appendicitis, but the more chronic variety—usually tuberculous—may cause symptoms less acute in character and spread over a longer time, so that confusion may arise, and it may not be possible to differentiate between the two conditions without operation. The adenitis may heal without having caused any symptoms, and may be discovered accidentally, as in a little girl operated on some time ago for recurrent appendicitis in whom, in addition to the appendicular lesion, were found a healed glandular lesion of the mesentery, an enteric intussusception, a Meckel's diverticulum, and a cystic right ovary.

6. *Foreign bodies*, such as shot, can lodge in the appendix, and are probably the cause of the pain and discomfort described. They can be seen by *x* rays; worms have also been found in the appendix at operation undertaken for similar symptoms. Stercoliths of large size may be associated with signs and symptoms of a chronic nature, but I have found them more frequently in acute cases, where they must, judging by their size, have been lodged for some time; and yet no history of any abnormality in the abdomen could be obtained from the patients till the acute attack started.

7. *Spinal and nerve conditions*—such as arthritis of the spine, psoas abscess—may cause pain in the right iliac fossa, but examination of the vertebral column should obviate error. Tabes should be ruled out as a routine measure.

8. *Carcinoma near the ileo-caecal junction* causes pain of a colicky character in the lower abdomen and right iliac fossa, but the age of the patient at the onset of the first symptom, the nature of the pain, and an investigation by barium enema may point to the diagnosis. If the diagnosis is in doubt, exploratory operation should be carried out without delay. Carcinoma of the appendix, or "carcinoid," has been found in a number of cases in which there were complaints of pain, etc., in the lower abdomen and the right iliac fossa. It is a rare condition: I have only had one case, and have unfortunately lost touch with it, so that I do not know whether the patient has improved as the result of appendicectomy. These cases usually run a simple course, but several instances are reported of secondary growths in the liver.

9. *Incipient hernia* in the right inguinal canal may cause pain in that region, and this may be confused with the pain of a chronic appendix.

DISCUSSION

My experience leads me to believe that the condition of chronic appendicitis does exist, and that it may follow an acute attack, or may not have an acute onset, but run a chronic course. It is not, however, a common condition, and its lack of definition in the clinical features makes me approach its diagnosis with caution, and take steps, where they are necessary, to exclude other lesions before reaching a conclusion. The history and general clinical examination are, I think, most important. The younger the patient the more probable it is that the appendix, if at fault, is the cause of his symptoms, and its removal will bring about restoration of function. In such cases I think incision through the right iliac fossa is justifiable and proper, and that an exploratory incision should not be used. For older patients, unless the diagnosis is almost certain, exploratory operation is probably better than the more limited operation.

If the appendix only is at fault, the operation results are good, and the patients soon return to normal health. Removal of the appendix for a lesion which is situated elsewhere can only bring the operation into disrepute, and the fact that such patients are secure from acute appendicitis in the future does not justify the procedure unless it is done specifically for that purpose.

There is great controversy as to whether a condition of chronic appendicitis does occur. The normal histology of the organ is also subject to discussion and varying opinions. It is said that as age advances, fibrosis takes place as a normal process, and that this is in no way connected with a chronic inflammation. Some pathologists agree that occlusion of the lumen by fibrous tissue and fibrosis of the walls point to chronic inflammation, while others state that these are only the usual processes of repair, and deny that there is a pathological basis for the diagnosis of chronic appendicitis. Others, again, say the fibrosis is due to disease of the sympathetic ganglia and Meissner's ganglia, and attribute the poor results which frequently follow appendicectomy to this condition. Radiologists are as variable in their views as pathologists, and there does not seem to be sufficient unity of opinion from *x*-ray examination to make the investigation a dependable diagnostic procedure. Surgeons, too, are not lacking in differences of opinion. Some say the condition must start with an acute attack, while others hold that it may be "chronic" from the beginning; still others deny its existence as a clinical entity. Many points of tenderness have been described, and many tests tried, but there is no general acceptance of them as cardinal signs of the condition.

SUMMARY

1. Chronic appendicitis may follow an acute attack, or it may have a gradual onset and run its course without any acute signs.
2. It is not a common condition, and the lack of a clear clinical picture makes its diagnosis dependent on the exclusion of other lesions.
3. Removal of an appendix, the seat of chronic inflammation, cures the patient, if it is the only lesion present.
4. The longer such an appendicular lesion is left unattended, the more probable is it that other lesions may develop, especially in the upper abdomen.

