been effected by a Christian mission. While such cases are exceptional, they illustrate the danger of a belief in early maturity which appears to have no foundation in fact.

In the case of boys, legislation for the protection of juveniles in employment should be closely related to the expected development and physical performance at a given age (Ellis, 1948). In Nigeria this applies particularly to the minimum age at which boys may emigrate to Fernando Po for work in the plantations. In educational grouping and in defining regulations with regard to school-leaving age, it may well be borne in mind that adolescence is not likely to be reached significantly earlier in Nigeria than in Great Britain.

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THE PATHOLOGY OF HYPERSENSITIVITY REACTIONS IN MAN*

BY

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The title of this paper could have been "The Pathology of the Allergic Reactions in Man," but for reasons that will be evident later I consider it best to avoid the term "allergy." In his book on diseases of the liver Himsworth said of the term "cirrhosis" that it "not only misleads by implying an entity whose existence is doubtful, but has become so worn and defaced by loose usage as to have lost all precision." The same might well be said about the concept of allergy, which nowadays is used as a collective term for various forms of hypersensitivity. In characterizing a reaction as allergic we have said nothing about the precise nature of that reaction. For a better understanding of the character of allergic diseases, however, it will be necessary to distinguish between the various types of hypersensitivity reactions. I must therefore first give an introductory survey of the various forms of these reactions.

Anaphylactic Shock

A well-defined type of hypersensitivity is, as is well known, anaphylaxis. It is characterized by shock occurring when the antigen is injected into the circulation of the

sensitized animal and by an immediate cutaneous reaction with weal-formation if it is injected into the cutis. The serum of the sensitized animal is precipitated by the antigen, and it is possible to transfer this hypersensitivity passively from one animal to another. The most important symptoms of anaphylactic shock are contraction of the smooth muscles and dilatation of the capillaries and smaller blood vessels. An anaphylactic reaction can be produced by a single injection of the antigen provided the dose is so large that sufficient antigen is left in the organism to react with the antibodies after their formation. A reaction of this kind often occurs in human subjects who have been injected with horse serum for therapeutic or prophylactic reasons. We call it serum sickness, and the symptoms are temporary pains in joints and muscles, temporary swelling of the joints, erythema, urticaria, purpura, angioneurotic oedema, etc.

If we sensitize an animal by repeated intracutaneous injections of the antigen at regular intervals the local reaction becomes stronger with every injection and finally the swelling ceases to disappear, haemorrhages and necrosis occur, and ulceration follows. This type of anaphylactic reaction is called Arthus's phenomenon. The haemorrhages are a sign of severe damage to the vessels, and necrosis is a result of this damage.

The same symptoms that characterize experimental anaphylaxis and serum sickness also occur in many hypersensitivity diseases in men. In American literature these diseases are often described as "atopic" hypersensitivity reactions. As is well known, the prototype of these is pollen hypersensitivity. One of the most prominent symptoms of anaphylactic shock is the contraction of the smooth muscles of the bronchi, where it is accompanied by dyspnoea. This symptom occurs in atopic hypersensitivity in the form of asthma. Besides the temporary cutaneous symptoms of serum sickness more chronic skin reactions sometimes occur in the form of eczema, particularly in children with hypersensitivity to food.

The antigen can be introduced by inhalation, through the digestive tract, or through the skin. This hypersensitivity is also transferable, as may easily be demonstrated by the Prausnitz-Küstner reaction. If the antigen is injected into the cutis there is rapid weal-formation as in anaphylaxis.

Drug Hypersensitivity

A special group of hypersensitivity reactions are those induced by a great number of substances of various kinds that are covered by the diffuse term "drugs." Many of these substances are not antigenic in themselves but become so only after having been conjugated with an albumin within or outside the body. These substances bring about two kinds of sensitivity reactions. The first is very like the atopic, the second more like the bacterial hypersensitivity reaction, which will be treated in greater detail later.

