ALLERGY OR PHENOMENA OF HYPERSENSIBILITY

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Hypersensitiveness in man may follow after both the enteral and parenteral introduction of many and varied substances. These inducing substances may be antigenic or non-antigenic in character, i.e., those which stimulate or those which do not stimulate the production of demonstrable antibodies. The response to these substances in man are usually thought of as due to personal idiosyncracy and the symptoms, however diverse the inciting agents may be, have a great deal of similarity. The term allergy, meaning literally altered energy or work, was first introduced by Von Pirquet after whom the well known skin test in tuberculosis has been named. Coca[1] has suggested that this term allergy be applied only to the phenomena of hypersensibility in which the reaction is not due to antigen-antibody combination, or at least where the antigenic property has no direct bearing on the reaction.

Symptoms elicited in man by the introduction of serums with or without antitoxin may, according to Parke[2], be divided into those following *first* the initial injection and *second,* those following the second or later injections. These reactions have nothing to do with the antibody content of the injected serum. Following the first injection three types of reactions may be noted:

(a) Collapse with or without fatal outcome;

(b) A symptom-complex termed "serum sickness", and finally—

(c) Local necrosis.

Each of these forms of response may also follow the second or later injections.

Collapse or Death.—This accident is rare and nearly always occurs after the first injection. The symptoms appear quickly after administration. According to the most reliable statistics, about 1 in 20,000 primary injections of antitoxin results in alarming symptoms (in about 1 out of 50,000 injections death occurs), the out-

standing features being those of extreme dyspnea and collapse. The dose may be small, in one instance reported about 1 c.c. (500 units) of antitoxin having been given subcutaneously. Kerley[3] reports a case of known-hypersensitiveness where the dose was gradually increased until 5 minims were given, resulting in alarming shock. Persons showing this type of reaction are frequently found to be subject to asthma or hay fever, being subject to the former particularly in the vicinity of horses or stables. Nearly all children dying after serum-shock are cases of "status lymphaticus".

After the intravenous injection of low-potency antitoxin even when the material is warmed to the body temperature and the injections given very slowly, chills more or less severe in character are observed in nearly half of the cases. Park[2] suggests that this is probably due to a special form of the protein possibly in the state of a fine flocculent precipitate. According to his experience less than 1 per cent of intravenous injections produce a chill when the best products are employed, whereas this undesired symptom occurs much more frequently when less perfect serums are used. In some instances the intravenous administration of antitoxin or other serum several weeks or longer after an initial injection which caused marked reaction, results in alarming symptoms of collapse. This effect is said to almost never follow a second subcutaneous injection. In other instances frequently repeated intravenous injections of serum develops instead of desensitization a hypersensitiveness so marked that even small amounts of serum give a sharp reaction. Such conditions are, fortunately, known to be relatively very infrequent.

Serum Sickness.—The occurrence of this type of reaction according to Park[2] varies considerably in different series of cases, from ten to sixty per cent or more, the size of dose influencing this incidence. Concentrated globulin preparations of antitoxin cause a relatively low incidence. Following the first injection of antitoxin or other serum there occurs an incubation period varying from three hours to twenty-four days (more commonly from three to twelve days). The symptoms primarily

consist of a skin eruption, edema, slight albuminuria, enlargement of the lymph nodes with pain and tenderness and pain in the joints. The eruption is variable in character, a local eruption usually appearing earlier than the general eruption. On the second or later injections the period of incubation may be absent or shortened (immediate or accelerated reaction). This does not, however, always occur. This condition is not considered serious and in many instances gives no greater discomfort than that of an itching rash. Some samples of antitoxic or other sera quite uniformly cause a skin eruption. The earlier rashes are usually scarlatinaform, while those occurring later are more frequently of an urticarial nature. Von Pirquet and Schick believe that this reaction is due to antigen-antibody combination, owing to the fact that the average incubation period coincides with the time of first appearance of precipitins in experimental animals. It is known, however, that precipitins may be present without any manifestations of allergy whatever.

Local Reactions.—The primary injection of antitoxic or other sera may lead to local necrosis. When repeated injections are given, a final subcutaneous injection will more frequently result in a sharp local reaction, which may terminate in necrosis. This may also occur with rabies vaccine as well as with serum and is thought to constitute a striking parallel to the so called Arthus phenomenon in rabbits. It has been shown that such necrosis is not due to bacterial contamination, but the necrotic area may become infected and serious or even fatal consequences follow.