THE ANAPHYLACTIC BASIS OF RHEUMATISM

BY

C. E. JENKINS, M.R.C.S., L.R.C.P.

PATHOLOGIST TO SALFORD ROYAL HOSPITAL, ALTRINCHAM GENERAL HOSPITAL, STRETFORD MEMORIAL HOSPITAL, ECCLES AND PATRICROFT HOSPITAL, MANCHESTER EAR HOSPITAL, AND MANCHESTER BABIES' HOSPITAL

This paper is an attempt to survey the possible connexion between rheumatism and anaphylaxis, a phase of immunity in which, as Besredka has said, all the rules of immunity are made to stand upon their heads. The aetiology of the rheumatic group of diseases is now entering upon a fresh phase, and the fact is at last receiving common recognition that streptococci have a causal relation to the group. The bacteriological and immunological problems involved have not been understood by many clinicians, but it is unnecessary to direct attention to some of the absurdities produced. The present position is that streptococci and possibly other organisms are causally related, but that the relation is not of the simple order that would satisfy Koch's postulates.

THE ORGANISM

Skin tests have been made by many observers, and there is fairly good agreement that most patients are allergic to the streptococcal group. There is no satisfactory evidence that a specific organism is responsible, and Topley and Weir (1921) have shown that similar lesions can be produced in rabbits by a variety of streptococci. Wright (1926) caused endocarditis in rabbits

by repeated injections of non-haemolytic streptococci, each dose of which was not in itself toxic. The flora of rheumatic and normal throats was examined by Hitchcock (1928), who found that they were identical. Irvine-Jones (1928) obtained similar evidence, and found, further, that the rheumatic cases were skin-positive to their own streptococci and to those obtained from normal throats. A non-methaemoglobin-forming streptococcus described by Birkhaug was tested by Kaiser (1928), who found that 72 per cent. of rheumatic cases were skin-positive to it. The probable explanation of the claims and denials of streptococcal specificity lies in the close antigenic similarity of different members of the group, and the position may be assumed to be the same for rheumatism as for scarlet fever. In the latter connexion, McLachlan and Mackie (1928) found that there was a certain amount of common agglutination in all streptococci.

Streptococci have been isolated by blood culture, when large volumes are taken, but there is no proof of specific relation to the disease in the ordinary usage of the term. It has to be borne in mind also that the sterility of the blood is not that of the inside of a furnace, but is only relative—even in health.

In the bacteriological examination of a case one of the problems that arise is to determine whether the organism isolated is causal, or at least whether its antigenic structure is such that it could have induced the allergic state found. Skin tests of the autogenous organism, with certain stock strains and a good control, make this possible. The control should always be a sample of the uninoculated broth in which the organisms were grown. Antigenic overlap can be minimized to some extent by the conditions of growth of the culture.

It is appropriate in this connexion to consider the *Micrococcus deformans* described by Crowe, which is a variety of staphylococcus. This worker's conclusions, possibly erroneous, have been rather arbitrarily dismissed by critics who in some instances do not seem to be specially well qualified to express an opinion. In man the only feasible method of testing for anaphylactic specificity is the skin test: this in my hands has given, with proper controls, a higher percentage of positive staphylococcal readings than I had hitherto thought possible, and it is pertinent to recall that in all the published skin tests in arthritis the percentage of positive streptococcal results has been appreciably short of the centum. It does not seem to have occurred to most workers to try the staphylococcus at the same time.

THE ALLERGIC REACTION

Various distinctions have been drawn between allergy and anaphylaxis, but for the present purpose the two terms will be used indiscriminately. The antigen that produces anaphylaxis is known as a "sensitogen," and it is allied to, or identical with, the precipitogens.

It has been stressed by the Arthritis Committee of the British Medical Association (1933), and by others, that vaccines when given should be in exceedingly small doses, and most users of vaccines will agree that there is no disease in which overdosage can produce a more retrograde state in the patient. The observation is consistent with the allergic hypothesis. Let us contrast this with protein-shock therapy. A fairly severe systemic shock usually does the patient no ultimate harm, the reason being that he is not allergic to the foreign protein used. For a short period the clinical condition may be improved, then a relapse occurs and the treatment has to be repeated indefinitely: in the few cases where shock treatment can be held to be successful the result is obtained after the first injection. Before leaving the matter it is as well to state that another question—non-specific desensitization—has for a number of reasons no relation to protein-shock therapy. The nature of the general and prodromal signs and symptoms of arthritis deformans is of the highest significance. Tachycardia, irregular pulse,

localized sweating, adenitis, swelling and pain around joints, muscular tremors, leucopenia with a relative lymphocytosis, increased sedimentation rate of the blood, and asthenia, are all present, and all of them are to be found in the usual type of human anaphylaxis—serum sickness. The phenomena of anaphylaxis vary according to the species of animal; but in any given species the signs and symptoms are the same, regardless of the nature of the sensitinogen in operation. If the description of the general and prodromal features of arthritis deformans, as given by the Arthritis Committee and by various standard textbooks, be compared with the description of serum sickness by Kolmer (1923), Muir and Ritchie (1919), Zinsser (1922), and others, it will be found that the two are exactly interchangeable.

