THE RHEUMATIC DISEASES

THE AETIOLOGICAL PROBLEM OF RHEUMATISM

BY WALTER LEVINTHAL

Our knowledge of the pathology of rheumatism has undergone a remarkable advance during the last quarter of a century owing to the discovery of three basic facts. The first is the definite recognition that the rheumatic damage 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 bloodvessel or a visceral organ is the dominating site of the disease, it is always the connective tissue of the involved organ which is the point of attack. The second fact is the general character of the disease, even if in individual cases one single organ or limited area appears to the patient and to the clinician as the only affected part. Rheumatism is a systemic illness. The third fact concerns the rheumatic tissue damage itself in its morphological characteristics and development. The discovery of the Aschoff nodule (1904) was the starting point of this line of research. The specific rheumatic granuloma of mesodermal cells, however, represents only the second, subacute stage of the alteration. It is preceded by a hyperacute exudative stage, an oedematous swelling of the ground substance and the fibril bundles with central necrosis (Frank, 1912; Talalajeff, 1921; Klinge’s “fibrinoides Frühinfiltrat”). The secondary immigration of cells into this early infiltration forms the granuloma with its central necrosis and surrounding inflammation, which may finally heal up by the proliferation of fibrous tissue and the formation of a minute rheumatic scar.

It is this feature of a characteristic mesenchymal structure with its developmental sequence, observed in all rheumatic conditions including gout, which has brought home to an ever-increasing number of investigators the idea that all forms of acute, secondary chronic, and primary chronic rheumatism belong to one nosological entity, the protean appearance of which is not
THE RHEUMATIC DISEASES

greater than that of tuberculosis. Final conclusions cannot, however, be drawn from pathological observation of tissues which only have at their disposal a limited range of response to a variety of irritants. A true nosological entity is based upon the evidence of a common causation. The final decision rests with the solution of the aetiological problem.

No enthusiasm for one or other aetiological claim can conceal the fact that the essential cause is still a matter of contention. The conception to be put forward in this article remains tentative. For the time being this conception seems to the writer the best working hypothesis able to explain all the available data.

It may be useful to review briefly some of the older theories. The discovery of deposits of uric acid led to the belief that gout is a disease due to the disorder of a metabolic function. Setting aside the mistake of interpreting the deposition of urates, which are an end product in man, as a metabolic disorder, it is now realised that the retention of uric acid is not the cause of gout, but a secondary phenomenon. On the analogy of gout, efforts have been made to attribute all rheumatic diseases to metabolic causes. These speculations are scarcely worth further consideration, although it must be borne in mind that factors of metabolic disorder might occur secondarily in the course of any systemic disease or could exert a precipitating effect on its development.

Recognition of the close relationship between the initial tonsillitis and rheumatic fever and the elucidation of the aetiology of the former infection initiated some fifty years ago the bacteriological era of rheumatology. A host of different bacteria, first amongst them the streptococci, have been held responsible for the disease, which thus was included in the group of infectious or infective diseases (Mantle, 1886; Achalme, 1891; Fraenkel, 1892; Netter, 1892; Poynton and Paine, 1900, and many others). This hypothesis regarded the rheumatic tissue damage as caused either directly by microbial invasion or indirectly by some bacterial toxin. Even for rheumatic fever, still less for the chronic rheumatic diseases, not much of the original idea has survived, stranded by failure to demonstrate with any regularity a definite germ at the site of the tissue change. The modified conception of an attenuated pyæmia (Sahli, Singer and others) was of no great avail, although it introduced an important new factor into the reasoning. In an attenuated infection there must be something that attenuates. The attenuating factor can only
come from the infected host. Consequently the outlook of these authors was more than before directed towards the reaction of the macro-organism.

The most modern variety of the old infection hypothesis is the suggestion that a virus is responsible. Be it admitted that this question is still sub judice, yet there seem to exist two arguments which speak rather eloquently against such a probability. The first is the difference between any virus-induced tissue lesion and the rheumatic granuloma. As Rivers, one of the most outstanding experts in the virus field, emphasises, 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 aetiological research.

