The first half of the present century has witnessed a phenomenal progress in the understanding, diagnosis, treatment and prevention of disease. While many of the medical achievements of this half-century have been built in logical progression upon foundations laid by the remarkable men of genius who flourished in the last century, many others are, as far as that is ever possible in science, new developments of a new era. One of the highly important and extremely interesting achievements of the latter class is the development of concepts and of knowledge relating to allergy. Prior to the present century, the word "allergy" did not exist. The phenomenon of bacterial hypersensitivity had been discovered by Koch at the end of the last century, but it was not until the present century that Richet and Portier discovered and named anaphylaxis; that Arthus discovered the phenomenon that bears his name; that serum sickness was first described, studied and named by von Pirquet and Schick; that the relation of antibody to hypersensitivity was first indicated by Hamburger and Moro; and that the phenomenon of desensitization was clearly exposed by Besredka. While most of the injurious effects now known to be caused by allergic hypersensitivity had, of course, been observed in the past, it was not even suspected, before the present century, that such a diversity of disease conditions could be caused by a single process of this nature; nor was there any suspicion that a vast number of different environmental substances, which are in themselves relatively harmless, can produce distressing and even fatal disease through their capacity to induce the allergic
state.
I have been asked to take as the subject of the present paper "Allergic Diseases and Diseases Accompanied by Sensitization". If one wishes to

1 Allergie-Kongre 1

separate the diseases of hypersensitivity roughly into two such categories, it is possible to designate as primarily "allergic diseases" those in which the disease state is the result of hypersensitivity to agents that are not, in themselves, intrinsically harmful on usual contact, and in which, had hypersensitivity not developed, no significant lesions or symptoms attributable to the agent would have occurred. In this category belong, of course, the hypersensitive reactions to pollens, dusts, foodstuffs and industrial chemicals; and the effects belong to the general group of anaphylactic reactions. The second category, i.e., "diseases accompanied by sensitization", would comprise those conditions in which the body becomes sensitized, and thereby more readily damaged, as a result of contact with an agent which, in itself and in the absence of hypersensitivity, ordinarily produces injury. Such agents are, particularly, microorganisms, viruses and animal parasites. The number of sensitizing agents in the first of these categories, i.e. agents which do not ordinarily injure the body unless hypersensitivity develops, is very large, for it includes not only naturally occurring substances such as pollens and foodstuffs, but also many industrial chemicals that are incorporated into a great variety of articles in our everyday environment, and in addition, a large and rapidly multiplying number of drugs used in the treatment of disease. The number of manufactured sensitizing substances to which the population is exposed is therefore continually increasing, and at a continually and rather alarmingly accelerated rate. If it is true that civilization has made great advances in the treatment and prevention of disease, it is no less true that in many directions it has created conditions favorable for the development of disease, and agents capable of producing disease. This is notably true in the case of allergic diseases. The number of sensitizing substances to which primitive man was exposed was relatively small, having been limited to the naturally occurring products of the plants and animals in his immediate environment. Civilized man, through intensive adaptation and domestication, has greatly multiplied the variety of sensitizing plants and animals in his environment, and has, in addition, introduced into his environment a multitude of synthetic sensitizing agents.

It was recognized in the early part of the century that proteins foreign to the body are active sensitizing substances. The failure of attempts to induce antibody formation or to sensitize animals by the injection of a number
of non-protein substances obscured for a considerable time the fact that there do exist many non-protein chemicals that are highly active sensitizing agents, and the ill effects of various drugs upon some of the persons to whom they were administered were attributed to individual "idiosyncrasy". It was, particularly, the well-known, brilliant work of Landsteiner and his associates1 which provided the basis for our present knowledge that a nonprotein substance can induce highly specific hypersensitivity if it possesses a chemical constitution that permits it, under favorable conditions, to attach itself to a normal protein of the body, thus forming, in effect, a new "foreign" protein which stimulates the production of an antibody specific for the chemical substance that attached itself to the protein. These studies of Landsteiner, and of other investigators, made it clear that most of the reactions to drugs

which had been attributed to a vague "idiosyncrasy" were, in fact, specific hypersensitivity reactions.

