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PROTEIN SENSITIZATION IN THE PRODUCTION OF SKIN DISEASE *

HARVEY P. TOWLE, M.D.

BOSTON

During the last decade there has grown up a voluminous literature on the subject of protein sensitization. Case after case has been reported in which it has been alleged that a skin disease of one form or another has been caused by the ingestion of some food substance. Laboratory workers have been equally busy with the clinicians and they, too, have done their part in adding to the literature.

In reviewing the papers on the various phases of protein sensitization the reader is soon impressed by the multiplicity of the substances accused of toxic action and the resulting anaphylactic shock and equally by the variety of the manifestations which these poisonous substances are alleged to produce. Moreover, the manifestations are not uniform in a given patient even in response to the same toxic stimulus but are various and varied. Neither do the symptoms seem to be constant, for not infrequently a food which was formerly not tolerated later may be innocuous for long intervals.

Prodromal symptoms are equally inconstant and fickle. The anaphylactic shock apparently develops, often within a few minutes. In other cases it is seemingly delayed even for twenty-four hours or more. In some cases, notably in children, there are constitutional symptoms present in the interval between the poisoning and the reaction which, to the observing mother, indicates the imminence of anaphylactic shock. Nervousness, irritability, loss of appetite, sometimes diarrhea and sometimes fever are common prodromal signs, when such signs occur.

Moreover, many students assert that if the blood be examined at the time of the anaphylactic shock eosinophilia will be found for twenty-four hours or perhaps longer.

As already stated, the response in the skin to the influence of the toxemia is varied. Certain forms of skin manifestations, however, so predominate that in certain quarters they are accepted as satisfactory

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evidence per se of the existence of a state of anaphylaxis, i. e., that they are pathognomonic of anaphylactic shock. Preeminent among these are urticaria, angioneurotic edema and eczema.

Moreover, the dominant testimony of today places bronchial asthma and hay fever in the same category as manifestations of anaphylactic shock. Among many, the belief prevails that bronchial asthma and the skin diseases mentioned are merely variations of the same influence and may appear simultaneously or interchangeably. Therefore, in considering protein sensitization as a cause of skin disease, it is both necessary and illuminating to study the work done in bronchial asthma and hay fever.

One of the most striking facts in connection with the study of protein sensitization is the discovery that in many instances it is possible to detect the offending toxic substance by inoculation or vaccination of the skin. It has been found that when the protein which has sensitized the body is inoculated into the skin certain signs will follow. Moreover, the skin reaction is specific in the sense that the maximum skin reaction occurs only in response to the offending substance.

Even here, however, as will be shown later, all is not clear sailing for just as we have seen the clinical signs vary and even fail, so in response to the food inoculation test the skin does not always react or, if reacting, does so in a manner not explicable by the other evidence present.

It is evident from the foregoing that we are not dealing with a clear cut subject with well defined limits, but rather with a subject in which much work yet remains to be done. This thought has been well expressed by Loewit, whom I take the liberty of quoting.

So great is the number of alleged shock producing substances and so manifold and changing is the picture drawn of the symptom complex attributed to anaphylaxis and so utterly unconfirmed and so lacking in character are the signs used in diagnosis that either suspicion is aroused of the great multiplicity and instability of the anaphylactic symptom complex or else we can only conclude that many of the processes laid at the door of anaphylaxis really possess only a superficial resemblance.¹

None can deny that it is difficult to reconcile the changing and confusing claims of the anaphylactic enthusiast with our previous beliefs. The bond between the one time accepted theories and the newer theory of anaphylaxis is not yet complete. We seem to have but one course open to us, either to reject all that we once thought true and accept unreservedly the new theory or to agree with Loewit that the old truths remain unchanged and neither conflict with nor impair the newer facts now coming to light.

1. Loewit: *Ztschr. f. Immunitätsf.* **27**:407, 1918.

We can perhaps make the situation clearer if we consider briefly, at this point, one or two clinical histories of typical cases of anaphylactic skin disease.