SUGGESTED EXPLANATION OF RHEUMATISM

Anaphylaxis is probably the most confusing branch of immunology, and it is necessary for the student to attune his mind to the anaphylactic concept. A suppositious example will illustrate the point. Intolerance to a drug means only that the individual develops the distinctive toxic picture with an unusually small dose, and the syndrome has nothing in common with drug allergy. The allergic syndrome of digitalis is high fever, adenitis, sweating, and swelling and pain in several joints. Bacterial anaphylaxis is considered by Amoss and Bliss (1927) to be an initial stage of general immunity, and Derrick and Swift (1927) concluded that it is an early stage of resistance in a localized focus, whilst general immunity is the response of tissues over a wide area to a reasonably maximum dose of antigen. Similarly, Bessau and Detering (1928) hold that specific cellular allergy is the primary reaction in immunity, circulating antibodies being a later effect. Nordman (1931) points out that the Arthus phenomenon offers an explanation of the endocardial lesions in acute rheumatism. Arthus (1903) found that repeated injections of sensitinogen into an anaphylactic animal gives rise to increasingly severe local reactions, which may pass on to necrosis; so that any original damage done by streptococci or their toxins during the early stage of infection may leave the damaged area open to attack by the circulating sensitinogen. The explanation implies, *a priori*, an original selective action by the organism: such is known to occur in man, because, during recovery from proved streptococcal septicaemia, a pyogenic infection of one or more joints is not uncommon. The observation of Arthus may have some relation to that of Auer (1930), who found that injury to the skin of a sensitized animal when antigen was in the circulation may produce a local allergic reaction due to the actual excretion of sensitinogen into the injured area. It could be inferred from this that once a joint is damaged a more or less continuous irritation is set up by the antigen in the blood, and a vicious circle is started which can be broken only by the removal or neutralization of the circulating antigen.

Since the anaphylactic syndrome is independent of the nature of the sensitinogen, it follows that there is nothing to prevent any organism causing the disease provided it is capable of producing allergy in man, and this may explain why cases are reported from time to time as being due to some bacterium not usually associated with the disease. A possibility that will not lessen the complexity of the whole question is that "rheumatism may conceivably be produced by the combined action of a selective toxin and a distinct sensitinogen. They may be derived from the same organism, or two species may be in action. The hypothesis is not very far-fetched because clinical anaphylaxis is almost invariably revealed during treatment of a bacterial disease by means of horse serum containing the appropriate antibody. A profound alteration in an animal's metabolism may induce some variation

in the anaphylactic syndrome peculiar to the species. Fleisher and Wilhelmj (1927) studied anaphylaxis in thyroidectomized guinea-pigs, and found that, although the operation did not influence the ease of production of shock in this animal, the syndrome was modified. In man, chronic villous arthritis is the only form of rheumatism in which thyroid deficiency is clearly suggested, and in which administration of thyroid recognizably benefits most cases. The clinical variation of this disease from the general type may constitute the parallel change.

The liability to allergy in general is a weakness of the host, inherited or acquired. That the actual allergic state to some particular substance is itself truly transmitted is very doubtful, since allergy in young infants has never been shown to have been transmitted by the father. Transmission through the mother has been recorded frequently, but this is probably due to passage of sensitogens through the placenta. Ratner, Jackson, and Gruehl (1927) find that antitoxins, precipitins, and sensitogens can permeate the human placenta, and believe it to be due to the fact that the layer separating the two blood streams is only one cell thick. A hereditary liability to anaphylaxis has been found in animals, and the adduced facts may explain why rheumatism is frequently a familial disease, and may also constitute an answer to the triumphant query as to why, if pyorrhoëa is a cause of rheumatism, every sufferer from the former disease does not also exhibit evidence of the latter.