While the complete spectrum of the injurious effects of hypersensitivity has probably not even yet been brought to view, our knowledge regarding the types of damage that can result from sensitization was greatly enlarged by the introduction of the sensitizing sulfonamide drugs. It has been shown by Schnholzer 30 and by Davis 31 that these drugs readily attach themselves to plasma protein, and thus fulfill the basic requirement for the conversion of a non-protein substance into a sensitizing antigen. Prior to the widespread use of the sulfonamides, an occasional report of an autopsy upon a patient suffering from a reaction to a drug 2,3 or to foreign serum 4 had provoked speculation regarding the relation of the observed lesions to sensitization; and several investigators, notably Klinge 5, Vaubel 6, Miura 7 and Apitz 33, had observed inflammatory and necrotizing cardiovascular lesions in animals subjected to intravenous injections of foreign protein. The extremely widespread use of the sensitizing sulfonamide drugs, which produce protracted hypersensitive reactions that are quite like serum sickness, soon provided an unprecedented opportunity to study the tissues of many patients who had developed hypersensitivity reactions shortly before death, and the striking findings restimulated interest in the experimental investigation of the tissue effects of generalized hypersensitive reactions of the protracted anaphylactic type. The results of these studies have made it unmistakably clear that a remarkable variety of inflammatory and necrotizing lesions of hitherto uncertain pathogenesis can result from protracted anaphylactic reactions to drugs and to foreign proteins.

Shortly after the introduction of the sulfonamides, for example, we began to encounter in our autopsy service an association of periarteritis nodosa and
sulfonamide hypersensitivity with a frequency that was altogether too great to be attributed to mere coincidence. Pursuing these observations experimentally, we were able to demonstrate unequivocally that this destructive, and commonly fatal vascular lesion can be produced in animals by subjecting them to a protracted hypersensitive reaction of the anaphylactic type.

(Demonstration of lantern slides.)

These studies have since been confirmed by many investigators. We have also reported the occurrence of periarteritis nodosa in a patient who died from a severe hypersensitive reaction to iodine, and in another patient who had exhibited hypersensitivity to aspirin. Others have since reported the development of periarteritis nodosa during hypersensitive reactions to other drugs, including dilantin, thiourea, phenobarbital and arsenicals. It is pertinent in relation to the hypersensitive nature of this vascular lesion that the analyses of autopsies in cases of asthma and of periarteritis nodosa by Kalls and Kalls-Deffner, Rackemann and Green and others, have shown an association of the two conditions with a frequency much greater than can be accounted for by mere coincidence. It is now thoroughly well established that periarteritis nodosa is one of the serious, injurious effects that the anaphylactic type of hypersensitivity can produce.

In addition to this destructive vascular lesion, the abundant material provided by cases of sulfonamide hypersensitivity, followed by clinical, pathological and experimental studies of hypersensitivity to other sensitizing drugs and to foreign protein, has firmly established that an extraordinary variety of other visceral lesions can result from hypersensitivity. These lesions include pneumonic consolidations, myocarditis, endocarditis, focal necrosis of lymph nodes and spleen, the formation of tuberculoid granulomata in the viscera, purpura, neuritis, arthritis and glomerulonephritis. It has long been suspected that some of these lesions could be caused by hypersensitivity, and indeed there was already evidence for that suspicion in the case of certain of them. The recent studies by numerous investigators have vindicated the suspicion of the potential role of hypersensitivity in the cases in which it was only a suspicion; they have provided convincing confirmatory evidence in the instances in which some evidence already existed; and they have revealed the role of hypersensitivity in the instances in which it was not previously suspected.

The information that the lesions mentioned can result from anaphylactic hypersensitivity, and that many drugs possess the sensitizing potentiality to produce them, is of major consequence for several reasons. In the first place,
it has become clear that unless a patient receiving a sensitizing drug is carefully watched for the occurrence of a hypersensitive reaction, and the administration of the drug promptly stopped if a reaction appears, he may suffer irreparable damage, or may even die, from the allergic effects of the drug that was administered to benefit him.