TYPICAL CASES

CASE 1.—First let me summarize Schloss' classic case. A boy, aged 8, had a pronounced idiosyncrasy to eggs, almonds and oats. The previous history is significant in its suggestion of contributing causes leading up to the subsequent anaphylactic developments. The little patient had suffered from seborrheic eczema, mild symptoms of rickets and repeated attacks of the respiratory tract. When 10 days old, the infant had a mild diarrhea for which he was given the white of an egg in barley water. No symptoms whatever followed its administration. When the boy received egg a second time he was 14 months old. Immediately he began to claw his mouth and tongue and the buccal tissues swelled to many times their normal size. Around the mouth typical urticarial wheals developed. Using von Pirquet's borer, Schloss was able to demonstrate the sensitiveness of the skin to egg white by the production of a typical wheal at the site of the inoculation. In the course of further study Schloss showed that the ovomucoid content of the egg white was the specific toxin.

A second case taken from my private records illustrates the multiple protein sensitization that so frequently occurs. It also exhibits the existence of a previous pathologic condition that suggests relationship to the later developing anaphylaxis. Finally, it illustrates the variability and instability of the cutaneous test reaction. The latter is most important as a majority of writers are inclined to accept the behavior of the cutaneous test as evidence of the progress of immunity. All these points will be considered later in greater detail.

CASE 2.—A shy, reticent boy of 7 years, while not appearing ill, lacked the activity and robustness of normal boys of like age. The history revealed that he had been well up to 3 years of age. At that time he had a light attack of measles. At first there was nothing noticeable about the attack and the disease followed the ordinary course. As recovery seemed about assured the boy suddenly had a convulsion and for some weeks was seriously ill with meningeal symptoms. When recovery finally came, the boy seemed to have lost all control over both the voluntary and involuntary nervous system. His mind was as clear and keen as ever, but, for example, when he tried to walk he could not make his legs move; when he tried to talk he could not indicate his desire in words although perfectly able to do so in signs. He had to learn all over again to walk and to talk.

From the point of view of the study of protein sensitization, the intolerance which had developed toward foods was most interesting. In Schloss' case just given there was a primary ingestion of a food substance without symptoms followed by sensitization and anaphylactic shock when the antigen, that is, the sensitizing food substance, was taken a second time. In this case, there was no such clear cut story. In his mother's words, the boy was converted from a perfectly normal child who could eat and digest everything given him to a child with a vasomotor system so instable and a digestion sensitized to so many foods that the possible diet was made extremely limited.

Cutaneous food tests were made with the following results: total number of substances tested, 59; total positive reactions, 26; total questionable reactions, 4; total negative tests, 29. The mother also reported her own clinical observations which, as she was more than ordinarily intelligent and observant, may be accepted without reserve. For example, she had learned that while the boy could not eat fresh bread he could eat toast. He could not eat the moist cereals. He could eat the dry cereals, shredded wheat, puffed rice, etc., i. e., those cooked by dry heat. In general, she had learned that foods baked or toasted, that is cooked by dry heat, were less liable to cause anaphylactic shock. Under the mother's careful guidance and by carefully cutting out those foodstuffs that gave a positive result to cutaneous tests, the boy has in the course of four years recovered much of his tolerance toward foods. He still cannot eat everything, but the number of toxic foods has been greatly reduced.

Up to within about a year the anaphylactic reaction manifested itself solely in the lungs. Following the ingestion of anaphylaxis-producing substances the child would have a most distressing asthma with noisy stridor and vomiting. He lost weight and strength during this time. For a year these asthmatic attacks have not been bad. For a year the explosion has manifested itself in the skin almost entirely, the lungs being often not at all or only slightly affected. After a period of irritability the skin breaks out in a generalized guttate eruption resembling both seborrheic eczema and psoriasis.

Preceding the attacks the boy was restless and apprehensive, was afraid to go to bed and would therefore sit up all night. The bowels would also become sluggish. An internist who had been consulted stated, after much study and experimentation, that he was convinced that the lower intestine and the large bowel were characteristically sluggish in functioning and in his opinion had much to do with the production of the anaphylactic state.

Repeated cutaneous food tests were made. During the early months of the case, while the anaphylactic state was at its height, the results were variable. A substance which one day gave a strongly positive reaction, three months later was often found to be negative only to become positive again after another longer or shorter interval. Likewise it was found that substances which when first tested were negative sometimes became, at a later time, positive and remained positive thereafter.

These complicated cases with their multiple figures and changing background at once invite the question, What does it all mean? We must seek the answer in the literature. It is, however, impossible to quote every reference or to consider every phase in detail. Both are too numerous. We can touch but lightly on the many phases of the subject and refer to but a few papers, choosing the most typical and best confirmed for quotation.