In the first type the sensitizing occurs through the respiratory tract, the digestive tract, parenteral injection, or epicutaneously, and the symptoms are similar to those occurring in serum sickness or in the atopic hypersensitivity diseases. In spite of this, however, it is usually not possible to produce an immediate reaction in the skin in the form of weal-formation by injecting the drug. Neither is it possible to demonstrate the hypersensitivity to drugs by the Prausnitz-Küstner phenomenon.

According to Chase the difference in this respect from the previously mentioned hypersensitivity reactions is due partly to the fact that the quantity of antibodies in the

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blood in drug hypersensitiveness is very small, and partly because it is not possible to perform a test with the antigen that produces the hypersensitiveness, as this antigen is formed only in the body. The latter difficulty, however, can be avoided, at least in certain cases, by conjugating the drug with an albumin *in vitro*.

In this connexion I would like to point out that in many cases the symptoms of hypersensitivity that occur in chemotherapy are not a reaction to the actual drug but a manifestation, provoked by the chemotherapy, of an already existing state of hypersensitivity. In these cases, therefore, the drug does not fill the role of antigen. The same is probably true of the great number of hypersensitivity reactions that have been observed in connexion with sulphonamide therapy. These reactions vary from mild symptoms like erythema and urticaria, or fairly serious symptoms like erythema nodosum and erythema exudativum multiforme, to very grave symptoms such as rheumatic pneumonitis and periarteritis nodosa. Several of my compatriots have proved that these symptoms often occur as early as one day after the treatment has begun, and consequently sensitizing to the drug in question cannot possibly have occurred.

The substances that bring about the anaphylactic type of drug hypersensitiveness can also produce a hypersensitiveness resembling the bacterial type. Clinically this type is manifested as contact dermatitis. Sensitization occurs through the skin, usually epicutaneously, and the clinical symptoms take the form of an eczema which appears when the sensitized skin is brought into renewed contact with the antigen. If the antigen is injected intracutaneously there is no reaction. If, on the other hand, the natural conditions are reproduced by the patch test there is of course a positive skin reaction. This reaction, however, does not appear immediately as in the atopic or anaphylactic type of hypersensitiveness, but only after 24 hours, like a tuberculin reaction or other hypersensitivity reactions of the bacterial type.

Haxthausen, in a series of very fine experiments, has established that the reaction is due to antibodies circulating in the blood. These antibodies cannot be transferred passively with serum. On the other hand Landsteiner, Chase, and Haxthausen have succeeded in transferring the hypersensitivity in another way. Landsteiner and Chase did this by means of suspensions of cells from peritoneal exudate produced experimentally in sensitized animals. Haxthausen did it by means of lymphocyte suspensions of thymus from sensitized animals: these were injected intraperitoneally into animals that had not been sensitized. Obviously the antibodies are in some way connected with the lymphocytes.

These facts provide a further resemblance between this type of drug hypersensitiveness and the bacterial type, which can be transferred in a similar way. Some investigations, however, also indicate a close relationship between the anaphylactic or atopic and the bacterial type of drug hypersensitiveness. Landsteiner and Jacobs have shown that certain substances give both a delayed and an immediate reaction, according to the way the antigen is introduced.

Bacterial Hypersensitivity

Finally, with regard to the bacterial hypersensitivity reaction, the prototype of which is the tuberculin reaction, it can, as is well known, be produced only by living or dead bacteria; but after sensitization the organism shows hypersensitiveness to the proteins of the bacteria in the form of a delayed reaction. If these proteins (for example, tuberculin) are injected into an animal it may be made

to react anaphylactically, with an immediate skin reaction. However, the typical tuberculin reaction which appears after 24 hours is obtained only if we infect the animal with tuberculosis or, with some difficulty, if we inject dead tubercle bacilli into it. It is known that tuberculin hypersensitiveness cannot be transferred passively with serum, but, as I mentioned previously, Chase and several others after him have succeeded in transferring the hypersensitivity by exudate cells, chiefly mononuclear, from sensitized to unsensitized guinea-pigs. Kirschheimer and Weiser have obtained similar results with suspensions of spleen cells.

