THE ÄETIOLOGY OF RHEUMATISM

By WALTER M. LEVINTHAL, M.D., F.R.S.Ed.

(Bacteriologist, Royal College of Physicians’ Laboratory, Edinburgh)

The pathology of rheumatism has achieved remarkable progress during the last thirty or forty years owing to the discovery of three basic facts. The first is the definite recognition that the rheumatic lesion is localised or at least originates in the mesodermal apparatus of the body; whether rheumatism manifests itself as arthritis or fibrositis or neuritis, whether the skin or a blood vessel or a visceral organ appears as the predominant site of the disease, it is always the connective tissue of the involved organs which is the point of attack. The second fact is the generalised character of the disease; even if one single organ or a limited area appears to the patient and to the clinician as the sole affected part of the body, rheumatism is a systemic illness. The third fact concerns the morphological pattern of the rheumatic tissue damage; the discovery of the Aschoff nodule (1904) was the starting-point of this research. The rheumatic granuloma, however, represents but the second stage of the alteration and is preceded by a hyperacute exudative swelling of the ground substance and the fibril bundles (Frank, 1912; Talalajef, 1921; Klinge’s “fibrinoides Frühinfiltrat”). The secondary immigration of cells into this “early infiltrate” forms the granuloma with its central necrosis and surrounding inflammation, and may be followed and finally heal by the proliferation of fibrous tissue and the formation of a minute rheumatic scar.

It is this feature of a specific mesodermal reaction with its developmental sequence, observed in all rheumatic conditions including gout, which has forced upon an ever-increasing number of investigators the opinion that all forms of acute, secondary chronic and primary chronic rheumatism in their protean multi-formity belong to one nosological entity. Final conclusions, however, cannot be drawn from mere pathological studies on tissues which have at their disposal only a limited range of reaction to a variety of irritants. A valid conception of a nosological entity is based upon the evidence of a common causation. The last word rests with the solution of the ætiological problem.

No enthusiasm for one or another ætiological claim can obscure the fact that the essential cause of rheumatism is still
a matter of contention. The conception to be put before the reader of this article remains tentative. It seems to the writer the best working hypothesis capable of explaining all the available data.

Unavailing Researches

A brief review of two unsuccessful approaches to the rheumatological mystery may clear the path. When in gout the deposits of uric acid were discovered, it seemed simple and convincing to explain that disease as the disorder of a metabolic function. Apart from the mistake of calling the deposition of urates, which are a digestive end-product in man, a metabolic dysfunction, it is now realised that the retention of uric acid is not the cause of gout, but a secondary phenomenon, comparable to the calcium deposition in certain tuberculous lesions. The analogous attempt to attribute other or all rheumatic diseases to metabolic causes was a sterile speculation, although it must be borne in mind that factors of metabolic disturbance may accompany and precipitate any systemic disease.

More propitious and durable appeared the bacteriological hypothesis of rheumatism, initiated more than fifty years ago by the recognition of the close relation between tonsillitis and rheumatic fever. A number of different bacteria, but chiefly streptococci, have been proclaimed as the specific cause of rheumatism, which thus was included in the group of infectious or infective diseases. Lately, the failure to demonstrate with any regularity a definite micro-organism at the site of the lesion or to find a rheumatogenic toxin has for some time side-tracked the research into the virus field. This line of research received a few years ago a fresh impetus from the discovery of a transmissible polyarthritis in rats (Collier) and the demonstration of an asterococcus (an organism similar to the causal agent of pleuropneumonia in cattle), isolated from affected rats and capable of producing the condition experimentally. Almost a sensation was created with the publication by an eminent American investigator who reported the isolation of such an asterococcus from mice injected with exudates from a case of rheumatic fever. The claim was solemnly withdrawn at the Annual Meeting of the American Rheumatism Association in 1940 at New York. The author was now satisfied that the organism, a widespread parasite of rodents, had originated from the inoculated mice and not from the patient. This impressive American symposium deserves to be commemorated
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as a landmark in the bacteriological history of rheumatology. From all quarters a complete breakdown of every attempt to tackle acute or chronic rheumatism from a bacteriological angle was emphasised, whether the research had been focussed on bacteria, such as streptococci, on staphylococci, or on viruses. Indeed, a universal dirge was sung at this meeting over the burial of a long and most laborious period of Ætiological research on rheumatism, summarised in the declaration of one speaker: “These totally negative reports of to-day are in the nature of a retraction, but that too is a really positive contribution to the subject.”