CAUSES OF PROTEIN SENSITIZATION

Heredity.—Our search naturally turns first to heredity as a cause of human sensitization. I could find no statistics bearing directly on the anaphylactic manifestations in the skin, but Cooke and Vander Veer²

2. Cooke and Vander Veer: J. Immunology, 1:201, 1916.

give certain suggestive figures for that allied anaphylactic symptom, hay fever.

They estimate the frequency of human sensitization with clinical manifestations at probably less than 10 per cent. Granted that, as asserted, hay fever is the most frequent manifestation of all anaphylactic phenomena, the frequency with which the skin manifestations occur must be small.

Their figures, with regard to the frequency with which a negative or positive history of sensitization in one or both parents or in a collateral family branch was obtained, are interesting. In sixty-three apparently normal cases, there was a history of sensitization in the father or in the mother in 9.5 per cent. and a positive direct or collateral antecedent history in 14.5 per cent. Among 621 cases of sensitization, the antecedent direct or collateral history was negative in 260; positive in 205; positive on both sides in thirty-nine; that is, in 504 cases out of 621 there was some antecedent history in 48.4 per cent. About 19 per cent of the sensitized persons gave an entirely negative antecedent history. These figures they compare with the 14.5 per cent. positive antecedent histories obtained in normal persons, concluding therefrom that inheritance is a definite factor in sensitization.

Moreover, still speaking of hay fever, their further studies led them to the conclusion that the more complete the inheritance, the earlier the appearance of manifestations in the child. They also concluded that sensitized persons transmit to their offspring not their own specific sensitization, but an unusual capacity for developing bioplastic reactivities to any foreign protein.

These facts and figures are characteristic and are generally accepted by all writers on the subject.

Remembering that hay fever is accepted as the great exponent of anaphylactic manifestations and bearing in mind Cooke and Vander Veer's conclusions as to the transmissibility of protein sensitization, the student will find food for thought in contemplating and comparing Schreiber's definition of arthritism or the arthritic diathesis. Schreiber³ says: "Certain infants are thus born with a 'vice of nutrition' which will manifest itself in them through a specific (individual) reaction to various pathologic agents and will also render them vulnerable to conditions which do not affect the normal organism."

Gastro-Intestinal Diseases and Protein Sensitization.—Enough has already been said to justify a hasty review of current opinion concerning the possible relationship of gastro-intestinal conditions and protein sensitization. Leri⁴ maintains that the anaphylactic state and the diath-

3. Schreiber: Arch. de med. des enfants **15**, No. 6, 1912.

4. Leri: Ann. de méd. et chir. **16**, No. 22, 1912.

eses possess too many characteristics in common for their similarity to be no more than apparent. Lesné and Dreyfus⁵ speak of alimentary anaphylaxis, meaning a process of protein sensitization arising in the alimentary tract. Johnston⁶ asserts that "anaphylaxis in the human being commonly expends its force not on the respiratory apparatus but on the gastro-intestinal tract, as is amply proved by cases of serum disease. After all, it matters very little whether indigestion is primary or secondary. It claims attention in either event." Johnston found that hyperacidity occurred more frequently than any other form of digestive disturbance. Sensitization, he says, occurs during the period of frank indigestion.

Combe⁷ supplements Johnston's views. He says that when the albumins, and especially the fats, in the body are destroyed too rapidly the organism becomes poisoned, a state of acetonemia or acid intoxication resulting. According to Combe, any inflammatory or atrophic changes in the intestinal mucosa favor intestinal putrefaction and hence intestinal toxemias. The same is also true of intestinal stasis.

Dr. V. C. Vaughan⁸ furnishes a further hint as to the possible rôle played by the digestive functions in the production of protein sensitization. Writing of the relation of anaphylaxis to immunity and disease, Vaughan says that in producing a state of anaphylaxis or immunity by the injection of certain proteins, the digestive secretions are modified according to the protein used, so that each protein has a specific ferment which acts on no other protein. This process he calls sensitization and states that it may be transmitted to the offspring.

The Liver and Toxemia.—Manwaring⁹ found that the liver played an important rôle in general toxemia. In dogs, cutting out the liver from the general circulation also cut out the anaphylactic shock. The reaction, he concludes, occurs chiefly in the liver. Rumpf¹⁰ verified Manwaring's observations by experiments on guinea-pigs, from which he too concluded that the chief effects of the anaphylactic process take place in the liver epithelium.