And yet, despite the ultimate failure of bacteriological research work in its efforts towards a final solution, there remains abundant evidence that infections are closely connected with classic rheumatic diseases, and that rheumatic symptoms may transitorily occur in the course of many, if not practically all, the classic infectious diseases. It was this knowledge which 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 rheumatism. The pith and pivot of this conception is the idea that the disease is not due to an external specific micro-organism, but to a specific reaction of the macro-organism to any invasion by a foreign protein, whether living or dead. The short paper by Weintraud states with remarkable lucidity nearly all the details which his successors have brought forward in favour of the idea that rheumatism is an anaphylactic condition. The much used and abused term of "allergy" will deliberately be banned from this article because of its ambiguity and vagueness. The useful paper by Freeman (1935) has discredited the word, but behind a word, even if wrongly or equivocally used, there sometimes lies a notion worth analysing. The essential point of the anaphylactic theory is the conception of the rheumatic syndrome as a
reaction of hypersensitive tissues to the agent which has specifically sensitised the cells.

Since Weintraud's pioneer article much pathological and experimental evidence has been brought forward to support the theory. Before 1913, quoted by Weintraud, Friedberger was the first to show that an aseptic arthritis can be produced by the intra-articular injection of horse serum in rabbits, provided the animals have previously been specifically sensitised. Klinge (1929) 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, bloodvessels, muscles, the myocardium and the endocardium. A great stimulus has been provided by the work of Roessle and his school (from 1914 on), who studied the pathomorphology of the local tissue reaction in sensitised animals at various sites of "Erfolg" injection, and discovered the striking fact that the damage selectively concerns the mesodermal apparatus and produces a type of inflammation closely resembling the classical rheumatic granuloma with its three developmental stages. The histological investigation of the Arthus phenomenon by Gerlach (1923) is an example of this line of research. The new term of "hyperergic inflammation," invented by Roessle and adopted by other writers, does not seem to stand a logical analysis of the facts, as will be seen later.

While these earlier studies were confined to the examination of the anaphylactic reaction in directly inoculated tissues, more recent experiments, chiefly by Klinge and his numerous co-workers, have been focussed on the development of disseminated anaphylactic effects after intravenous injection of foreign substances in specifically sensitised animals. There is not room here to review in detail the important results. It is enough to state that the sequence of events is exactly the same following both modes of inoculation, with the self-evident difference that the attack from the general circulation produces anaphylactic reactions in many and sometimes in all parts of the hypersensitive mesenchyma. The second result of these investigations is the elucidation of the secondary factors which are able to direct the attack after intravenous injection to chosen areas, a problem to be discussed later.

To interpret all these investigations and experiments it is instructive to start with the point of view of Roessle, which has
been accepted by Klinge, Talalajeff, etc., and is summarised in the term "hyperergic inflammation." It is known that the first contact of a tissue with a harmless foreign substance, called antigen, releases only a slow local process of resorption, cleavage and digestion which has been pertinently called normergic. It is known that the contact of the same harmless substance with the same kind of tissue gives rise to a violent reaction, if the tissue has had previous experience with the particular antigen in question and has developed a greater ability to deal with it. It is generally accepted that this increased digestive capacity is due to the formation of specifically acting ferments or ferment-like functions, called antibodies, during the previous contacts. No objection could be raised against the name "hyperergic reaction" as long as the application of the term remains reserved for the increased function of digestion. But where does the essential element of inflammation arise? Roessle apparently regards the normergic reaction as a sort of micro-inflammation and looks upon the exudative degenerative process in the sensitised tissue as a mere enhancement of the normal physiological response. Klinge, following the same line of reasoning, admits almost unconsciously on several occasions that "in the normergic organism many antigens are resorbed without or almost without any tissue reaction"; he states that the antigen (foreign protein) does not act at all in the normergic organism or releases no signs of inflammation whatsoever (italics mine). No doubt the sensitised tissue responds with increased or hyperergic activity on the antigen, but this hyperactivity concerns only the digestion and elimination of the foreign substance. Can the increase of a normal metabolic function give rise to the intensive tissue damage that we call inflammation? An inflammation is the response to an irritation. The presence of an antigen in a tissue which is hyperergically equipped with the means for its elimination cannot be regarded as such an irritant. Briefly, the hyperergic metabolic function of the specifically trained tissue is an incontestable fact, but not the cause of the inflammatory reaction following with regularity the contact of the antigen with the tissue in a previously treated organism. It is not this inflammation which can reasonably be called hyperergic.