In the second place, when faced clinically with one of these disease states in the absence of any other recognized etiological agent, it is of some importance to keep in mind the sensitizing potentialities of numerous drugs in common use by the laity, such as aspirin, various sedatives and the Phenolphthalein laxatives. Finally, while it is, of course, thoroughly well recognized by the medical profession at large that asthma, hay fever, vasomotor rhinitis, gastrointestinal disturbances and a variety of cutaneous lesions can be caused by hypersensitivity, it is of no less importance to be aware of the fact that these other types of serious and even life-threatening visceral lesions can also result from hypersensitivity. This is not yet sufficiently widely appreciated by physicians who are not specialists in allergy. There can be little doubt that many patients who suffer from lesions of this class fail to receive the benefit of a proper search for an offending antigen because of the lack of appreciation of the fact that hypersensitivity is one of the causes of the condition in question.

I should like to illustrate briefly several of the visceral lesions that are now definitely known to be producible by hypersensitivity. The view that pneumonitis may result from hypersensitivity was first brought into focus by the important clinical and pathological observations of Loeffler 15 and of von Meyenburg 16; and the studies of Harkavy 19, Vaughan and Hawks Cole and Korns 18, Elkeles 20 and numerous others have established that relationship by demonstrating the close association of transient pulmonary infiltrations with asthma, urticaria, angioneurotic edema, periarteritis nodosa and other allergic conditions. While blood eosinophilia and an abundance of eosinophils in the pulmonary lesions are characteristic features of the classical Loeffler's syndrome, I should like to emphasize that, just as serum sickness can occur without eosinophilia, so can anaphylactic pulmonary infiltrations occur in the absence of significant blood or tissue eosinophilia. Such lesions occur, for example, in patients during hypersensitive reactions to the sulfonamide drugs 21. They are characterized by damage to the alveolar capillaries, leading to exudation of fluid, sharply focal exudation of leucocytes and, when the damage is more severe, to thrombosis of capillaries or to rupture with hemorrhage into alveoli. Lesions of this type, in all probability, represent the pulmonary analogues of cutaneous urticaria, angioneurotic edema and purpura. Precisely similar pulmonary lesions occur in periarteritis nodosa,
rheumatic fever and disseminated lupus erythematosus. (Lantern slides.)

It is now clearly established that myocarditis can result from hypersensitivity. Fifteen years ago, ikl 2 encountered myocarditis, characterized by the presence of many eosinophils, in a patient who died with exfoliative dermatitis following the administration of neoarsphenamine. This association has been noted in other cases 3. ikl suggested that the myocarditis might represent an allergic reaction to the drug. The correctness of that suggestion has received ample confirmation from the exceptional opportunity provided by the sulfonamides to study the tissues of patients who died during hypersensitive reactions to these drugs. It was soon found by French and Weller 22, ourselves 8 and others that hypersensitivity to these drugs can produce focal collagen degeneration and an inflammatory infiltration of the myocardium consisting of mononuclears, polymorphonuclears and usually many eosinophils, quite like that observed by ikl in what is now well recognized to have been a hypersensitive reaction to neoarsphenamine. It may be recalled that Landsteiner and Jacobs 32 and others have demonstrated that guinea-pigs can readily be sensitized anaphylactically to arsphenamine. Further evidence for the hypersensitive nature of this myocarditis resides in the fact that the same type of myocarditis has been observed in cases of human serum sickness by Clark and Kaplan 4 and by ourselves 8; and we have observed its occurrence in a fatal hypersensitive reaction to iodine 10. (Lantern slides.)

It is obvious that cardiac damage of this character, occurring during therapy with sensitizing drugs, can be a decided hazard to life.