In connection with these serum reactions, there are certain preventive measures which should be mentioned briefly:

(1) *Desensitization to Serum.*—It is a well known fact that different lots of antitoxic or bactericidal sera will vary widely in their rash and temperature-producing qualities. This may have a bearing on the development or non-development of untoward symptoms. The administration of small doses of serum prior to the first injection or previous to subsequent injections of those known to be sensitive to the same is frequently resorted

to in order to desensitize. This procedure in man does not, unfortunately, give the same uniform results as noted in experimental animals. It may be said, however, that divided doses, although they may fail to give the reaction, or repeated small doses may induce a tolerance, but this is not considered proof that we are inducing the mechanism of desensitization so uniformly observed in experimental animals.

(2) *Prevention of Serum Reactions.*—Persons who give a suspicious history should be tested cutaneously for evidences of hypersensitiveness. The appearance of a wheal at the site of injection indicates that the person so tested will show a fairly immediate serum reaction, such as rise of temperature or urticarial rash, but is no indication of the probable severity of the same. The absence of such a skin reaction indicates, but does not prove, that there will be no undesired results following the administration of the serum. The procedure usually followed and recommended is to inject the antitoxin or other serum in divided doses every 20 to 30 minutes, starting with 0.1 c.c., until symptoms are observed or until sufficient is given. If symptoms develop one can then attempt repetition of smaller doses which previously did not cause symptoms. Where serum is to be administered intravenously, dilution and exceedingly slow administration in the beginning will tend greatly to prevent undesirable results. Intraspinous injections should also be given slowly, especially the initial portion following a recent previous injection. Hypodermic injection of atropin or epinephrin will usually relieve the less severe attacks of serum shock. In cases of extreme collapse, artificial respiration should be resorted to.

Allergy to Foods, Pollens, Etc.—After the ingestion of specific foods, rashes and other forms of reaction occur in a small percentage of individuals. These may follow the eating of eggs, certain kinds of meat, including fish, fruits, etc. As stated above, the inducing substances may or may not be antigenic in character. Hay fever is an example of mucous membrane hypersensitiveness. Persons suffering from this condition may also show skin sensitiveness and even develop rashes or other

symptoms when the inciting substance is injected. Such hypersensitiveness may be manifested toward certain pollens, dust from the hair or skin of animals, powders of various kinds, etc.

Experimental study of pollen extracts appears according to Park[2] and others to show that they do not stimulate antibody production nor will they sensitize experimental animals. One might infer from this that hay fever (and probably food allergy also) is not due to sensitization of the individual, but possibly to some inherent or early acquired predisposition. Where hypersensitiveness toward a specific agent exists, the same is not necessarily an inherited condition. Increased tolerance to these classes of allergy may frequently be developed through the repeated use of small doses of high dilutions of the inciting substances. This is, however, only relative and is not comparable to the regularly induced and quantitatively greater resistance of desensitized animals. Varieties of dermatitis due to poison-ivy, sumac, etc., are claimed by some to be caused by similar hypersensitiveness. This, however, is questioned by many.

Drug Allergy or Idiosyncracy.—Allergic symptoms due to drugs follow a dose or doses which are not appreciably toxic for most individuals. The symptoms resulting are said to be due to idiosyncracy, because they are different from those obtained with larger and uniformly toxic doses. Substances which usually give rise to this kind of allergy are mercury in various forms, salvarsan, iodides, quinine, morphine, antipirin, salicylic acid, turpentine, cubebs, sandal-wood oil, etc. The symptoms usually observed are quite severe, with or without chill, skin eruptions, local edema or gangrene at the site of injection, swelling of the joints and lumph nodes.

Speaking of human allergy in general, there appears as already intimated to be little or no evidence that the basis of these phenomena is an antigenic-antibody reaction. The dominant feature in human allergy rather appears to be that of idiosyncracy. A condition resembling anaphylaxis has been observed only in a small number of cases. We refer here particularly to symptoms of

collapse after a second injection and local necrosis after repeated injections. Failure to get in man the typical picture frequently observed in experimental animals may be due to the relatively smaller doses given, the usual dosage being much lower per unit body weight than necessary to cause shock in animals such as the guinea pig. In case of intravenous and intraspinous injection in man the factor of quick absorption must not be lost sight of and guarded against.

Hypersensitiveness and Infection.—In many communicable diseases there develop varying degrees of hypersensibility to causative agent. The most extensively studied and best known examples of this are infections due to the tubercle and the glanders bacillus. Tuberculin, which consists of the soluble products found in a broth culture of the tubercle bacillus, is only toxic for an infected animal, i.e., infection results in hypersensitiveness. Such hypersensibility may be demonstrated in the skin, mucous membranes and also by a systemic and focal reaction (site of lesion) when injected in sufficient doses. Too large a dose may result in death of the sensitive animal. Tuberculin is highly resistant to heat, and is specific but not anaphylactogenic. A relative tolerance may be induced in the tuberculous animal by gradually increased doses. This substance differs further from all similar substances in that animals cannot be rendered hypersensitive by its injection experimentally. On the other hand, the proteins of the tubercle bacillus are anaphylactogenic. This is a distinctly different phenomenon. The real mechanism of the tuberculin reaction is still obscure.

