EXPERIMENTAL OBSERVATIONS ON THE AETIOLOGY OF RHEUMATIC FEVER

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In spite of continued research the pathogenesis of rheumatic fever remains a problem of much complexity. In the pursuit of its aetiology during the past 60 years, intensive bacteriological studies have been carried out, metabolic disturbances have been considered, allergic mechanisms have been incriminated, the role of heredity, dietary deficiency and a host of other factors have been investigated, but all with equivocal results. No matter from what angle the problem has been viewed, most workers have been unanimous in the opinion that rheumatic fever is in some obscure manner related to streptococcal infection, and that if this relationship were understood, the evolution of the disease might be elucidated.

Since rheumatic fever is a condition which presents a characteristic pathological picture, an important approach to the investigation of its aetiology has been the attempt to reproduce the disease in the experimental animal. It is generally accepted that the Aschoff nodule is a specific lesion, peculiar to rheumatic carditis, and from time to time there have been claims that the process has been duplicated experimentally by a variety of procedures. Recently, interest has been renewed in the experimental approach to the study of the pathogenesis of rheumatic fever, and it may therefore be of value to survey briefly the various experimental observations which have been made.

Bacterial Hypothesis

Most of the early work was devoted to the isolation of various organisms from the rheumatic patient, and attempts were made to reproduce the disease by inoculation of animals with these bacteria. In 1891 Achalmé discovered a bacillus in the blood of a patient succumbing to rheumatic fever, which on injection into animals caused death from septicaemia but not a true picture of acute rheumatism. His work was supported by Thiroloix (1896) who isolated a similar organism, and inoculation into rabbits produced what he claimed to be the typical picture of rheumatic fever.

In 1900 Poynton and Paine described a diplococcus in eight successive cases of acute rheumatism, an organism which had previously been isolated by Wassermann *et al.* (1899), and which

was accepted by many for some time as the causative agent. They supported their claims to its specificity by animal inoculation which yielded cardiac lesions, with vegetations on the valves, pericarditis and arthritis. They demonstrated the diplococci in the affected tissues, but the absence of Aschoff-like lesions was considered of no significance, for as they pointed out 'to rely on their presence as a criterion of acute rheumatism would narrow the horizon of acute rheumatism down to a single element in morbid histology.' Even in 1924 Coombs pleaded acceptance of the diplococcus rheumaticus. He felt that no one who had examined carefully the experimental lesions produced by animal inoculation with the diplococcus could fail to be struck by their similarity to human rheumatic carditis. He believed that any differences observed were due to the fact that it was not yet known how to reproduce in animal experiments the actual steps by which the organism gains access to the cardiac tissues in the human subject.

With the failure to isolate consistently the micrococcus of Poynton and Paine, and in view of the clinical observations on the apparent close relationship of various types of streptococci to rheumatic infection, this group of organisms became the subject of intensive research. It would serve no useful purpose to describe the various attempts made to establish the streptococcus as the direct cause of rheumatic fever. Briefly, it may be stated that many different types of streptococci were isolated from rheumatic patients during life and at autopsy, and in addition Small (1927) described a new specific type, the streptococcus cardioarthritidis. Intravenous inoculation of animals with these organisms produced lesions of the heart and joints, and opinion was divided as to their significance. Coombs, Miller and Kettle (1912), Clawson (1925), Small (1928) and Belk *et al.* (1928) were impressed with the resemblance which the experimental lesions bore to rheumatic carditis, whilst Thalheimer and Rothschild (1914), Topley and Weir (1921) and many others felt there was no true similarity.

From a careful study of the experimental cardiac lesions described by these workers it seems evident

that the condition they frequently reproduced was bacterial and not rheumatic endocarditis. Many of the organisms used by them were post-mortem contaminants or the result of agonal infection or transient bacteraemias, and others were derived from cases of a septic rather than rheumatic nature. Some of the animals died in the early stages of the experiments, undoubtedly from septicaemia. The presence of large vegetations on the valves, embolic lesions in the heart and other organs, the 'stuffing' of the blood vessels with cocci and the demonstration of organisms in the tissues all indicate an infective condition of this type. A further cause for confusion in the interpretation of experimental results was the lack of control material and the failure to appreciate the frequent occurrence of spontaneous interstitial myocarditis, a condition which was encountered and described by Miller (1924) in his attempts to transmit rheumatic fever to guinea pigs and rabbits.

The whole question of a direct relationship between streptococci and rheumatic fever was extensively investigated by Gross, Loewe and Eliasoph (1929), who were entirely unconvinced by the alleged rheumatic-like lesions hitherto produced in the experimental animal by these organisms. In their own experiments they injected a great variety of streptococci into many species of animals and used a great variety of procedures. They failed to reproduce any lesion which resembled the rheumatic process, a conclusion which they believe held true for all the work previously reported in the literature.