TREATMENT BY DESENSITIZATION

There are two methods of desensitization. Non-specific desensitization has been induced by a number of substances, and a list of them is chiefly remarkable for the dissimilarity of its constituent members. They range from sodium chloride to proteins, and it is certain that if each of them in turn was tried upon a sufficient number of rheumatic cases a brilliant result would be effected by each—once. In animals they are neither reliable nor permanently successful: Isaacs (1928) finds that non-specific desensitization is successful in about 50 per cent. of guinea-pigs, and that the result disappears in about twenty-four hours. Specific desensitization is the alternative and rational method. It consists in treating the animal with the sensinogen that caused the condition. In the case of rheumatism that substance is the bacterial antigen in its crude form, or some modification of it that will stimulate the supply of specific antibodies. The inevitable inference from this is that some type of bacterial antigen is the cardinal line of treatment, and that all the drugs employed are but adjuvants to it. A point as to the selection of an immunizing antigen arises here. Toxoid, whilst free from toxicity, is known to be a good immunizing agent, and at first sight it might be preferred to toxin, assuming that the latter was the operating sensinogen; but if the precipitate theory of the mechanism of shock be accepted—and much modern work suggests that it is true—then there is no reason why shock should not be produced by either substance indifferently. The antibody is already present, and one introduces an antigen which can combine with it. Common toxicity may not enter into the question.

USE OF SHOCK-DEPRESSANT DRUGS

A certain number of drugs have long been known as depressants of anaphylactic shock—that is, they can mask the severity of any particular shock and may even abort it. None, however, have any influence upon the anaphylactic state itself. The animal is just as sensitive as before. Among these drugs are salicylates, aspirin, salol, antipyrine, some narcotics and anaesthetics, calcium, magnesium, bromides, iodides, and some resins. The *salicylates* in acute rheumatism illustrate the limitations of shock depressants. They lower temperature and make

the patient more comfortable, but they have no influence upon the incidence of subsequent endocarditis, a result which agrees with their role in anaphylaxis. The action of salicylates in experimental streptococcal arthritis in rabbits was studied by Davis (1915), who found that they had no effect in preventing endocarditis or the localization of organisms in the joints. Moreover, they did not affect the course of the infection once it was established. His results were confirmed by Fantus, Simmonds, and Moore (1917), and substantially so again by Swift and Boots (1923). *Salol* has a reputation as an intestinal antiseptic in allergic diseases of the skin, and has been used in rheumatism. Yet it can be shown that its bactericidal power in the intestine is negligible. Viewed as a shock depressant its occasional successes are understandable. (It is of interest to note that in serum sickness Kolmer recommends aspirin for the muscular and neuritic pains, and sodium salicylate with bicarbonate when the joints are involved.) In lowering temperature and abolishing joint pain and swelling, *atropine* hypodermically is more efficient than salicylates and is equally useless for true curative purposes.

Magnesium is one of the commonest constituents of spa waters, and it is a depressant of unstriated muscle, the reaction of which is one of the basic anaphylactic phenomena in all animals. But it is possible that its utility as a remedy does not end there. In man fatal cases of anaphylaxis permitting post-mortem examination are rare, but Dean (1922) found that the liver cells were much injured, and was able to confirm Weil's view that dilatation of the hepatic capillaries is an important factor in human shock. Parallel to that is the finding of Mendenhall, McClure, and Cate (1926) that magnesium sulphate in small doses is a true cholagogue, and it is therefore not unreasonable to suppose that the daily action of small doses may assist the liver in its resistance to anaphylactic irritation. The intake of great quantities of water, with some small proportion of dissolved salts, may also be advantageous, since Raulston (1927) has shown that during shock anaphylactic rabbits mobilize water and electrolytes from the tissues. It is believed that many of the simpler sensitizing agents, such as *iodine*, owe their effects to combining with a protein of the host, and in so doing altering it sufficiently to cause it to act as a foreign protein: this is supposed to be particularly true of *iodine*. Klopstock and Selter (1927) used diazotized *atoxyl* with serum, and considered that the mixture reacted with natural proteins to give a denatured protein changed enough to act as a foreign protein. (The activating agent of a shock can be very simple. Thus Smetana (1927) sensitized animals to haematoporphyrin and shocked them by exposure to sunlight.)

The bearing of the foregoing observation upon rheumatism is on the question of desensitization. It has been found by many workers that if a substance capable of sensitization be administered to an animal, anaphylactic to another sensinogen, a few hours before a shock dose of the animal's sensinogen is given, then the shock is frequently averted. This action may explain the beneficial effects of *iodine* in arthritis deformans, the action being one of non-specific temporary desensitization. However one chooses to regard the action of *iodine*, it is a fact that its beneficial effects are chiefly seen in the chronic infective diseases which are considered to have an allergic factor in their pathogenesis—namely, syphilis, yaws, tuberculosis, and disease due to the higher vegetable parasites.

