method of Todd, and the haemolytic streptococcus used both in Aberdeen and in Buxton in the preparation of streptolysin was a scarlet fever strain obtained from Dr. Todd. The exact technique of preparation will not be described here. The term "subacute rheumatism" in this and subsequent tables is used to designate a type of polyarthritis with sudden onset following an upper respiratory infection, simulating or indistinguishable from rheumatic fever, but in which there is little or no pyrexia, and pain and stiffness persist in one or more joints without leaving permanent joint changes.

It will be seen from this table that in the Aberdeen series 100 per cent. of cases of acute rheumatism showed a value of over 50 units, compared with 27 per cent. of

to three times as high in the Aberdeen series of cases of rheumatic fever, chronic infective arthritis, and streptococcal disease as in the control series. In the Buxton group 34 per cent. of cases of subacute rheumatism and 28 per cent. of chronic infective arthritis cases give positive tests, as compared with negative readings in the control series. Intradermal tests with *Streptococcus viridans* extract show no significant difference between rheumatic

TABLE IV

Disease	No. of Cases	Total Positive	Total Negative
<i>Intradermal Tests with Haemolytic Streptococcal Extract</i>			
Aberdeen Series	Rheumatic fever and chorea	85	77 %
	Controls (corresponding ages)	25	32 %
	Chronic infective arthritis	80	76 %
	Controls (corresponding ages)	25	24 %
	"Streptococcal" diseases	18	69 %
Buxton Series	Subacute rheumatism	154	34 %
	Chronic infective arthritis	137	28 %
	Controls (osteo-arthritis)	30	0
<i>Intradermal Test with Streptococcus viridans Extract</i>			
Aberdeen Series	Rheumatic fever and chorea	60	27 %
	Controls (corresponding ages)	25	24 %
	Chronic infective arthritis	80	11 %
	Controls (corresponding ages)	25	20 %
	"Streptococcal" diseases	18	38 %
Buxton Series	Subacute rheumatism	154	3 %
	Chronic infective arthritis	137	9 %
	Controls (osteo-arthritis)	30	3 %

diseases and the control series. The results of these intradermal tests therefore support the view that haemolytic streptococcal infections are more frequent in rheumatic diseases than in the rest of the population. The higher incidence of positive skin tests in Aberdeen is partly explained by the higher concentration of the antigens employed, as is clearly demonstrated by the control figures—namely, approximately 30 per cent. positive in Aberdeen and 0 per cent. in Buxton. There is, however, an additional explanation of great interest.

Correlation of Clinical Findings

TABLE V

	No. of Cases	Progressive			Stable			Unstable		
		No. of Cases	Posi- tive	Nega- tive	No. of Cases	Posi- tive	Nega- tive	No. of Cases	Posi- tive	Nega- tive
Subacute rheumatism	154	88	1.2%	98.8%	27	88.8%	11.2%	39	71.7%	28.3%
Chronic infective arthritis	137	86	2.5%	97.5%	32	34.5%	15.5%	19	58%	42%

Table V shows a classification of the Buxton series of cases into progressive, stable, and unstable, a classification which is based on clinical data. "Progressive" indicates a stage of the disease at which several joints are involved and the process is in a very active state. In the stable or inactive stage pain and swelling are absent from all joints; and in the unstable stage there is intermittent involvement of one or two joints, but the disease is at a comparatively quiescent phase. It will be seen that a high proportion of the stable and unstable forms of both diseases give positive reactions, the figures being actually higher than those in the Aberdeen series. In striking contrast the incidence of positive reactors in the progressive group is very low.

Two possible explanations of the latter finding can be suggested: (a) that in the progressive forms of the disease the organism concerned is one other than the haemolytic streptococcus, or (b) that the negative skin test indicates a lack of antibody formation to the endotoxin of the *Streptococcus haemolyticus*, it being assumed that for a positive reaction to appear both toxin and antitoxin must be present. In the stable inactive stage, where adequate anti-endotoxin has presumably been formed, positive skin tests appear in a high proportion of cases.

An inspection of the results of intradermal tests in the Aberdeen series tends to support this latter view, as negative intradermal reactions to the haemolytic streptococcus were most often found in severe progressive cases; moreover, cases which have been studied in Aberdeen over a long period have shown a negative skin test at a progressive stage of the disease, and a positive one months later, when the disease had settled down.

A study of the case records at Buxton and Aberdeen indicates a higher proportion of progressive cases in the former centre. Accordingly the higher percentage of positive skin tests in the Aberdeen series can be explained partly by the difference in the strength of the haemolytic streptococcal extract used and partly by the lower activity of the disease at the time the tests were performed.

Discussion

While it must be admitted that the aetiology of chronic infective arthritis has not yet been elucidated it is probable that for its production several factors are essential. It is unnecessary to deal in detail with this subject here, since our views have been recently published.³ The constitutional factor, as emphasized by an abnormal capillary circulation, often from childhood, is of great importance. When a person with this type of constitution is exposed to factors such as cold, damp, occupational strain, or infection, singly or in combination, a chronic arthritis is apt to appear far more often than in an ordinary individual. Of the factors which predispose to arthritis we believe infection to be the most important, and of the many organisms which can sensitize the predisposed individual the above evidence incriminates the haemolytic streptococcus as the most frequent infective agent.

Summary

1. The evidence favouring the view that some aetiological correlation exists between rheumatic fever and chronic infective arthritis is discussed.

2. An investigation of 500 cases of acute and chronic "rheumatic" diseases is reported, with particular reference to the immunological evidence of previous haemolytic streptococcal infection. Agglutination and anhaemolysin estimations, and intracutaneous and intravenous tests for sensitivity to the haemolytic streptococcus indicated that previous haemolytic streptococcal infections had been more common in patients with "rheumatic" diseases than in a control series of healthy individuals comparable as regards age and social circumstances.

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REFERENCES

- ¹ Poynton, F. J., and Paine, A.: *Lancet*, 1900, ii, 861 and 932.
- ² Dawson, M. H., and Tyson, T. L.: *Journ. Lab. and Clin. Med.*, 1936, xxi, 575.
- ³ Davidson, L. S. P., and Goldie, W.: *Reports on Chronic Rheumatic Diseases*, 1936, No. II, p. 1, H. K. Lewis and Co., London.