All these inconsistencies disappear at once if we follow the interpretation of the anaphylactic phenomena developed by the modern experts—e.g., Dale, Doerr, Zinsser, etc. What happens
THE RHEUMATIC DISEASES

first and instantaneously, whenever and wherever an antigen meets with the corresponding antibody, is an interaction between these two substances, a combination and mutual fixation leading to 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 represents a poison (anaphylactotoxin) has been abandoned. No toxic effect of such an antigen-antibody product per se can be demonstrated, unless the reaction takes place inside tissue cells. The modern science of anaphylaxis has universally accepted this intracellular localisation of the antigen-antibody clash as the salient point of the phenomenon. Not a toxic chemical product, but the purely physical effect of the intracellular reaction is the irritation which damages the cells.

The fundamental difference between the conceptions of Roessle and Doerr becomes at once evident. For Roessle it would be irrelevant whether the meeting of antigen and antibody and the succeeding intensified digestion occurs in the cells or in the tissue fluid around the cells; for Doerr it is only the intracellular reaction which irritates the cells and stimulates their inflammatory response. This is therefore the simple and shortest definition of tissue hypersensitiveness. Those tissue cells are hypersensitive to a given antigen, or potentially anaphylactic, which contain the corresponding antibody. The anaphylactic irritation becomes manifest if and whenever the antigen gains access to the sensitised (that is, antibody-equipped) cell. The inflammation which follows, the response to the physical cell irritation, is not hypertergic, but anaphylactic.

The name "anaphylactic," although clearly defined above, requires one more word of explanation from the historical angle. Originally the term was only applied to the dramatic phenomenon of shock produced by the intravenous injection of a sufficient amount of antigen in a specifically sensitised animal. This type of reaction, however, represents but the extreme example of a mechanism conditioned by exactly the same factors which govern any milder and more protracted form of hypersensitive reaction. The death of the anaphylactic guinea-pig is due to the sudden extensive and intensive irritation of the mesenchyma in the bronchioli, but in fact the reaction occurs in all parts of the sensitised organism—e.g., in the uterus and the intestines as
demonstrable by the experimental arrangement of the Dale or Massini technique, or in the liver. This irritation of the liver mesenchyma is quite harmless for the guinea-pig, but is responsible for the anaphylactic collapse and death of the dog. In fact, the anaphylactic irritation occurs in the whole of the sensitised mesenchyma, 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. The rarely fatal anaphylactic shock of man gives evidence of the participation of many, if not all organs (cardiovascular apparatus, lungs, intestines, central nervous system, etc.). The vehemence of these anaphylactic shocks is only 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 repeated or continuous influx indicates the successive irritation which could be properly called anaphylactic micro-shock.

The quantity in space (amount) and time (once, repeatedly, continuously) is an essential factor governing the type and the clinical and pathological consequences of an anaphylactic reaction. It is equally obvious that the point of access has a decisive influence in determining the localisation of the anaphylactic damage. The sensitisation of a hay-fever patient is not confined to the subepithelial mesodermal skeleton of the respiratory mucous membranes (proof: skin test), but it is only here that the pollen antigen from outside comes into contact with the hypersensitive tissues. It will be seen later that a circulating antigen, too, can be restricted to special points of access, to a single part of the sensitised system, by the influence of non-specific secondary factors. The reader's imagination is invited to visualise all the possibilities of type, intensity and localisation of changes which are essentially of the same nature—namely, consequences of an anaphylactic cell irritation.

Hypersensitiveness depends upon cell-fixed antibodies. These antibodies are the result of previous contacts with the antigen which has stimulated the mesodermal system to the specific response. The next step in this argument is therefore the definite conclusion that every kind of contact with an antigen must lead to sensitisation of the antibody producing tissue cells. The great bulk of such contacts consists of microbial
invasions, whether saprophytic or pathogenic. Indeed, this theoretical conclusion is borne out by the facts. In the course of every infectious disease there arises a specific tissue hypersensitivity demonstrable, for instance, by skin tests. It starts soon after the infection; in acute diseases it outlasts the presence of the infecting germ for a considerable but variable period, and disappears by the gradual elimination of the antibodies which are no longer reproduced in the absence of the antigen; it persists permanently, if the antigen persists, as in chronic infections. It is important to emphasise that this hypersensitivity is strictly confined to those tissues which are concerned with the function of antibody production. Hypersensitivity is a unique feature of the mesenchyma.