It is cheap to be a prophet after the event, but I may quote from an article published more than a year before the American meeting, where anticipating the failure of my own virus investigations on rheumatoid arthritis I drew attention to two arguments operating a priori against the probability of the virus hypothesis: “The first is the difference between any virus-induced lesion and the rheumatic granuloma. Every virus lesion shows as the primary change a hyperplastic cell reaction, usually followed by an exudative necrotic destruction. The basic pathological feature of primary fibrinoid degeneration in rheumatism followed by invasion of cells and secondary formation of a granuloma is inconsistent with everything known hitherto of any virus infection. The second objection concerns the strange selective affinity for the connective tissue which the supposed virus would have to possess. It is this specific localisation, the recognition of the mesenchyma as the point of attack, which should guide every Ætiological research.”

The Conception of Rheumatism as an Anaphylactic Disease

There remains abundant evidence that infection is closely connected with rheumatic disease, and, conversely, that rheumatic symptoms may occur in the course of many infectious diseases. It was this knowledge that led Weintraud as early as 1913 to an entirely new conception, first applied to rheumatic fever and later extended by others to the whole group of rheumatic diseases. Weintraud assumed that the disease is not due to a specific micro-organism, but to a specific reaction of the host to any invasion by a foreign protein, whether living or dead. His short paper comprises nearly all the details which his successors...
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have brought forward in favour of the idea that rheumatism is an anaphylactic condition. The essential point of this conception is the interpretation of the rheumatic syndrome as a reaction of hypersensitive tissues to the agent that has specifically sensitised the cells.

Since Weintraud's pioneer article much pathological and experimental evidence has been collected to support the hypothesis. Before 1913, Friedberger, quoted by Weintraud, was the first to show that an arthritis can be produced by the intra-articular injection of horse serum in rabbits, provided the animals have been specifically sensitised. Klinge (1933) and Sonnenberg (1934) have demonstrated with the same technique the appearance of inflammation and degenerative tissue changes not only in the injected joint, but also in remote organs such as tendons, blood vessels, muscles, the myocardium and the endocardium. A great stimulus came from the work of Roessle and his school (from 1914 on), who studied the histological pathology of the local reactions in sensitised animals at many sites of the provocative injection (Erfolgsinjektion) and discovered the striking fact that the damage selectively affects the mesodermal apparatus and shows a type of inflammation closely resembling the classical rheumatic granuloma with its three developmental stages. Gerlach's histological investigation of the Arthus phenomenon, the anaphylactic skin reaction of the rabbit, is an example of this research.

While these studies were confined to the examination of the anaphylactic reaction in directly inoculated tissues, more recent experiments, chiefly by Klinge and his many co-workers, have been focussed on the development of disseminated anaphylactic effects after intravenous injection of foreign substances in sensitised animals. These are the main findings extracted from numerous publications. The sequence of events is exactly the same after either mode of inoculation, local or intravenous, with the self-evident difference of localisation, for the attack from the general circulation produces anaphylactic reactions in many and sometimes in all parts of the hypersensitive system. Secondly, certain factors have been determined that enable the experimenter to direct the attack after intravenous injection at will to chosen areas, a result to be discussed later in connection with the problem of localisation in rheumatic diseases.
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The Mechanism of Anaphylaxis