Virus Hypothesis

It has long been suggested, as in connection with so many other diseases of uncertain aetiology, that the lesions of rheumatic fever are produced by a virus. In 1912 De Vecchi reported the development of a myocarditis, which he regarded as similar to that of rheumatic fever, by inoculating animals with bacteria-free blood from patients suffering from acute rheumatism. Attempts to confirm this work by Miller (1924) failed, only the lesions of spontaneous myocarditis being encountered. Similar negative results were obtained by Gross, Loewe and Eliasoph (1929), who inoculated seven different species with blood, plasma and exudates from patients suffering from rheumatic fever.

In 1935 Schlesinger *et al.* obtained suspensions of virus-like particles by centrifugation of pericardial and pleural exudates from patients dying from rheumatic fever. Such bodies, however, were found in non-rheumatic exudates by Cole (1935), and Eagles *et al.* (1938) tested their infectivity in monkeys both alone and in combination with streptococci, but failed to produce any

significant myocardial lesion. Much doubt was cast on the virus theory by the suggestion of Eagles and Bradley (1939) that the so-called virus bodies in rheumatic exudates were not true elementary bodies but had their origin in tissue and blood elements arising under abnormal physical conditions, such as obtain in rheumatic fever. The contention, therefore, of Schlesinger and his co-workers has failed to be supported by subsequent investigations, and the virus theory has been more or less discarded.

Vitamin C Deficiency

It has been shown by Findlay (1923) that guinea pigs, on a diet deficient in vitamin C, succumbed to a smaller infecting dose of bacteria than animals fed on a complete diet. This led to extended studies on the changes in the heart in scurvy and in scurvy combined with infection. Rinehart and Mettier (1934) noted definite degenerative changes in the connective tissue of the heart valves and myocardium in scorbutic animals, changes which were accentuated when infection was present. Multinucleated cells were found around areas of eosinophilic hyaline material, and verrucous lesions were also noted on the valves along their line of closure. It was felt by these workers that in the animals subjected to scurvy and infection the myocardial lesions were fundamentally similar to the reactions seen in rheumatic carditis. In favour of their concept they pointed out that to explain rheumatic fever simply on the basis of streptococcal infection was inadequate in several respects, noticeably the unique pathology of the disease, the failure to reproduce it experimentally with simple streptococcal infection and finally the lack of uniformity of the type or strain of organisms found associated with it. With a concept of vitamin C deficiency as the essential background for rheumatic fever, the need for a strain specific infection would appear unnecessary.

Schultz (1936) repeated their work and studied the cardiovascular lesions of chronic scurvy and chronic infection with the haemolytic streptococcus. Whilst valvulitis, with fibrinoid degeneration and an intense proliferative reaction was a feature of the experimental lesion in the heart, its occurrence was infrequent and showed only a slight resemblance to the rheumatic process. As Schultz (1938) produced similar myocardial lesions in guinea pigs affected with chronic focal infection while receiving large doses of thyroid extract or insulin, the question of the role of vitamin C deficiency in relation to rheumatic fever became less certain. He believed the important factor was the increased metabolic rate in scurvy during the course of infection. No conclusive evidence, therefore, has been presented as to the possible

part played by dietary deficiency in the pathogenesis of rheumatic fever, and the hypothesis has been abandoned by most workers since it has failed to be supported by clinical observations on vitamin C levels in the rheumatic patient and the effects of vitamin C treatment on the course of the disease.

Allergic Hypothesis

With the continued lack of proof that rheumatic fever is an infection of the heart, it has been suggested that the disease may be the result of hypersensitivity, and much evidence has accumulated in favour of this concept. Even the earlier workers, in their failure to reproduce the disease with bacteria isolated from the rheumatic subject, felt that perhaps the specificity of the rheumatic response depended not so much on the character of the infecting organism but was perhaps related to some individual mechanism of the rheumatic subject. For example Menzer (1902) expressed the belief that rheumatic fever was not due to any specific organism but was a particular reaction in a predisposed person to various microbes, especially streptococci. Such a theory lends itself to experimental proof, and this has been abundantly sought by many investigators.

Vaubel (1932), Klinge (1933) and Junghans (1933-34) sensitized rabbits with small doses of horse serum by various routes and claimed to have produced a cardiac lesion in every way similar to the specific lesion of rheumatic fever. The focal necroses in the myocardium and perivascular infiltrations of round cells described by them do not present the characteristics of rheumatic carditis, and Aschoff (1935) analyzing these and other experimental attempts to reproduce rheumatic fever, denied that any worker had so far succeeded in duplicating the morphological structure of the rheumatic nodule. In spite of this pronouncement the allergic theory has not been discarded but rather has been investigated more intensively in recent years. A great impetus to research in this direction has been given by the work of Rich and Gregory (1943) and their observations on the myocardial lesions incidentally found during the experimental production of polyarteritis nodosa.