Does such a mesenchymal sensitisation constitute a condition of general hypersensitivity? The answer is simple and clear: obviously only if a second condition is fulfilled. The intracellular antigen-antibody reaction is only possible if the antigen reaches the antibody containing cells. Artificially this access can be forced by a direct local inoculation. Under natural conditions, however, the antigen has no avenue to most tissues except by way of the circulation. This might appear to be easy of achievement, but in fact it is not. All the routes leading from the site of infection, where the microbes have settled, where they live, multiply, die and pour out their dissolved body substance (the antigen) into the surrounding tissue fluids—all these routes from the antigen source to the mesodermal tissue cells (the blood stream, the lymph spaces, the tissue fluid) do not allow free passage for the antigen. What does hamper and check the antigen and prevent its straight access to the cells and the cell-fixed antibodies? Let us look at a typical case of typhoid fever, or watch an experimental rabbit subjected to a course of injections with horse serum. The specific antibody (antityphoid here, antihorse there) is gradually produced in the cells of the mesodermal system, but very soon is also to be found freely circulating in the body fluids—e.g., in the blood stream. The production centres do not retain the whole amount of their output to store it as cell-fixed antibody (Ehrlich's sessile receptor), but cast off a portion of it and pour it out into the circulation (Ehrlich's free receptor). Now imagine the sequence of events in a system equipped with fixed and freely circulating antibody, when the antigen enters the body fluids and starts its journey to the tissues. All the way along it meets
with the antibody, combines with it, is fixed and arrested within the circulation, so that not a trace of unchecked antigen escapes and reaches the cell-stored antibody.

This, indeed, is the second condition for the establishment of general hypersensitiveness: the absence of free antibody in the circulation. "Absence," of course, is an exaggeration, describing the extreme case of a quasi 100 per cent. condition of anaphylaxis. The quantitative factor is decisive. 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.

It is advisable to introduce here the term for the fully developed state of antibody equipment in all parts of the system—immunity. Originally derived from the clinical observation of specific resistance against the infective or toxic aggression of a germ, the term is equally applicable and, indeed, applied to every form of specific counteraction against a foreign substance by means of antibodies. We "immunise" a rabbit against horse serum. Sensitisation is a legitimate part and stage in every immunisation. The hypersensitiveness of the mesenchyma is an inseparable feature of immunity, but the general hypersensitiveness or the anaphylactic condition is characterised by a particular distribution of the antibodies with a preponderance in the mesodermal cells and a deficiency in the circulation.

The conception of rheumatism as an anaphylactic condition was based on clinical intuition (Weintraud) and pathological and experimental observation (Roessle, Talalajeff, Klinge), showing the correspondence between the rheumatic and the anaphylactic lesion in localisation, development, and histomorphology. The basic serological feature of anaphylaxis, the characteristic distribution of antibodies, has but rarely and in an indirect way attracted the attention of rheumatologists. Out of a vast sea of serological studies on rheumatism following the familiar track of investigations on infectious diseases, as a legacy from the bacteriological era of rheumatology, only a limited number of publications relate to the anaphylactic problem. Prominent among them are the experimental studies of Swift and his co-workers on the distribution of antibodies after different modes of immunisation and Coburn’s illuminating observations on rheumatic fever. The sole direct evidence of this anaphylactic
antibody distribution in rheumatic patients appears to have been contributed by my results from comparative precipitation and agglutination tests of serum and joint fluid in cases of chronic rheumatism (Levinthal, 1938).

That a joint fluid is a suitable material for serological examination was shown by Nicholls and Stainsby (1931) in three cases of rheumatoid arthritis with a "surprisingly high" titre of streptococcal agglutinins, but no comparative study was attempted and no conclusion was drawn from the demonstration of the intra-articular antibody in this small series. Simultaneous tests of serum and joint fluid for agglutinins against streptococci were reported by Blair and Hallman (1935). A table summarising the results of five cases of rheumatoid arthritis, three cases of gonorrhoeal arthritis, three cases of osteo-arthritis, and nine controls contains in the first group one case with a serum titre of 640 and a joint-fluid titre of 5,120, but no attention is called to this striking contrast.

My serological investigations, carried out at the Royal National Hospital for Rheumatic Diseases in Bath from 1936 on, were based on agglutination and precipitation tests with a strain of *Streptococcus haemolyticus*, group A, type 3, isolated from the throat of a rheumatoid arthritis patient, and sometimes in addition with the mucous variety of a *Streptococcus haemolyticus*, group A, type 13, isolated from the sore throat of a non-rheumatic individual.