Thus by a vast amount of investigation and experiment a picture of the anaphylactic lesion, confined to the mesodermal system, developing in three characteristic stages, has been established which bears the closest resemblance to the rheumatic lesion. The interpretation of the phenomena follows the lines laid down by leading authorities such as Dale, Doerr, Zinsser, and now universally accepted. The first direct contact of a tissue with a foreign protein or proteid, called antigen, if non-toxic and harmless as such, produces no manifest reaction of the tissue cells and leads only to slow resorption, cleavage and digestion of the antigen. The contact of the same kind of tissue with the same substance gives rise to a violent reaction, however, if the tissue has had previous experience with the particular antigen and so has acquired a greater ability to deal with it. This increased digestive capacity is due to specifically acting ferments or ferment-like functions, called antibodies, formed during the previous contacts in certain cells which belong to the mesodermal system and are found in all parts of the body as undifferentiated elements of the connective tissues. Whatever their anatomical position they all have in common the function of antibody production. Aschoff was one of the first who recognised the functional entity of these cells, and he grouped them together under the name of reticulo-endothelial system. A primary contact of these cells with an antigen, producing no visible pathological reaction, stimulates the characteristic response, the formation of the corresponding, specific antibody. It is obvious that the first portion of the newly produced antibody adheres to the productive cells themselves; only when the production exceeds the cell capacity of storage are the surplus amounts detached from the cells to appear free in the circulation. If after the development of the antibody the antigen is introduced again, an entirely new situation is encountered and a series of new events follows. Whenever and wherever an antigen meets the corresponding antibody, an instantaneous interaction between these two substances takes place, a combination and mutual fixation, followed by a reaction similar to or identical with the well-known precipitation which we observe in our test tubes under such conditions. The older hypothesis (Friedberger) that this combined product of an innocuous antigen and an innocuous antibody constitutes a poison (anaphylactotoxin) has been abandoned. No
toxic effect of such an antigen-antibody compound *per se* can be demonstrated, unless the reaction occurs inside tissue cells. The modern science of anaphylaxis has generally accepted this intracellular localisation of the antigen-antibody clash as the salient point of the anaphylactic phenomenon. Not a toxic chemical product, but the purely physical effect of the intracellular reaction is the irritation that damages the cell and initiates its inflammatory response. The irritability of the cell to an antigen, originally tolerated without ill effect, has received the appropriate name of *hypersensitiveness*. This, then, is the simple and shortest definition of tissue hypersensitiveness: *Those tissue cells are hypersensitive to a given antigen which contain the corresponding antibody.* The irritation becomes manifest, if and whenever the antigen gains access to the sensitised (i.e., antibody-equipped) cell. The ensuing inflammation, the response to the physical irritation by the intracellular antigen-antibody clash, is the anaphylactic reaction.

Originally (Richet) the term was applied to the dramatic phenomenon of shock produced by the intravenous injection of the antigen in a specifically sensitised animal. This type of reaction, however, represents but the extreme instance of a mechanism conditioned by exactly the same factors which govern any milder and more protracted form of hypersensitive reaction.

The death of a guinea-pig in anaphylactic shock is due to the sudden intensive and extensive irritation in the bronchioles, but actually the reaction occurs in all parts of the sensitised organism, for example in the uterus and the intestines (as demonstrable *in vitro* by the Dale and Massini methods) or in the liver. This irritation of the liver mesenchyma is immaterial for the guinea-pig, but is responsible for anaphylactic collapse and death in the dog. In fact, the anaphylactic irritation after intravenous injection of the antigen occurs in the whole of the sensitised organism, but the fatal issue is only related to that small sector of the general reaction which concerns the so-called shock organ, different in different animal species. In man, the rarely fatal anaphylactic shock gives evidence of the participation of many, if not of all organs, cardiovascular apparatus, lungs, intestines, central nervous system, etc. The vehemence of these shocks is caused by the suddenness and intensity of the effect if the antigen inundates the whole organism. No immediate and dramatic effect is produced by the same antigen if only minute amounts reach the sensitised tissues, but the inflammation following a
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repeated or continual influx indicates the successive irritations which could be properly called anaphylactic micro-shocks.

The more usual name for such local and mitigated manifestations of the anaphylactic reaction is allergy. A number of objections to the term allergy and allergic diseases could be raised on historical and etymological grounds, but no great harm would be done if only the word were strictly confined to the specific phenomenon of intracellular antigen-antibody reaction and were not applied in the loose way of present fashion to sundry kinds of selective sensitiveness. The misuse of the fashionable word need not go as far as with the old lady who had to leave London in the time of the air raids because she felt so "allergic to bombs"; but even within the medical profession we find the name allergy applied to certain chemical idiosyncrasies in which too little is known of their real nature. It is with an eye on such and other misuses of a perfectly legitimate scientific notion that the ambiguous term allergy is avoided in this paper.