These workers noted that when rabbits were sensitized to horse serum by the intravenous injection of a single large dose, or by a second injection following an initial sensitizing one, not only did they develop polyarteritis nodosa, but also cardiac lesions with the histological characters of the specific rheumatic granuloma. In the hearts of the experimental animals focal accumulations of cells, in some instances strongly resembling Aschoff bodies, were found in relation to the

myocardial blood vessels, and in addition to the presence of large mononuclears, multinucleated cells occurred in the vicinity of foci of degenerating collagen. The nodules were present in the valve leaflets, the endocardium of auricle and ventricle and in the septa of the heart. The lesions in the valve substance and valve angle produced projecting cellular proliferations, but no definite thrombus formation was noted. They were also associated with arteritic lesions of the coronary vessels. Rich and Gregory have demonstrated with adequate and convincing illustrations that the distribution of the lesions and their histological structure compare very closely with the human disease. Whilst the lesions are attributed to a hypersensitive reaction of the anaphylactic type no claim is made to have reproduced rheumatic fever as it occurs in man, but in view of the striking similarity they feel the results provide a fair measure of support for the view that the specific rheumatic lesions themselves may be manifestations of an anaphylactic hypersensitive reaction.

Their experimental work has been repeated by Fox and Jones (1944), Hopps and Wissler (1946), McKeown (1947) and Ehrich *et al.* (1949) with more or less confirmatory results. More and McLean (1949) obtained cardiac lesions by the same method but were reluctant to accept them as the equivalent of Aschoff nodes. Localized granulomatous foci were found in the valve cusps, but in their material the histopathological change which most resembled an Aschoff nodule occurred in a control animal. Alston *et al.* (1947) were unsuccessful in producing any cardiac lesion whatsoever following the method outlined by Rich and Gregory.

A study of the lesions of experimental serum carditis reveals similarities to rheumatic carditis which are undoubtedly more striking than any hitherto observed. The distribution of the lesions and their cellular structure show a close resemblance to the human Aschoff nodule, though whether they are identical is a matter of dispute. Those who question the role of hypersensitivity in rheumatic fever point out that the experimental lesions encountered in serum carditis, whilst produced by hypersensitivity of the anaphylactic type, are much more similar to the lesion complex of serum sickness and polyarteritis nodosa and fail to find any true resemblance between the experimental granuloma and the Aschoff nodule. It is even suggested by some that the tremendous doses of antigen used may actually produce reactions in vessels as a result of direct injury rather than by an actual immune response. Furthermore, the apparent specificity of the rheumatic lesion has been advanced as an argument against the role of hypersensitivity.

Saphir (1941) believes that those who support the allergic theory must discard the Aschoff body as the specific histologic entity of rheumatic myocarditis, otherwise it cannot be assumed that the Aschoff body signifies merely a hyperergic reaction of the patient to a non-specific cause. Yet from the morphological standpoint most workers are agreed that rheumatic carditis is a specific disease.

On the other hand, those who favour the idea of hypersensitivity believe that in the rheumatic subject the allergic state is part of an abnormal immunological mechanism, and the interreaction of antigen and antibody in certain selective sites such as the connective tissue of the heart leads to the production of the specific lesions. The nature of the sensitizing agent is uncertain, but it is felt that there is much evidence in favour of the haemolytic streptococcus or one of its products. In view of the frequency of streptococcal infections it is obvious that the development of rheumatic carditis does not depend only on the character of the infecting organism but on some individual reaction of the rheumatic subject or some peculiarity of the vascular mesenchyme. The alteration in the 'soil' might be explained on the basis of hypersensitivity.

Wissler *et al.* (1947), who studied the effects of various horse serum fractions in the production of carditis, and found that alpha and beta globulins were the most effective, suggested that in rheumatic fever the infecting organism or one of its products may render one or more of the patient's serum proteins antigenic. As it was found in experimental serum carditis that massive doses of protein were required, it would indeed seem that alteration in the patient's proteins by infection would be a more likely mechanism of sensitization than by bacterial protein alone. The possibility of autosensitization has also been investigated by Cavelti (1947). Rats were given injections of mixtures of killed streptococci and emulsion of rat heart, and cardiac lesions developed superficially resembling rheumatic carditis. On the basis of his results he formulated an hypothesis of the genesis of rheumatic fever, assuming that streptococcal products combine with components of the host's tissues and the specific antibodies produced react *in vivo* with the antigen in the tissues. On the other hand Bauer (1946) failed to find any consistent lesions of the heart which resembled Aschoff nodules in rats treated with anti-rat-heart immune serum.