It is of considerable interest and importance that sufficient evidence has been accumulated through recent studies to establish the fact that the anaphylactic type of hypersensitive reaction to soluble antigens is capable of producing not only the banal types of inflammatory lesions, but also lesions of a distinctly tuberculoid character, i.e. accumulations of epithelioid cells and giant cells, which may closely simulate tuberculous lesions. While lesions of this type are a much less common manifestation of hypersensitivity than are acute inflammatory lesions, they are no great rarity. They have been observed in patients dying with hypersensitive reactions to sulfonamides, to iodine 10, to neosalvarsan 3 and to dilantin 12; and I can report that we have produced them experimentally by subjecting animals to serum sickness resulting from the intravenous injection of foreign serum. Why only some of the individuals exposed to a given antigen develop lesions of this type, and why, in the same body, some of the lesions of hypersensitivity may assume this tuberculoid character, while others are of the more usual inflammatory type, are matters which invite especial study for the light that might be
thrown upon the general subject of the pathogenesis of lesions of the tuberculoid type. (Lantern slides.)

It is of particular importance to discuss briefly the relation of the anaphylactic type of hypersensitivity to glomerulonephritis. It has long been suspected that acute glomerulonephritis may be a result of hypersensitivity. Particularly suggestive in this regard has always been scarlatinal nephritis and the nephritis that is associated with tonsillitis, both of which, as is well known, do not appear during the height of the infection when the streptococci and their products are present in greatest abundance, but only after a lapse of time sufficient to permit an active development of antibody and of hypersensitivity. In the early part of the century, Schick 27 and others compared this delay in the appearance of scarlatinal nephritis to the situation in serum sickness, in which the presence of the foreign antigen in the circulation provokes no symptoms until a sufficient amount of sensitizing antibody has been produced, at which time symptoms make their appearance.

In 1913, Longcope 28 reported that he had observed lesions, similar to those in human glomerulonephritis, in animals subjected to repeated injections of foreign protein, and during the succeeding 30 years one or two other investigators mentioned similar observations. Doubt was always cast upon these reports, because the illustrations did not provide convincing evidence that lesions typical of those of human glomerulonephritis had been produced. Several years ago, Dr. Gregory and I 9 reported the production of glomerulonephritis in rabbits subjected to a protracted hypersensitive reaction under conditions which permit a circulating antigen to interact with the antibody that is produced as a response to its presence. This can be accomplished most simply by introducing into the circulation a bland foreign protein, such as horse serum or egg albumen, in an amount that will permit some of it to remain in the circulation until antibody makes its appearance. Under these conditions a considerable percentage of the animals will develop glomerulonephritis. In further experiments of this type we have observed all degrees of nephritis, ranging from marked proliferation of the endothelium of the glomerular tufts to the destructive types of glomerular damage that are encountered in the most severe forms of human glomerulonephritis. Hawn and Janeway 24, Ehrich and his coworkers 25 and others have repeated our experimental procedure and have obtained the same results. The pictures that I shall show you are taken from a large series of photographs that we are publishing to illustrate fully the character of the lesions. (Lantern slides.) These experimental lesions demonstrate plainly that all of the glomerular lesions characteristic of human glomerulonephritis can result from a simple, protracted anaphylactic reaction of the serum sickness type, produced by an antigen possessing no primary toxicity; and they provide support for regarding the latent period
between the onset of an infection and the appearance
of acute nephritis as being the period during which sensitizing antibody is
being formed. It will be remembered that in human serum sickness there
commonly occur, though usually in only moderate degree, disturbances of

renal function of the type encountered in glomerulonephritis. That nephritis
in man can result from hypersensitivity to non-toxic, non-bacterial antigens
is also indicated by cases such as those described by Ehrstrom 26 and by Long-cope
and Rackemann 29, in which an attack with the clinical characteristics of
acute nephritis would promptly occur following the ingestion of a foodstuff
to which the person had become sensitized.