Anaphylactic hypersensitiveness depends upon cell-fixed antibodies. These antibodies are the result of previous contacts with the corresponding antigen which has stimulated the mesodermal or reticulo-endothelial system to the specific response. The next step in this argument is therefore the conclusion that every contact with an antigen must lead to sensitisation of the antibody producing tissue cells. By far the majority of such contacts are due to dissolved microbial substances in the course of infections. This assumption is, indeed, borne out by the facts. In the course of every infectious disease there arises a specific tissue hypersensitiveness, demonstrable, for instance, by skin tests. It starts soon after the infection; in acute diseases it outlasts the presence of the infecting micro-organism for a considerable, but variable, period and disappears with the gradual elimination of the antibodies which are no longer produced in the absence of the antigen; it persists permanently, if the antigen persists, as in chronic infections. It is important to emphasise once more that this specific hypersensitiveness is strictly confined to those tissue elements which are concerned with the function of antibody production and storage. Anaphylaxis is uniquely a feature of the reticulo-endothelial system.

Does such mesodermal sensitisation constitute a condition of general hypersensitiveness? Obviously only if a second condition is fulfilled. The intracellular antigen-antibody reaction is only possible if the antigen reaches the antibody-containing cells.
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Artificially such an access can be forced by a direct local injection. Under natural conditions, however, an antigen has no avenue to most tissues except by way of the circulation. This seems to be easy of achievement, but in fact it is not. The analysis of a typical case of typhoid fever or the observation of an experimental rabbit subjected to a course of injections with horse serum makes that clear. The specific antibody (anti-typhoid here, anti-horse there) is gradually produced in the cells of the reticulo-endothelial system, but these production centres do not retain the whole amount of their output to store it as cell-fixed antibody (Ehrlich's sessile receptor); they cast off a portion and pour it into the circulation (Ehrlich's free receptor). Now visualise the sequence of events in a system equipped with fixed and circulating antibodies, when the antigen enters the body fluids and starts its journey to the tissues. All the way along it meets the antibody, combines with it, is fixed and arrested within the circulation so that not a trace of antigen escapes and reaches the cell-stored antibody.

This, then, is the second condition for the establishment of general hypersensitiveness; the absence of free antibody in the circulation. "Absence," of course, describes the extreme case of a quasi 100 per cent. condition for anaphylaxis. The quantitative factor is essential. Whenever the amount of free antibody is insufficient to neutralise the total amount of circulating antigen, that portion which escapes and makes contact with the antibody in the cells gives rise to an anaphylactic tissue reaction.

The name for the fully developed state of antibody equipment in all parts of the system, tissues and body fluids, is immunity. Derived from the clinical observation of specific resistance against the infective or toxic aggression of a micro-organism, the term is equally applicable and, indeed, applied to every form of counter-action against a foreign substance by means of antibodies. We "immunise" a rabbit against horse serum. Sensitisation is an intrinsic part and stage in every immunisation. The hypersensitivity of the reticulo-endothelial cells is an inseparable feature of immunity, but the general hypersensitiveness or the anaphylactic condition is characterised by the particular distribution of the antibodies with a prevalence in the mesodermal cells and a deficiency in the circulation.

Rheumatism and Anaphylaxis

The conception of rheumatism as such an anaphylactic condition was based on clinical intuition (Weintraud) and pathological
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and experimental observation (Roessle, Talalajeff, Klinge), showing the correspondence between the rheumatic and the anaphylactic lesions in tissue affinity, development and morphology. The basic serological feature of anaphylaxis, the typical distribution of antibodies, has but rarely and in an indirect way received attention from rheumatologists (Swift's experimental studies on the distribution of antibodies after different modes of immunisation, Coburn's illuminating observations on streptococcal antibodies in rheumatic fever). Direct evidence of this anaphylactic antibody distribution in patients with chronic rheumatism has been contributed by comparative precipitation and agglutination tests of serum and joint fluids (Levinthal, 1938).

It is clear that the hypothesis of rheumatism as an anaphylactic condition leaves no room for the assumption that one specific microbe is responsible for the disease. No particular bacterium can be regarded as the specific causal agent of any rheumatic condition. Many observations and tests, however, point to the predominant part played by streptococci in almost all cases of acute rheumatic fever and in many cases of chronic rheumatism. In some cases a rheumatic arthritis may develop in the course of a chronic gonorrhœal infection—not to be confused with the infection of joints in cases of gonococcal arthritis. Any infection with its influx of antigenic substances from the site of the bacterial depot may produce rheumatic manifestations, provided that the process of immunisation does not proceed to the full equipment of the body in all its parts, tissues and fluids, with antibodies, but is arrested half-way at the stage of sensitisation. It is obvious, moreover, that this state of hypersensitivity is not confined to invasion by a living micro-organism. The antigenic effect of any foreign protein that enters the circulation on an individual with the peculiar type of response leading not to immunity, but to hypersensitiveness, is bound to produce rheumatic disease. The acute attack of rheumatic fever is related to the infective agent of the preceding tonsillitis; the insidious and slowly progressing development of a chronic rheumatic disease points to the persisting influx of an endogenous antigen, originating at the site of a chronic infection. The explosive onset of gout is more consistent with the assumption of an exogenous antigen, for example an element of the food, in such persons who through a breach in the intestinal epithelium absorb antigenically acting substances before their digestive cleavage and denaturation.