All the evidence points to a profound difference between the hypersensitivity of anaphylactic type and bacterial hypersensitivity, as the former reaction seems to take place only in the smooth muscles and the endothelium of the vessels, whereas the latter seems to affect all the cells of the body. Our knowledge of this problem has been greatly increased by the experiments of Rich and his collaborators.

In order to prove that the anaphylactic hypersensitivity reaction takes place in the endothelium of the vessels, rabbits were sensitized with serum in the usual way, after which the antigen was injected into the cornea. This has no vessels, but nevertheless it contains antibodies derived from the surrounding circulation. There was no effect. If, however, the cornea of the sensitized animals was damaged so that vessels grew into it, and the antigen afterwards injected close to the vessels, there was a strong reaction with haemorrhages. Other experiments demonstrated a quite different behaviour in bacterial hypersensitivity. If tuberculin was injected into the cornea of non-tuberculous guinea-pigs there was only a slight reaction, whereas the cornea of tuberculous guinea-pigs treated in the same way showed marked changes and necrosis. Experiments with tissue cultures gave results which also support this theory.

It is clear, therefore, that a number of observations indicate a close connexion between the experimental anaphylactic reaction and some diseases in man. It may well be asked whether the pathological anatomy can give any support to the theory of such a connexion. This question must be unconditionally answered in the positive. The pathological anatomy of the anaphylactic reaction is now fairly well known, and damage to the endothelium of the vessels seems to be the most prominent change. In addition, very characteristic changes appear in the connective tissue. According to the theory held by Rich, that only the smooth muscles and the endothelium of the vessels are affected in anaphylaxis, the changes in the connective tissue ought to be secondary. There is, however, no conclusive proof that this is the case. All these changes are also found in various hypersensitivity reactions in man, as appears from works by Klinge, Laporte, Rich, and others.

Capillary Damage

The capillary damage has been described mainly by Rich. I would like to quote the following extract from his description of the capillary damage in rheumatic pneumonitis: "Focal necrosis of the capillary endothelium may occur, and the lumen may become plugged with a fibrinous or hyalin thrombus. Sometimes the capillary damage permits the occurrence of intra-alveolar haemorrhages. . . . Focal necrosis of the entire alveolar wall may occur where the capillary damage is severe. The lesions are decidedly focal, sometimes affecting only a segment of one capillary in an entire low-power field, though they often involve the vessels of a sufficient number of adjacent alveoli to produce confluent areas of consolidation." I would like to demonstrate a change of this kind (Fig. 1).

The section is from the lung of a 46-year-old woman who since the age of 15 had suffered from heart disease following scarlet fever. Three weeks before her death she became ill, with severe cough and dyspnoea. At the post-mortem examination mitral stenosis was demonstrated, with infarct-

FIG. 1.—Photomicrograph of foci in lungs showing characteristic changes of rheumatic pneumonitis.

like foci in the lungs. Microscopical examination of these showed changes characteristic of rheumatic pneumonitis with focal fibrinous thrombi in the heavily dilated capillaries and focal necrosis of the alveolar walls and some degree of intra-alveolar haemorrhage but very little exudate.

I have observed identical changes in the lungs of an old man who since childhood had suffered from various symptoms of hypersensitivity such as asthma, eczema, migraine, etc., and who finally died during an acute attack after he had been unconscious for 24 hours. This patient, however, also showed numerous pin-point haemorrhages in the white but not in the grey matter of the brain, which on microscopical examination appeared to be due to capillary changes that were in principle of the same kind as the ones I have just described and which are shown in Fig. 2. Here we see a small centre of necrosis surrounded

FIG. 2.—Photomicrograph showing pin-point haemorrhages in the white matter of the brain appearing to be due to capillary changes.

by a circular haemorrhage. A capillary runs through the circular haemorrhage and expands at the edge of the necrosis. Further along in the necrosis the wall is dis-

integrated and the lumen plugged by a fibrinous thrombus. The circular haemorrhage has naturally occurred because the capillary wall central to the thrombus has been so damaged that it has become permeable to red blood corpuscles.