Combe says that the body has three lines of defense against intoxication and autointoxication, the first being the intestinal mucous membrane, the second the liver and the third the ductless glands. Anything that interferes with the functioning of the liver exposes the organism to invasion by toxins. It is not for nothing, Combe says, that all the blood

5. Lesné and Dreyfus: *Ann. de méd. et chir.* **16**, No. 22, 1912.

6. Johnston: *J. Cutan. Dis.* **30**:96, 1912.

7. Combe: *Intestinal Autointoxication*, New York, Rebman, 1910.

8. Vaughan, V. C.: *Am. J. Med. Sc.* **145**:161, 1913.

9. Manwaring: *Ztschr. f. Immunitätsf.* **8**:1, 1911.

10. Rumpf: *Ztschr. f. Immunitätsf.* **27**: 1918.

from the intestine must flow through the liver where the liver cells rob it of its poisons. In this, Combe verifies Rumpf and Manwaring.

Ductless Glands and Toxemia.—Janney and Isaacson¹¹ furnish corroborative testimony as to the value of the ductless glands in the defense of the body from their study of thyroidectomy and thyroid diseases on protein metabolites. Stated briefly, they found that thyroid disease favors protein catabolism thereby linking the thyroid to anaphylactic disease in which, according to the majority of writers, protein catabolism is a prominent feature.

Fordyce writes that owing to the frequent association of urticaria with hay fever and asthma, conditions commonly found in hyperthyroidism, the glands of internal secretion so influence the vessel tone by their products that they form an important factor in the production of anaphylaxis.

Johnston maintains that the study of a case of urine anaphylaxis in any skin disease is not complete which does not determine the percentage of these bodies (the nitrogen compounds) in the urine. In his experience the most frequent change was a decrease of urea and a corresponding increase in the rest nitrogen fractions, and that when it was marked, symptoms could be looked for.

Eosinophilia.—Among other points most commonly emphasized in the diagnosis of anaphylaxis is the occurrence of eosinophilia. Some writers, indeed, lay so much stress on this phenomenon as to create the impression that they believe it a pathognomonic symptom. Others, perhaps the majority, consider it of lesser importance.

Weinberg and Sequin¹³ state that in the anaphylactic process an eosinophilia appears in from one to three days after reinfection of the antigen. They explain the appearance by the hypothesis of a direct irritation of the hemopoietic system by the antigen. Rackemann¹⁴ adopts Staubli's theory to explain that a foreign protein acts as an eosinotactic substance.

These quotations sufficiently illustrate the general trend of opinion.

In contrast to this use of an eosinophilia as a symptom of anaphylaxis is the similar use of eosinophilia as a characteristic of the arthritic diathesis. For example, Schreiber, writing of the diatheses of infancy, quotes Dr. Finkelstein's assistant, Rosenstern, as having brought out a new point in connection with infantile arthritis. Rosenstern says, "Having practiced the examination of the blood of infants suffering from troubles in the skin or mucous membranes of the arthritic series

11. Janney and Isaacson: Arch. Int. Med. **22**:160 (Aug.) 1918.

12. Fordyce: J. Cutan. Dis. **30**:128, 1912.

13. Weinberg and Sequin: Compt. rend. Soc. de biol. **76**.

14. Rackemann: Arch. Int. Med. **22**:517 (Oct.) 1918.

(eczema, prurigo, asthma, various catarrhs, etc.), I was able to demonstrate an eosinophilia, sometimes reaching 20 per cent." Schreiber therefore concludes that an eosinophilia is common to all diathetic manifestations.

Combe considers an eosinophilia a manifestation confidently to be expected in intoxications and autointoxications.

The questions arise, What value shall we attach to eosinophilia? On eosinophilia as a basis, what relationship shall we assign to protein sensitization and the diatheses and intoxications?

If we turn to a consideration of the prevailing theories of anaphylaxis to help us to a decision we are met with disappointment. In spite of the just expectation that the immense amount of work and research, of which the large and rich literature on the subject is evidence, would yield some definite opinion or standard, we find controversy raging in this field also.