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All these conditions have in common not one specific causal agent, but the specific factor of a sensitised host, deprived of the protective barrier of freely circulating antibodies to prevent the intracellular antigen-antibody reaction and subsequent anaphylactic inflammation of mesodermal tissues.

**The Problem of Localisation in Rheumatism.** — If the rheumatic tissue damage is due to the effect of a circulating, evenly distributed antigen on antibody-containing cells scattered through all the regions of a sensitised body, the question arises why the disease manifests itself in different cases at different sites. Here a rheumatic fever affects chiefly the joints, there the heart. Chronic rheumatism appears as arthritis, as neuritis, as fibrositis of the muscular apparatus or one single muscle. What is the reason for this elective localisation of the rheumatic lesion? The very striking Auer phenomenon has shed a revealing light on the problem. The experimenter is able to localise at will an anaphylactic tissue reaction after intravenous antigen injection and to concentrate the attack in a predetermined area. The Auer phenomenon is as follows: in a sensitised rabbit no visible reaction occurs after intravenous injection of a small amount of the antigen; but if in the period of antigen circulation one skin area—for example, an ear—is temporarily congested by xylol, a violent anaphylactic inflammation and necrosis, an Arthus phenomenon, results after some time on the spot of the transient artificial hyperaemia. The application of a great variety of thermic, traumatic, chemical irritants is capable of steering the attack of the circulating antigen to any selected part of the sensitised mesodermal system. The explanation is obvious. The common factor in all these operations is the production of a temporary local hyperaemia with dilated capillaries, stasis, retarded rate of blood flow, and an increased permeability of the endothelial lining in the blood vessels. Short-lived as this reaction may be, it suffices to concentrate the circulating antigen in a circumscribed area and to open here the blood-tissue barrier. The accumulated antigen diffuses from the blood stream into the surrounding tissue.

The parallelism with the localisation of rheumatic symptoms is most convincing. The tenderness of the heart in a growing child; traumatic, postural, occupational strains on joints; the irritation by a draft of cold air on a neck muscle, are familiar examples of those factors which determine the localisation of a rheumatic attack. However, it must be borne in mind that these
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adjuvant irritants direct only the brunt of the attack. As emphasised in the introduction, no isolated localisation tells the whole story of a rheumatic disease, and the experienced clinician, as well as the pathologist, will also detect the minor signs of the systemic dissemination.

The Cause of Anaphylactic Sensitisation in Rheumatism

The anaphylactic explanation of rheumatism appears to supply the best interpretation of the disease and all its conditioning factors, but is it much more than the substitution of one riddle for another? Why is it that one individual becomes immunised under the antigenic impact of a foreign substance, while another is sensitised, the antibodies being exclusively or predominantly located in the cells? Only a convincing answer to this question would offer a real solution of the ætiological problem of rheumatism. An approach from a simple quantitative angle suggests a satisfactory solution (Levinthal, 1938 and 1939).

Immunisation and sensitisation are phenomena not qualitatively, but merely quantitatively different, sensitisation representing a state of imperfect immunisation. Three chief groups of individuals can be distinguished, differing quantitatively in their capacity of response to any immunising stimulus.

Group I is characterised by a more or less complete debility of the antibody producing system, either constitutional or temporary under the strain of paralysing factors such as intoxications. Individuals of this type perish as helpless victims of general sepsis following infections.

Group III, at the other extreme, is the ideally vigorous type with fully developed capacity for antibody production. The prompt and abundant response not only checks at once the spread of an infection, but equips the whole organism with a surplus of antibodies, overflowing from the centres of their manufacture into the circulation, sufficient to deal with and to dispose of any amount of persisting antigen. A perfect immunisation is the result of this full capacity of defence.