The technique of the agglutination tests followed the usual lines; 0·5 c.c. of an eighteen to twenty-four hours broth culture was mixed in ½-inch tubes with an equal amount of serum or joint fluid in falling dilutions and kept for two hours in a water bath of 56° C. with only one half or a little less of the fluid column submerged. The first reading, after slight shaking, was checked the next morning, the tubes having been kept overnight in the ice chest. Only the clear-cut formation of conglomerates was counted, a mere sedimentation, even if very marked in comparison with the homogeneous suspension in an always included negative control serum, being considered as negative. The broth used was the plain medium, prepared from tryptically digested veal meat by extraction at pH 6·9 to 7·1, containing the whole range of proteins from heat-stable but acid-coagulable albumen to the amino-acids (Levinthal, 1931, simplified since).

The same medium was used for the preparation of a very simple precipitation antigen. An abundantly grown twenty-four hours culture was spun, the almost clear supernatant fluid adjusted to pH 7·4 with N NaOH and filtered through a small Berkefeld V candle. A corresponding preparation from a strain of yeast (*Saccharomyces cerevisiae*) was used as a control. Besides the broth filtrate antigen, representing all the microbial body substances which go into natural solution during growth, a crude C su-
WALTER LEVINTHAL

stance (group A specific carbohydrate) was often employed, prepared from the same streptococci strains in the following way:

The washed sediment of a young broth culture (six to eighteen hours) and/or the growth of a twenty-four hours culture on blood agar (the agar being the same "albuminate tryptone" medium as the broth) were dissolved in a slightly warmed 10 to 15 per cent. aqueous solution of alkaline hypochlorite (antiformin substitute B.D.H.), the smallest total amount necessary for the complete solution of the cocci being used. The clear fluid was boiled up and acidified with HCl until the maximal precipitation of the protein was obtained. After standing overnight at room temperature and centrifuging, the clear supernatant fluid, which should be completely negative to the most rigorous sulphosalicyl test (saturated solution, first ring test, then mixed), was mixed with 30 volumes of acetone. After some hours the copious flocculent precipitate was collected by centrifuging, washed with acetone, dried and redissolved in the smallest necessary amount of distilled water. The readily dissolved substance, after discarding the trace of insoluble sediment, was precipitated with acetone and treated in the same way as before for a second time. The white powder was dried and stored in an exsiccator. A standard solution of this C antigen, \( y_{12} \) or \( y_{11} \) in a phosphate buffer pH 7·4, was diluted for the tests with saline to \( y_{02} \), \( y_{01} \) or more.

All the precipitation tests were done in 1-inch tubes with 0·2 c.c. of antigen and 0·1 c.c. of undiluted serum or joint fluid. Any alteration of this quantitative relationship, as increase or decrease of either the broth antigen (from 0·5 to 0·1 c.c.) or the serum (or fluid) (from 0·2 to 0·01 c.c.), carried out repeatedly in order to counter the possible objection that the condition of optimal proportions (Dean and Webb) had not been taken into account, has never changed the original result.

It goes without saying that serum and joint fluid have to be as clear as possible. Blood was withdrawn from the patient three and a half to four hours after breakfast, which gave almost invariably a serum free of chylous turbidity. The clarification of a joint fluid is more difficult. The aspirated fluid was kept in a large test tube for some hours or overnight at room temperature and spun after any coagulum had been broken up by shaking or whipping with a platinum wire. This procedure had to be repeated the next day, because even a perfect clarity after the first centrifugation proved too often to be fallacious. Although I always succeeded even with exudations of rather high viscosity in obtaining by this simple method a perfectly suitable fluid on the second day, I should like to quote the personal suggestion of Dr. Douglas H. Collins (Harrogate) to use a sand and paper pulp filter for the final clarification of a particularly obstinate joint fluid.

The serum or fluid was run along the glass wall into the antigen to form a separate layer at the bottom of the tube. At the first reading after twenty to thirty minutes in the incubator the formation and eventually the intensity of a ring was noted, serving as an inconclusive forecast for the final result. The tubes were kept overnight at 37° C. The amount and type of the precipitate was noted by the number of crosses, the sign \( \times \times \times \times \) indicating the formation of a compact disc, as characteristic of the precipitation of a carbohydrate. After this reading the tubes were spun for half a minute and the result checked macro- and microscopically. The
THE RHEUMATIC DISEASES

precipitates with the C substance consisted always of transparent confluent yeast-like droplets, the sizes of which corresponded with the intensity of the reaction. The broth antigen usually gave compact floccules composed of small granular particles or minute droplets. A loose friable flocculation, consisting of a fine network of filaments, characterises a protein precipitation (noted by the ordinary cross, +), as seen in the serum of some rabbits treated with infected subcutaneous agar clots, if tested with the broth antigen or pure broth as control.