The second category of allergic states, i.e. "diseases accompanied by
sensitization", comprises those conditions in which disease is produced by
injurious agents such as micro-organisms, viruses and parasites, but the
disease process becomes accentuated or modified by the sensitization that
develops during the course of the infection. While the anaphylactic type of
sensitivity occurs not infrequently as a result of parasitic infestation, and may
also result from sensitization to some of the products of bacteria and fungi,
particularly carbohydrate products, the more characteristic form of sensitization produced by
infection with micro-organisms is sensitization to the
proteins of the agent, and it differs in a number of ways from the anaphylactic
type of sensitivity. This hypersensitivity of infection is commonly referred
to as "tuberculin type" sensitivity, for its prototype is the hypersensitivity
to tuberculoprotein that develops during tuberculous infection. As is well
known, the local inflammatory response to the antigen is delayed and prolonged, in contrast to the
explosive and evanescent character of the anaphylactic urticarial wheal; in contrast to the ease of
passive transfer of the
anaphylactic type of sensitivity by injecting the serum of the sensitized body
into a normal one, passive transfer of tuberculin type sensitivity cannot be
accomplished by serum; the smooth muscle of the anaphylactically sensitized
body is thrown into spasmodic contraction on contact with the antigen, but
this does not occur in the case of tuberculin type sensitivity; and finally, as
we were able to show some years ago 34, washed cells of the body with tuberculin
type sensitivity are killed in vitro by contact with the antigen, whereas those
of the anaphylactically sensitized body are unharmed by such contact 51.

One of the most interesting and important of the recent contributions to
the study of tuberculin type sensitivity is the discovery by Chase 35 that,
though passive transfer of this type of sensitivity cannot be accomplished
with the serum of the sensitized body, it can readily be accomplished by
transferring washed, living mononuclear cells from the sensitized body into
a normal one. It is of particular interest that for the successful transfer of the sensitivity, the transfer cells must be alive. This surprising observation, which has been amply confirmed, deserves the most careful analysis, the results of which cannot fail to throw much-needed light upon the mechanism of tuberculin type sensitivity.

The method of cellular transfer invites study, also, in relation to acquired immunity. A beginning in this direction has already been made by Metaxas and Metaxas-Bhler 38, with suggestively positive results. A second important recent contribution is the demonstration by Raffel 36 that hypersensitivity, conforming in all respects to tuberculin sensitivity, can be established by the injection of tuberculoprotein mixed with a lipid fraction of the tubercle bacillus. Neither substance, alone, will induce this type of sensitivity. Obviously, the isolation of the specific fractions of bacteria that

are responsible for inducing the states of hypersensitivity and of immunity is of major importance, both for theoretical and for practical reasons. While there have been previous reports relating to the sensitizing action of various substances derived from bacteria, Raffel's experiments represent the only studies in which it is recorded that all of the criteria, required for the demonstration that the sensitivity was truly of the tuberculin type, have been fulfilled.

The role played by tuberculin type hypersensitivity, especially in chronic infections, is an important one, for it can greatly intensify the tissue damage and the systemic effects that a given amount of the infecting agent is capable of producing. It was believed for many years that the hypersensitive inflammation was an essential mechanism of acquired immunity in tuberculosis and certain other infections, and that the exaggerated necrosis of tissue resulting from hypersensitivity was a necessary evil that had to be accepted in order to obtain the benefit of the exaggerated inflammation. Studies in our laboratory, extending over a number of years, demonstrated in a variety of different ways, and in a variety of different infections, including tuberculosis, that the exaggerated inflammation of hypersensitivity is not necessary for the best operation of acquired immunity. Those studies, which demonstrated that immunity remains completely intact when local and systemic hypersensitivity is abolished by desensitization, have been confirmed by many investigators in different countries 37; and the recent work of Raffel 36 has dissociated hypersensitivity from immunity by a different attack, for he has reported that a high degree of tuberculin type hypersensitivity can be established by the method mentioned above without any concomitant enhancement of resistance to the infection. It is now clear that the tuberculin type
of hypersensitivity is no more necessary for protection against infectious agents than is the anaphylactic type necessary for protection against the antigens of the allergic diseases. In both types of hypersensitivity, the prevention of the hypersensitive reaction spares the body from unnecessary damage.