In Group II the response is of an intermediate order. The patient neither completely fails to react nor is he able to proceed to the state of perfect immunity. Individuals of this type, too, become finally immunised as far as the specific protection of the tissues is concerned, but the antibodies, more sluggishly and less
amply produced, remain chiefly confined to the cells without a surplus for the circulation. It must be stressed that even such an imperfect immunisation is quite sufficient to overcome the specific infectious disease. A typhoid fever ceases to be typhoid fever, a streptococcal infection is no longer the typical streptococcosis. An entirely new pathological condition has been created, namely the state of anaphylaxis, due to the same antibodies which have achieved the recovery from the original disease. They have established the hypersensitiveness of the reticuloendothelial system to the antigen which gains access to the tissues because unchecked by freely circulating antibodies. These “second diseases” are essentially identical whatever infective organism or other antigen may have initiated the original immunising impact.

Obviously this partial inability of the mesodermal apparatus, too, can be constitutional or temporarily acquired under the influence of secondary factors such as malnutrition, climate, strain, endocrine disorders, physical and mental trauma, or housing conditions. All such precipitating factors do not directly act upon the disease, but indirectly by way of their debilitating effect which weakens the antibody-producing system and incapacitates the carrier of a chronic antigen depot from proceeding to the state of perfect immunity.

The difference in the individual response to an antigen is a fact well-known to experimental pathologists. In a discussion on active immunisation at the Royal Society of Medicine (1941) Maclean reported the common experience with animals where in spite of careful selection from a healthy and well-kept stock a failure of 10 per cent. has to be expected. He amplified his statement by observations on human beings gathered in several series of tests, partly in collaboration with Fleming. In a set of healthy adults similar in age, sex, and living conditions, when tested with a tetanus toxoid, 20 per cent. responded at least 20 times as well as the minority, and 2 to 5 times as well as the average. In every prophylactic experiment a few are found who appear to make no immune response to the antigens administered and these poor responders to one antigen are poor responders to other antigens. Maclean concludes from numerous experiments that about 10 per cent. of human beings will be poor responders, 70 per cent. will be average responders, and 20 per cent. will be good responders.

I have tried in a small number of rheumatic patients to demon-
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strate directly the characteristic slowness and incompleteness of the antibody response. The opportunity presented itself in connection with unspecific vaccinations for therapeutic purposes by means of a yeast vaccine. A preliminary skin and serum test with a yeast extract proved by its negative result the absence of any yeast antibody at the beginning of the experiment. A course of subcutaneous injections with a yeast vaccine was performed, and the time was determined at which (1) the skin test became positive, and (2) the precipitating antibody appeared in the serum. A number of most useful but rare cases afforded a still better opportunity to observe the anaphylactic distribution of the newly produced antibody in direct relation to the rheumatoid condition. The knee fluid aspirated at the outset of the yeast vaccination and ascertained to be as free of yeast precipitin as the serum, slowly accumulated again during the vaccination and could be retested simultaneously with the serum. While the skin tests became positive to the yeast antigen after a few vaccine doses, the first serum precipitin appeared in some cases only after several months and in poor quantity; similarly, precipitin and agglutinin in the knee fluid preceded the appearance and exceeded the amount of the antibodies in the serum.

All my studies on natural antibodies such as antistreptococcal or experimentally produced responses to a yeast vaccine were confined to patients suffering from chronic rheumatism. I have had so far no opportunity for comparative tests of serum and joint fluid in fresh cases of primary rheumatic fever who may show the phenomenon of an anaphylactic antibody distribution in a particularly striking way.