Such capillary changes may be an explanation of the Arthus phenomenon, purpura, and, in their less pronounced forms, of erythema, urticaria, angioneurotic oedema, and swellings of the joints.

The changes in the larger vessels have, as we know, the character of periarteritis nodosa. It is here worth mentioning that Rich has produced periarteritis nodosa in rabbits by a single large dose of albumin. The most prominent changes in periarteritis nodosa are focal fibrinoid necrosis of the vascular wall, intramural and perivascular cell infiltration, and proliferation of the vascular endothelium which may sometimes be so pronounced that the whole lumen is plugged. Sometimes the proliferating endothelial cells take on the characteristics of giant cells.

If the above-mentioned theory is correct, that the vascular endothelium is the only organ directly affected in anaphylactic hypersensitivity, we must seek an explanation of the fact that the whole wall is damaged in this way in periarteritis nodosa. Here a theory presented by Schürman, MacMahon, and Doljansky to explain the vascular changes in malignant hypertension may be applicable. It is known that the vascular changes in malignant arteriosclerosis are also characterized by focal fibrinoid necrosis rather similar to the changes in periarteritis nodosa, which has induced some writers to assume that arteriosclerosis also may be a hypersensitivity reaction. There is hardly any difficulty in distinguishing between these vascular changes histologically—anyway, in the human subject—as the inflammatory cellular infiltration in and around the wall is lacking or very insignificant in arteriosclerosis. The writers I have just mentioned are, however, of the opinion that the fibrinoid necrosis of the wall in arteriosclerosis is due to damage of the vascular endothelium which serves as a “Blutgewebeschanke.” They consider that if the blood comes into immediate contact with the tissue a necrosis occurs.

Connective-tissue Changes

The changes in the connective tissue in man have been studied primarily in cases of polyarthritis rheumatica, and are therefore often termed “rheumatic.” They are characterized by oedema and by focal splitting up of the collagen fibres into reticulin fibrils with changed colour reactions. They are coloured black by silver, whereas connective-tissue fibres take on a brown colour. Furthermore, the fibrils show positive fibrinous stain. The next step in the development is the fragmentation of the fibrils with proliferation of the fibroblasts around the centre of disintegration. Thus rheumatic granulomas occur, one type of which is the so-called Aschoff body. Finally a scar may be formed. The changes in the connective tissues may be very transient, but they may also remain for months or years.

All writers agree that these changes are localized to different organs in a way that seems quite capricious and that the changes within these organs are of a markedly focal character. Little is known of the reasons for this, but investigations made by Hawn and Janeway indicate that the nature of the antigen involved may play a part in determining which organ is affected. By sensitizing rabbits with pure serum albumin they obtained vascular changes similar to periarteritis nodosa, but only in some of the

animals. If, on the other hand, pure gamma globulin was used glomerulonephritis was the most prominent change in nearly all the animals.

The capricious localization is expressed clinically by the many forms of disease in man that seem to be hypersensitivity reactions of the kind I have just described, such as polyarthritis acuta, endocarditis, pancarditis, periarteritis nodosa, arteritis temporalis, rheumatic pneumonia, transient infiltration of the lungs, glomerulonephritis, lupus erythematosus disseminatus, Liebman-Sachs disease, urticaria, angioneurotic oedema, migraine, etc. These diseases, however, may also occur in numerous combinations. It happens sometimes, however, that so many of these so-called diseases appear simultaneously in the same person that it is doubtful how the case should be designated.

Thus, whereas the anaphylactic type of hypersensitivity reaction, at least in its most advanced form, presents a characteristic pathologico-anatomical picture, this is by no means true of the bacterial hypersensitivity reaction, as it appears, for instance, in the tuberculin reaction, which resembles an ordinary inflammation.

With regard to contact dermatitis, the pathological anatomy is of no help whatever in deciding whether this is of anaphylactic or bacterial type. For long there has been controversy on whether the changes are primarily localized to the epidermal cells or whether they are secondary to changes in the capillaries of the cutis. Haxthausen has recently made experiments that support the latter assumption.