A similar skin reaction may be obtained in a considerable proportion of syphilitic cases by the intracutaneous injection of "luetin," an emulsion of the Treponema pallidum. Indications of hypersensitiveness have also been noted in typhoid fever or following the injection of typhoid vaccine. Likewise, positive skin reactions have been found to follow the injection of the genococcus and in such conditions as Leprosy, Sporotrichosis and other diseases caused by fungi and in pregnancy. All these

reactions are relatively specific but have been observed mostly in experimental animals.

Vaughan[4] believes that the parenterally administered protein excites the release of specific ferments that are capable of splitting the protean molecule in such a manner as to give rise to a toxic product. In a similar manner, he contends that the symptoms in the acute stage of the various contagious and infectious diseases are produced, the protein of the various bacterial growths being split by the ferments set free from body cells. The term albuminal he applies to these diseases. The comparatively few bacteria gaining entrance into the body must multiply, and this is accomplished during the so-called period of incubation. There is no apparent resistance during this time on the part of the body cells. The latter must be sensitized before they can begin their combat with the invading organisms and it is not until this actually takes place that active disease symptoms manifest themselves. This theory is dependent on the assumption by Vaughan and Wheeler[5] that the process which results in the production of protein poison causes a splitting of all of the molecules in the material subjected to it. This assumption they consider proved by the observation that the non-toxic residues sensitize animals against the original protein but not against itself. This opponents claim is fallacious because the amount of protein required to sensitize a guinea-pig is but a minute fraction of that necessary to intoxicate or desensitize the sensitized animal.

Hypersensitiveness and Immunity.—Sir Edward Jenner observed that the reaction following vaccination after a previous typical vaccinia (cowpox) appeared earlier and ran a shorter course that is the case in typical primary vaccinia. Of recent years this observation has been studied by Von Pirquet, Tieche, Force and others, and the evidence clearly indicates that such an accelerated response to vaccination is an indication of immunity. In case of tuberculin the reaction is also said to be indicative of immunity to reinfection. The disappearance of the reaction in a person with a latent lesion, during measles for instance, is not infrequently followed by

extension of the lesion and active tuberculous disease. Professor Gay[6], of the University of California, attempted to show that the appearance of a positive skin reaction to typhoidin is an indication of immunity to typhoid fever. This, however, is not exactly the case, since this reaction is absent or disappears at a time after infection or vaccination when immunity is still known to exist. More recently an intracutaneous method of diagnosis of whooping cough[7] during the first weeks of this disease was advocated. This, however, has been shown not to be a specific reaction. In fact attempts to duplicate published results by Hull and Nauss[8] show conclusively that identical reactions may be obtained through the injection of quite different inciting substances.

Within a few months also an intracutaneous method of diagnosis of scarlet fever based on recent investigations of the etiology of this disease has been published[9]. This, if satisfactorily confirmed, will prove to be a great boon not only to the practicing physician but also to the health administrator. It may be pointed out further that the possibilities of development in this field have not by any means been exhausted. The exact and rapid laboratory diagnosis of both infection and immunity in many other communicable diseases offers sufficient stimulus to both investigator and hygienist as to warrant the most exhaustive researches.

As a recent development of the application of this principle, the Schick test in diphtheria deserves special mention. Similar to most allergic reactions in man, this is not of the nature of anaphylaxis. In fact, it may be looked upon as a comparatively simple case of a biological chemical reaction confined for the most part to the site of injection of the active diphtheria toxin. The Schick test runs quite a definite course, which will be illustrated in connection with a series of lantern slides, which are to be thrown upon the screen, showing various local manifestations of allergic skin reactions.

As aids to the diagnostician, these various local manifestations of allergy may be divided into two general classes; namely, those which serve as *indices of infection*

and those which serve as *indices of immunity.* To recapitulate, among the former are the tuberculin, mallein, luetin and other similar and theoretically possible tests. Among the indices of immunity, the principal ones are the accelerated and immediate responses to vaccination against smallpox, the serum test preliminary to the administration of antitoxic and other sera, the Schick test in diphtheria, and the many and varied tests utilized in the determination of sensitiveness in food idiosyncracy, hay fever, asthma, etc.

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