It may be permitted to reproduce here Table III. from the above-mentioned publication, summarising a comparative study of serum and joint fluid from forty-four patients, thirty-nine of them representing the Group II. of rheumatoid arthritis (thirty-five) and acute infective arthritis (four), and the other five Group I., with a diagnosis other than rheumatoid arthritis—namely, two gout, two spondylitis, one doubtful rheumatoid on an old osteo-arthritis.

SERA AND JOINT FLUIDS COMPARED.

<table>
<thead>
<tr>
<th>No.</th>
<th>Fluid Positive, Serum Negative</th>
<th>Fluid Stronger than Serum</th>
<th>Both Equal</th>
<th>Fluid Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 = 100.0 %</td>
</tr>
<tr>
<td>II.</td>
<td>39</td>
<td>8 = 20.5 %</td>
<td>12 = 30.8 %</td>
<td>16 = 41.0 %</td>
</tr>
</tbody>
</table>

The results demonstrate the extreme case of an exclusive presence of the streptococcal antibodies in the joint fluid in 20.5 per cent. and their preponderance in the fluid over the serum in 30.8 per cent. more cases of Group II. The following interpretation was given:

"A synovial fluid being of dual origin, one part being derived locally from the intra-articular tissues, the other merely a serum- or lymph-derived transudate, it is obvious that substances demonstrable in a joint fluid while absent in the serum must come from the diseased and broken-up joint tissue itself. The serological results therefore point to a particular distribution of antibodies, to their presence in tissue cells and their absence or lesser amount in the circulation."

This direct evidence of an antibody distribution characteristic of the anaphylactic condition could be confirmed by skin tests with the same antigens. The significance, however, of skin tests
with an antigen of such almost ubiquitous occurrence as streptococci remains restricted. A positive result proves nothing more than a previous contact with the antigen, and is common to the sensitised and the immunised individual.

The scrutiny of the table suggests one more conclusion. It is seen that almost 8 per cent. of cases in the rheumatoid group show no serological relationship at all to the streptococci. On the other hand, in a series of tests with serum alone from 266 patients, comprising all groups of chronic rheumatism, a relation to streptococcal infections was also revealed in approximately 25 per cent. of cases of osteo-arthritis, fibrositis and spondylitis (as compared with 71·8 per cent. in the rheumatoid group, if only the serum results are considered). It is therefore evident that the results do not warrant the conclusion that streptococci are specifically connected with rheumatoid arthritis. In a number of cases in this group and in the majority of cases of fibrositis, spondylitis, etc., which are only topographically different from rheumatoid, but possess the same mesodermal localisation and histomorphology, other germs of chronic infection may be held responsible for the initial invasion which has developed into the consequent rheumatism. No particular microbe can be regarded as the specific causative agent of any rheumatic condition. Even a variety of antigenic factors may simultaneously and identically act in one and the same individual.

It becomes clear, moreover, that the state of hypersensitiveness is not confined to invasions by a living micro-organism. The antigenic effect of any foreign substance on an individual with the described type of response would be bound to produce a rheumatic or similar condition if the antigen were to attack the mesenchyma from the circulation. The insidious and slowly progressing development of a chronic rheumatic process points to the persisting influx of an endogenous antigen, originating from the site of chronic infection, either focal or superficial on respiratory and intestinal or other mucous membranes. The explosive onset of classical gout is more consistent with the assumption of an exogenous antigen which only enters the circulation occasionally—e.g., an element of the food. The connection of gout with alimentary factors, always suggested by clinical experience, includes, of course, the supposition that antigenically acting substances from the food are absorbed through a breach in
the intestinal epithelium before their complete cleavage and denaturation.