CONCLUSION

The parallelism that exists between the syndromes of the two diseases—anaphylaxis and rheumatism—and between the drugs used in their treatment are, when itemized, far too numerous to be dismissed as a series of co-

incidences. There being no other theory that will account for all the phenomena of rheumatism and its treatment, I submit that the anaphylactic explanation must be accepted as the only alternative to a position that is no more than a contradictory muddle of mysteries.

A dictum of Kolmer is a fitting conclusion: "Under proper conditions it is reasonable to suppose that anaphylactic shock or shocks may occur during the course of a given disease, and that the effects of these may contribute to the lesions and symptomatology in no small degree."

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THROMBOSIS, EMBOLISM, AND THEIR TREATMENT

BY

GEORGE BANKOFF, M.D., M.S.

HONORARY SURGEON, ST. JOSEPH'S HOSPITAL, MANCHESTER

With the recent progress of surgery, especially in major operations, there has been an increase of thrombosis and embolism, constituting an ever-present threat to the success of such operations. With this fact in mind I conducted experiments directed towards an inquiry into the cause of these pathological conditions. The results have been published by the *Klinische Wochenschrift*, 1932, ii, 502. On account of the interest taken in this work I will set forth the method of treatment which I have found very successful in the practical application of the principles established therein.

THEORIES OF CAUSATION

Before entering into details of the treatment we must discuss briefly what is the origin of thrombosis, so that it may be determined in which patients the disease is likely to occur. On this point scientific opinion is divided into two main groups—one believing it to be due to bacterial infection, and the other to a special constitutional predisposition. The first group—the supporters of bacterial infection—have reported cases of thrombosis and embolism in which they have tried to prove conclusively that certain infectious diseases are the cause of the

thrombosis. In the majority of cases the cause of infection was attributed to such non-virulent bacteria as the organisms found in influenza, bronchitis, etc., and in cases in which it was impossible to demonstrate any definite organism it was explained that the disease was due to some unknown ultra-filterable virus. The principal advocates of the germ theory—Franke, Kuskow, Kinzel, and Pathy—while subscribing to it in a general way, differ slightly in their conclusions. Either they believe thrombosis to be a direct result of bacterial action or they think that the virus or its toxin affects the individual, producing irregularity in the blood circulation, hypotonia, and damage to the blood vessels, thus giving rise to thrombosis.

The second group deny that infection has any connexion with thrombosis. The supporters of this theory—Payr, Morawitz, and especially Rehm, who is its founder—believe that all patients affected by thrombosis belong constitutionally to one type. They call this condition thrombopathy, and emphasize that in all such cases the patients are found to have a special construction of the sympathetic nerve system. Some members of this group qualify their opinion by stating that thrombosis may be due, not necessarily to a permanent, but to a temporary, difference in this system. Others—Koenig, for instance—in cases in which no cause can be found for thrombosis, nevertheless deny it to be the result of an infection. It is not my intention to criticize this theory at length, but I believe from the experiments I have made that it is absolutely wrong to state that there is a special idiosyncrasy which gives rise to thrombosis, because, if this were admitted, it would be impossible to explain why a patient, operated on two or more times, on one occasion suffers from thrombosis and on another does not, and why the conditions for thrombosis are not present at each operation. If we admit that temporary damage to an organ can bring about thrombosis, why must we exclude damage from a germ? To explain further: if damage to the intima of the blood vessels can produce thrombosis, that damage may arise from bacterial action. It cannot therefore be denied that infection may be a direct cause of thrombosis. On the other hand, one cannot agree with the supporters of the germ theory who believe that thrombosis is due only to infection. There are many cases in which it is absolutely impossible to find any organism, and in which, on the contrary, it is easy to find some special organic construction. The presence of a non-visible germ in these cases is not an acceptable theory.

METHOD OF DETECTING LIABILITY TO THROMBOSIS

I now wish to emphasize my opinion that thrombosis can never be regarded as due to only one class of causes: it is a pathological state which can arise from different causes at any time the equilibrium of the patient is destroyed. (It is irrelevant to discuss here the aetiology of this destruction of the equilibrium.) I do not believe that all patients are liable to thrombosis. In order to be affected by this condition it is not enough to have present the causes for producing it. I divide patients into two groups. In the first and, fortunately, the largest are the patients who can never suffer from thrombosis, even if the organs are damaged. In the second group there will always be a risk without any external influences. In making my experiments my intention was to find a means of detecting which patients can be affected by thrombosis and which can not. I began to search for some agent which would produce definite symptoms enabling me to divide the patients into two groups: those predisposed to thrombosis, and those whom I believed to be immune to it. After long and involved experiments it was possible to demonstrate that by the hypodermic injection of thyroxine the reaction of each group was different.