Acute Rheumatic Fever

A problem perplexing at the first glance is raised by the contrast between the course of acute rheumatic fever and the insidious and progressive development of rheumatoid arthritis. How different appears, from the onset to the end, the clinical aspect of the two diseases attributed to the same aetiological factor. To say that the one disease is the type of rheumatism in the juvenile organism and the other characteristic of the adult is no explanation and, moreover, not quite consistent with the facts. Rheumatoid arthritis has been observed, though rarely, in children; rheumatic fever may occur, though not often, at an advanced age. Still, age remains a conspicuous factor and
gives the clue for the following interpretation. The first contact with an antigen raises the antibody curve from zero to increasing values. The period of the critical antibody distribution, creating the state of general hypersensitiveness and associated with the rheumatic reaction, is reached with dramatic suddenness at a time when the serum is still completely void of antibodies. The average adult, on the other hand, has lived for years with many organisms in a well-balanced and undisturbed symbiosis by dint of a more or less perfect immunisation, until at a later period his weakened system gradually loses the capacity of re-producing the necessary amount of antibodies to keep abreast with the antigen trickle from focal depots. Here the phase of the critical antibody distribution is reached by a slow decrease of the serum antibody, and the decisive deficiency in the circulation is established step by step. This interpretation is strongly supported by the observation that all rheumatic symptoms occurring in the course of acute infectious diseases with their supply of a new antigen, and serum sickness after sero-therapeutic injections imitate the type of rheumatic fever and not of chronic rheumatism.

The literature on rheumatic fever, old and recent, confronts us with another puzzle. There is a striking discrepancy between the ultimate failure of all bacteriological search on the living patient—witness the eloquent verdict of the American Conference in 1940—and the claims by a number of authors to have isolated with regularity haemolytic streptococci from articular, cardiac, and other lesions studied in post-mortem examinations. I want to be unmistakably clear in my argument. I do not doubt in the least the validity of those observations. I agree with the investigator of such fatal lesions in heart, pericardium, etc., who sees in them the indubitable manifestation of infection. But I ask, is that still "rheumatism"? Let us agree that here is a clear-cut picture of streptococcal sepsis, as we also agree on the nature of the initial streptococcal tonsillitis. Although primary infection may be the indispensable condition of a rheumatic attack in a predisposed patient, the disease itself no longer bears any resemblance to an infective process. If the long and painful struggle of the rheumatic patient terminates in a septicæmic breakdown, he is no longer representative of the disease rheumatism. This terminal sepsis, however, must not be regarded as a complication similar to a streptococcal bronchopneumonia which terminates a case of influenza or measles. The rheumatic patient belongs to the
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intermediate group between the good and the poor responder. Here he fights his precarious struggle on the plane of imperfect immunity, just sufficiently immunised to prevent the invader from unchecked spread, but hypersensitive to the antigen that breaches the insufficiently fortified blood barrier. Here he fights, using up the scanty stock of tissue antibody in a system constitutionally weak and constantly weakened by the anaphylactic strain. Here he fights, often dangerously near the border-line between Group II and Group III. One more drain on his meagre resources, one more strain on his toiling reticulo-endothelial system, and the border is crossed. The shield of the rheumatic semi-protection is broken, and an unprotected carrier of infection succumbs to sepsis. I look upon the bacteriological findings in fatal cases of rheumatic fever as a confirmation of the views expressed in this paper.

Summary

Rheumatism, acute and chronic, is an anaphylactic disease with multiple lesions in the mesodermal system produced by continual antigen-antibody reactions in or on tissue cells. The antigen in most cases—gout is probably a conspicuous exception—consists of dissolved bacterial substances derived from the sites of subacute or chronic infection. The corresponding antibody is distributed in the faulty way characteristic of sensitisation with a prevalence in the cells and a deficiency in the blood stream. This deficiency permits the antigen or a portion of it to pass unchecked the antibody obstacle in the circulation and to reach the antibody-storing tissues.

The anaphylactic distribution of the antibody is due to its quantitatively insufficient output in a person with a constitutional or temporary debility of the reticulo-endothelial system; such a person represents an intermediate type between the sufficiently good responder to immunising stimuli and the complete non-responder. This debility of the antibody-producing system is the basic cause of rheumatism. All agents detrimental to health and the functional integrity of the body, such as disease, malnutrition, exposure, physical and mental exertion, act as indirect and precipitating factors, interfering with the function of antibody production and with the capacity of reaching or maintaining the state of perfect immunity.

It will be recognised that the border-line between Groups I and II, and between II and III, are threshold demarcations on a
continuous scale of gradation. An individual of Group III may under the strain of an overtaxed life glide off into Group II of potential rheumatism: a rheumatic patient may break down and sink into the abyss of complete defencelessness and perish in sepsis. One rheumatic patient may be favourably placed near to Group I and be capable of recuperation and cure, denied to a fellow sufferer who is struggling along close to the lower threshold line.

In the light of this, the anaphylactic theory of rheumatism and its implications, I shall endeavour, in an additional article, to survey therapeutic possibilities in rheumatic diseases.

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