Erythema Nodosum

Finally, in order to show the importance of distinguishing between the various hypersensitivity reactions, I would like to say a few words about a disease which has traditionally interested Swedish research workers—erythema nodosum. In 1921 Ernberg coined the slogan that erythema nodosum is the body's own tuberculin reaction. This statement contains two important assertions—first, that erythema nodosum is always caused by tuberculosis; secondly, that erythema nodosum is a hypersensitivity reaction of the bacterial type. The former declaration has been strongly opposed and successfully refuted. We know now that erythema nodosum also occurs in connexion with lymphogranuloma inguinale, streptococcal infections, etc. Little interest has, however, been taken in the latter assertion, though it has in general been accepted. But it might also be possible that erythema nodosum is a hypersensitivity reaction of anaphylactic type.

This view is not unreasonable. Already in 1929 Tillet and Frances showed that patients who are convalescent after pneumonia may show an immediate reaction to the carbohydrate component of the pneumococcus and a delayed reaction, similar to the tuberculin reaction, to the protein component. It is also known that an anaphylactic reaction can be produced by the carbohydrate component of the tubercle bacillus. Thus it is possible that in a tuberculous infection we have two parallel sensitizations—one to the protein component of the tubercle bacillus which results in bacterial hypersensitivity and is manifested in the tuberculin reaction, the second an anaphylactic reaction to the carbohydrate component of which erythema nodosum is an expression. That erythema nodosum often occurs when the tuberculin reaction becomes positive would then only mean that it takes approximately the same time for the two kinds of antibodies to form. This rule, however, is not quite without exceptions, for sometimes erythema nodosum occurs before the positive tuberculin reaction.

The clinical symptoms of swelling of the joints, urticaria, etc., which sometimes accompany erythema nodosum give additional support to this theory.

In my opinion the pathological changes in erythema nodosum also point in the same direction. For in the subcutaneous fatty tissue we find fibrinoid degeneration of the interstitial connective tissue, as has recently been shown by Wahlgren and Löfgren, and sometimes also vascular changes of the periarteritis nodosa type. I have myself had an opportunity of demonstrating this.

This question can naturally be solved only by testing patients suffering from erythema nodosum with partial antigens from tubercle bacilli and streptococci in order to find out whether they show any immediate reaction against these antigens. Strangely enough, investigations of that kind do not seem to have been made.

Finally, I should like to stress the importance of correlating our clinical, serological, and pathologico-anatomical knowledge of these problems better than in the past. The theory that the great number of clinical entities that I have mentioned here are only anaphylactic tissue reactions would then perhaps not be relegated to the world of fancy, as now quite often happens.

THE STRUCTURE AND FUNCTIONS OF THE SYNOVIAL MEMBRANE*

BY

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A thorough knowledge of the structure, nature, and functions of the synovial membrane is essential both for an understanding of the normal functioning of joints and for the interpretation and assessment of the changes which occur in disease. Despite the undoubted importance of this topic, knowledge of it is still to a great extent rudimentary. The literature is full of conflicting statements and is lacking in original observations, while textbooks on physiology in general tend to shun the problem. It is not intended to give here a comprehensive review of the subject, but to discuss some aspects in the light of my experience over the past twelve years. A few of the major problems remaining unsolved are raised in the hope that further investigation will be encouraged.

Development

The synovial membrane is the last of the joint tissues to be fully differentiated, and, as compared with the capsular structures and the skeletal elements, it is the least specialized, as shown by the frequency with which it is the source of heterotopic chondrification and ossification. The skeletal elements first take the form of mesodermal condensations (precartilage), which in turn are converted into cartilage and ultimately bone. Between the chondrifying skeletal elements is undifferentiated mesoderm—the so-called interzonal mesoderm or articular disk marking the site of the future joint and limited externally at an early stage by a cuff of condensed tissue delineating the capsular ligaments. Proximally and distally this capsular condensation blends with the more tardily differentiated perichondrium and later periosteum clothing the skeletal elements.

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