It will be seen that most of the methods used in experimental attempts to reproduce rheumatic fever in animals have shown little relation to the probable mechanism of the naturally occurring disease. Of special interest, therefore, is the work

of Murphy and Swift (1949), for in certain respects their experimental procedure follows the pattern of the disease encountered in man. They induced successive cutaneous focal group A streptococcal infections in rabbits, each caused by a serological type heterologous to those previously used. The hearts of some of the rabbits showed myocardial Aschoff-like nodules, a variety of lesions of the cardiac blood vessels, granulomatous endocarditis and valvulitis and occasionally localized pericarditis. The overall histopathological picture in these rabbits bears a very close resemblance to that of human rheumatic carditis and differs from the lesions of serum carditis notably in the absence of arteritis in the coronary vascular system. The production of these experimental lesions is probably also the result of hypersensitivity, and may be attributed to the 'conditioning' of the tissues brought about by repeated streptococcal infections. Whilst, therefore, these experiments support the idea that the lesions of rheumatic fever may be the result of acquired hypersensitivity, many of the observed clinical facts suggest that the rheumatic patient shows an abnormal susceptibility, expressed in the mesenchyme of his cardiovascular system and joints, to the acquisition of this state of hypersensitivity.

Just as with asthma, there would appear to be certain familial trends in rheumatic fever, and it may well be that the inheritance of a particular 'soil' has much importance in the evolution of the specific lesion recognized as rheumatic fever. This idea that the nature of the 'soil' is as important as the aetiological agent in determining whether or not rheumatic fever may develop is perhaps supported by the work of Selye. This author claims to have reproduced in the experimental animal a carditis, arthritis and arteritis structurally resembling that seen in acute rheumatic fever by lyophilized anterior pituitary extract, mineralocorticoids and renal pressor substance. This led him to suspect that acute rheumatism is primarily a disease of maladaptation due to deranged or excessive hormonal response to various stressors. An increase in corticoid production, though advantageous for resistance to stress, may defeat its purpose as the resulting endogenous overproduction of corticoids may elicit the pathological manifestations of rheumatic fever. He believes that the stressor agent is frequently the preceding streptococcal infection and the rheumatic lesions the outcome of an abnormal adaptive response of the adrenal cortex. In support of this concept Darrow and Miller (1942) showed that a myocarditis could be produced experimentally in rats by daily subcutaneous administration of desoxycorticosterone. The lesions of muscle necrosis and fibrosis in the myocardium show little similarity to

rheumatic carditis. In a repetition of this experiment, however, Selye and Rentz (1943) observed granulomatous foci in the myocardium which they accepted as the experimental counterpart of Aschoff bodies, but the illustrations provided are not entirely convincing.

Selye further asserts that clinical confirmation of his view is afforded by the therapeutic effect of ACTH and cortisone in rheumatic fever, and that the remarkable results are due to the provision of adequate amounts of glucocorticoids which apparently counteract the effects of excessive mineralo-corticoid activity. Exogenous administration of protein is also capable of eliciting the general adaptation syndrome and therefore the lesions of serum carditis might be attributed to this mechanism. It has been found that these lesions are inhibited by cortisone (Rich, 1950; McKeown, 1951), but since the effective dosage of this substance in the experimental animal was so large, it would seem that its action is pharmacological rather than physiological, and takes place at a cellular level, possibly by altering cell permeability or interfering with enzyme systems. Its mode of action may in effect be regarded as a nonspecific desensitization, but the whole subject requires further investigation and study.

Conclusions

In the search for the aetiology of rheumatic fever every known method of investigation has been utilized. The almost general failure to culture bacteria from the lesions, the lack of constancy of any particular species of bacteria in those reports where culture has been claimed

successful and the failure to reproduce the disease by injection of such organisms rule out the usual role of bacteria in this condition. The search for a virus has also failed, and inoculation of rheumatic exudates into animals has produced no comparable lesion.

A review of experimental work suggests that the only lesions reproduced in animals which bear a histological resemblance to the specific rheumatic Aschoff nodule have been obtained by rendering these animals hypersensitive. Reactions of the anaphylactic type occurring in the collagenous tissues of the heart are of granulomatous nature, and the problem remains as to whether they are, in fact, Aschoff nodes or merely granulomas of similar appearance. If the clinical association of streptococcal infection of the upper respiratory tract and the occurrence of rheumatic fever is accepted then it may well be that the specific carditis develops as the result of an acquired hypersensitivity to the proteins of such streptococci. Sensitization to streptococci can readily occur, and experimentally in rabbits has led to the development of cardiac lesions bearing a marked resemblance to those of the human disease. There is evidence that some patients, possibly on a genetic basis, are more readily rendered hypersensitive than others, and it is suggested that rheumatic fever is the product of these two factors: (1) the inheritance or acquisition of a mesenchyme which is readily sensitizable; and (2) the development of hypersensitivity to the products of the streptococcus. It may be that the state of endocrine balance may also influence the ease with which the tissues can be sensitized.

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