Gout, released by the systemic invasion of an exogenous antigen, appears in this conception as a link between the anaphylactic "attack diseases" (Aschoff) like hay fever and asthma, released by the local contact of an exogenous antigen with sensitised surface structures, and the insidious forms of rheumatism, released by the systemic attack of an endogenous antigen. They all have in common the specific factor of a sensitised host, deprived of the protective barrier of freely circulating antibodies to prevent the detrimental intracellular antigen-antibody reaction and consequent anaphylactic inflammation of mesodermal tissues.

There is not room here for more than a condensed reference to the important and most illuminating studies concerning the problem of the organ localisation. What is the reason for the elective localisation of the tissue damage when all parts of the organism are liable to attack by a circulating, evenly distributed antigen? The very striking Auer phenomenon was the clue and starting point for numerous experiments by Klinge and his co-workers (summed up by Roessle, 1936, and Klinge, 1937). It is possible to localise at will an anaphylactic tissue reaction after intravenous antigen injection and to concentrate it in a predetermined area. The so-called Auer phenomenon is as follows: In a sensitised rabbit no visible reaction occurs after intravenous injection of a small amount of antigen; but if during the period when the antigen circulates one skin area—e.g., one ear—is temporarily congested by xylol, a violent anaphylactic inflammation or Arthus phenomenon results after some time at the spot of the transient artificial hyperaemia. The application of a great variety of thermic, traumatic and pharmacological stimuli enables the experimenter to direct the brunt of the attack by the circulating antigen to a selected part of the sensitised mesenchyma. The explanation is obvious. The common factor of all these operations is the production of a temporary hyperaemia with dilated capillaries, stasis, retarded rate of blood flow, and an increased permeability of the endothelial lining of the blood-vessels. Transient as this reaction may be, it suffices to accumulate the circulating antigen in a circumscribed area and to open here the endothelial barrier, so that the concentrated antigen diffuses into the surrounding tissue. Roessle has proposed the
term "epigogy" for the phenomenon (ἐπίγεια, to guide down, to conduct).

It must be remembered that the very same phenomenon has been well known for many years (without the new word) from wide clinical and experimental observation of generalised infections, dating back to an experiment by Calmette and Guérin in 1901. The whole history of the relationship between local tissue injury and the localisation of generalised infections has been reviewed and enriched with new data by Findlay (1928), who suggests that the liberation of histamine by the injured tissue is the essential denominator of all the various chemical, thermal or mechanical stimuli which cause "(1) the primary and local dilatation of the capillaries, (2) a widespread dilatation of the neighbouring strong arterioles brought about through a local nervous reflex, and (3) locally, increased permeability of the vessel walls."

However, it must be borne in mind that these adjuvant irritants direct only the conspicuous 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 symptoms of the systemic dissemination.

The anaphylactic theory of rheumatism appears to supply the best explanation for all the protean traits of the disease and its conditioning factors, but is it much more than the substitution of one riddle by 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 mainly located in the cells? Only a convincing answer to this question would offer a real solution of the aetiological problem of rheumatism. An approach to this problem from a simple quantitative angle suggests a solution.

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

Group I. is characterised by a more or less complete debility of the antibody producing system which might be called anergic. This debility can be constitutional or temporary, under the influence 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 normal 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 production 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 which could be called panergic.

In Group II. the response is of an intermediate order. The patient neither completely fails to react nor is 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 tissue 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 specific infectious disease. An entirely new pathological reaction, no longer typhoid or streptococcal, or whatever the case may be, has been conditioned—namely, the state of anaphylaxis by virtue of the same antibodies which have caused the recovery from the original disease. They have established the hypersensitivity of the mesenchyma to the antigen, which gains access to the tissue because unchecked by freely circulating antibodies. These "second diseases" are essentially identical whichever infective germ or other antigen may have initiated the original immunising impact. The partial deficiency of the antibody producing system which is the basic factor responsible for this imperfect immunisation is neither anergic nor panergic, but could pertinently be called hypoergic. It seems a paradoxical result of this analysis that the term hypoergic offers itself for the condition which leads to the anaphylactic diathesis, contradicting the illogical concept of "hyperergic inflammation."

Obviously this hypoergic state of the mesodermal apparatus also can be of a constitutional or of a temporarily acquired nature, influenced by secondary factors such as malnutrition, climate, strain, endocrine disorders, physical and mental trauma or housing
WALTER LEVINTHAL

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.