Finally, time permits only the most cursory mention of a highly important group of diseases, in most of which the role of hypersensitivity has not yet been conclusively demonstrated, but which exhibit in common a wide variety of pathological manifestations that are known to be effects which the anaphylactic type of hypersensitivity is capable of producing. These are the "collagen-vascular diseases", so called because they are characterized by focal degeneration of collagen fibers with alteration of the connective tissue ground substance, and by endothelial and vascular injury. This group includes, particularly, rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus and periarteritis nodosa. Some instances of dermatomyositis and scleroderma exhibit similar collagen and vascular injury. It is now clearly established that one of these diseases, periarteritis nodosa, can be caused by hypersensitivity, as has already been mentioned. The studies of Coburn 39, Klinge 5 and others strongly suggested that hypersensitivity plays an important role in the pathogenesis of rheumatic fever. Dr. Gregory and I 41,21, in studies confirmed by Hawn and Janeway 24, Ehrich and his coworkers 25 and numerous others, have illustrated the close similarity of the basic characteristics of the cardiac, pulmonary and vascular lesions of rheumatic fever with those that can be produced experimentally by protracted anaphylactic reactions. In our experimental studies non-bacterial foreign protein was used. Murphy and Swift 40 have since produced cardiac lesions of the same character by sensitization with hemolytic streptococci. I have elsewhere presented and illustrated in detail evidence that the basic characteristics of the lesions of the group of collagen-vascular diseases are those that are known to occur in anaphylactic reactions 11. I should like to show you very briefly a Table that lists the impressive number of lesions that these diseases exhibit in common with the protracted anaphylactic reaction typified by human and experimental serum sickness and by drug hypersensitivity (Table 1).

TABLE 1

++ Observed Association ; + Occurs, but infrequent or slight ; 0 No apparent association ; ? Insufficient study.

Teilum 42, Bergstrand 43, Pagel 44 and others have likewise discussed the potential role of hypersensitivity in the pathogenesis of these diseases.
Identity of lesions is, of course, no absolute proof of identity of etiology or pathogenesis; and until further study defines precisely the cause of the collagen-vascular diseases, we can say only that the evidence for the role of hypersensitivity in the pathogenesis of rheumatic fever, rheumatoid arthritis and disseminated lupus erythematosus is highly suggestive, though it is conceivable that some other, as yet undiscovered, process may be able to produce the same multiplicity of effects as those known to be caused by hypersensitivity. Because of the wide variety of lesions which rheumatic fever and rheumatoid arthritis exhibit in common with protracted anaphylactic reactions, shortly after Hench and his coworkers reported the spectacular effect that cortisone and ACTH exert upon rheumatic fever and rheumatoid arthritis, my associates and I sought to determine whether the production of the experimental cardiovascular and renal lesions of hypersensitivity would be suppressed by these hormones. This was found to be the case (Table 2).

**TABLE 2**

**Effect of Cortisone and ACTH on Experimental Lesions of Hypersensitivity**

Harvey and his associates, and others, have reported the dramatic suppressive effect of these hormones upon a wide variety of hypersensitive conditions in man, including asthma, allergic rhinitis, drug hypersensitivity reactions and periarteritis nodosa. A similarly marked suppressive effect is exerted upon disseminated lupus erythematosus. I may mention, in passing, that we have found that cortisone, in appropriate dosage, is, itself, capable of producing severe glomerular damage of a peculiar type.

If we began this discussion by commenting upon the remarkable advance in knowledge relating to allergy during the past fifty years, we must end it by recalling that it is one of the paradoxes of science that each new extension of the realm of the known, instead of decreasing the area of the unknown, increases it. In conformity with this, the marked progress in knowledge relating to allergy has generated unnumerable new and unsolved problems, many of them of fundamental importance. Why do only some, and not all persons who are equally exposed to a sensitizing agent become sensitized, and why does contact with the antigen produce injurious effects in some but not in all of those who become sensitized? Why is one tissue attacked in some who are sensitized to a given substance, and a different tissue in others who are sensitized and exposed in the same manner to the same substance? What are the conditions
under which antigen will interact with antibody to produce injurious effects, and what is the mechanism through which the tissue injury is produced? What is the basic meaning of this remarkable process through which the body so alters itself that non-toxic substances become able to produce highly injurious effects? These and many other fundamental problems remain to be solved before we shall be able adequately to understand the allergic process; and their solution cannot fail to have important practical effects upon the prevention and treatment of the manifold allergic disorders that plague mankind.

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