I have tried in a limited number of patients to demonstrate directly this essential slowness and incompleteness of the antibody response. A preliminary skin test with the yeast antigen, mentioned above, proved by its frankly negative result the absence of any yeast antibody at the beginning of the experiment. A course of subcutaneous injections with a yeast vaccine twice per week was performed, and the time was determined at which (1) the skin test became positive, and (2) the precipitating antibody appeared in the serum. The result on one patient may be reported in comparison with a rabbit subcutaneously injected with the same vaccine. C. T. A. was a twenty-year-old man with an intensive rheumatoid arthritis of long standing refractory to all forms of treatment for a considerable time. Whereas his skin test became positive after the third injection, the first trace of a serum precipitation (\(\uparrow\)) was only obtainable after eighteen injections two months nine days from the start of the vaccination. It increased a month later after a total of twenty-four injections to a weakly positive result (\(\times\)). The rabbit, on the other hand, showed a strong precipitin response (\(\times\times\times\)) after the first four injections. It is proposed to pursue this promising scheme of investigation on a bigger scale, including all types of chronic rheumatism.

A last question arises concerning the contrast between the course of acute rheumatic fever and the insidious and progressive development of rheumatoid arthritis. In his serological studies of rheumatic fever Coburn comes to the conclusion: "In the rheumatic subject the development of the antibody response appears to be delayed." A similar conclusion was arrived at for rheumatoid arthritis in my paper before the Bath Congress. And yet, how different appears the clinical aspect of the two diseases from the onset to the end, apart from the dissimilarities in the topographical involvement. To say that one disease is the type of rheumatism in the juvenile organism, while the other is characteristic for the adult, is no explanation and, moreover, not quite consistent with the facts. Rheumatoid arthritis has been observed, although rarely, in children; rheumatic fever may
THE RHEUMATIC DISEASES

occur, although not often, at an advanced age. Still, the age factor remains a conspicuous element and gives the clue for the following interpretation. The first contact of an individual with an antigen raises the antibody curve from zero to increasing values. The period of the fateful antibody distribution associated with the rheumatic reaction is, as it were, reached from below. The average adult, on the other hand, has lived for years with many parasites in a well-balanced and undisturbed symbiosis by dint of a more or less perfect immunisation, until at a later period his weakened mesenchyma gradually loses the capacity to reproduce the necessary amount of antibodies and to keep abreast with the output from his antigen depots. Here the phase of the fateful antibody distribution is reached by a slow decrease of the serum antibody curve—that is to say, quasi from above. This interpretation is strongly supported by the fact that all rheumatic symptoms in the course of acute infectious diseases, supplying a fresh antigen, imitate the type of rheumatic fever and never of chronic rheumatism.

A glimpse may be thrown upon therapeutic experiences and possibilities in the light of the anaphylactic conception. It is evident that the natural or artificial elimination of the responsible antigen from the body interrupts with one stroke any rheumatic reaction. The transience of rheumatic symptoms in the course of acute infectious diseases is therefore partly explicable by the final disappearance of the antigen, partly by the fact that the anaphylactic state in these diseases is an intermediate phase in the process of immunisation before the appearance of the antibodies in the blood stream. In chronic infections the artificial removal of a septic focus (tonsils, teeth, inflamed gall-bladder) can only lead to the desired result if the removed organ contains the sole or at least the predominant source of the antigen, certainly a rare event. Even a full first success would be no guarantee against the recurrence of the disease at the very next occasion of a fresh infection.

The effect of gold, sulphur, protein shock, spa treatment, specific and non-specific vaccination rests with their stimulating influence upon the antibody producing system. Such influence is limited by the degree of reactivity left in the individual patient. Salicylates and calcium suppress temporarily the anaphylactic cell reaction, just as a general anaesthesia suppresses the anaphylactic shock.

A real cure of the rheumatic diathesis could only be expected
WALTER LEVINThAL

if a restitution of the antibody producing system were obtainable or a substitute therapy after the model of insulin were discovered, making up for the loss of a possible hormonal factor involved in the physiological function of antibody production.

My sincere thanks are due to the governors of the hospital for their generous support, and to the Medical Research Council for a grant-in-aid, which have enabled me to carry out this work.

REFERENCES

KLINGE, F. (1933): "Der Rheumatismus." Bergmann, Munich.
The Äetiological Problem of Rheumatism
Walter Levinthal

Ann Rheum Dis 1939 1: 67-85
doi: 10.1136/ard.1.2.67

Updated information and services can be found at:
http://ard.bmj.com/content/1/2/67.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/