THEORIES OF ANAPHYLAXIS

Humoral Theory.—There are two theories in existence today, the humoral and the cellular. Both have their advocates and their opponents. Friedberger¹⁵ may be taken as a representative of the humoral theory. His theory teaches that the process which results in sensitizing the organisms takes place in the blood. The argument runs that if egg albumin is injected into an animal it causes antibodies to be formed in the injected animal's blood. If the antigen (egg-albumin) is reinjected into the animal thus prepared, a reaction takes place in the blood between the reinjected antigen and the antibodies prepared by the previous injection of the antigen. The presence of complement is, however, necessary. Further, as a result of this reaction between antigen, antibody and complement, the albumin molecule is broken down and a toxic product is formed known as anaphylatoxin. It will be readily seen that this theory agrees closely with the old views of the toxemias.

More recently a second theory has sprung up, and is seemingly growing steadily in favor, which opposes the humoral theory on the ground that the mere meeting of antigen and antibody in a complement containing medium does not adequately explain the symptomatology of anaphylactic shock, particularly the latent period of passive transmission.

According to Weil,¹⁶ the humoral theory is committed to the belief that the circulating antibody may exercise either a protective or an injurious function whereas the cellular theory is strictly correlated with the view that the circulating antibody is invariably protective and the cellular antibody is invariably the agent of anaphylactic symptoms

15. Friedberger: *Ztschr. f. Immunitätsf.* 4:218, 1910.

16. Weil: *J. Immunol.* 1:1, 19, 35, 47, 1916.

Cellular Theory.—Weil had previously stated that as a result of his study he had come to the conclusion that antigen and antibody could not coexist in the same field without union.

All writers agree that time is needed to produce the conditions necessary to anaphylactic shock. As Vaughan¹⁷ expresses it: "If a reinjection of protein is made before a large amount of specific ferment is formed, no anaphylactic shock results. Anaphylactic shock is not to be feared if less than twelve days intervene between the first and second injections. Goodall¹⁸ says that on an average a week or more is required for "incubation" between the primary sensitizing dose and the second activating dose.

Fordyce described the process of anaphylaxis as follows:

A foreign protein introduced into the organism causes an increase of antibodies for this protein. If after a so-called incubation period a second dose is given, the protein will be so rapidly disintegrated by the antibodies that toxic products are set free which give rise to the clinical phenomena. A further disintegration renders them harmless and the attack subsides.

Barduzzi says toxic substances that are formed in the blood or organic fluids act on the nerve cells. Urticaria is due to anaphylaxis. The symptoms are due to an irritation of the endothelium.

Rumpf found that the anaphylactic state persisted when the blood of a sensitized guinea-pig was removed and the blood of a normal animal substituted. Had the active agent of the anaphylactic phenomena resided in the blood desensitization should have ensued. Such was not the case, thereby proving that the reaction was cellular.

In brief, we may summarize the cellular theory, taking the facts from heterogeneous sources. A foreign protein is introduced into the organism. No symptoms follow. Antibodies are formed for the injected protein which are absorbed, anchored by the cells. Until enough antibodies have accumulated and have been anchored in the cells there will be no response to injections of the protein. Finally, however, the introduction of even a small dose of the sensitizing protein causes an explosion. "The reaction is an expression of the alteration of cellular equilibrium which results when external antigen is brought into contact with the cellular antibody" (Weil).

This theory is held by the proponents to answer all the objections raised against the humoral theory. It particularly explains the latent period of sensitization which the humoral theory could not. It is the period during which the process is gathering headway, when the cells are capturing and anchoring the antibodies as they are formed.

17. Vaughan: *Am. J. Med. Sc.* **145**:161, 1913.

18. Goodall: *Brit. J. Child. Dis.* **9**:433, 1912.

The antibodies are so essential to the process of anaphylaxis that, naturally, much work has been expended in trying to demonstrate their presence.

Von Fenyvessy and Freund's¹⁹ report of their studies is to the effect that the presence of antibodies in the circulation is not necessary to anaphylactic shock. As has already been shown in discussing other topics, this agrees with current opinion.

Perhaps one reason for lack of success in finding circulating antibodies lies in the results indicated by Hilda Hempl's²⁰ studies that in general a foreign serum disappears more quickly from the blood of an animal sensitized to that serum than from that of a normal animal, and that it disappears more quickly from the blood of a highly reacting animal than from that of a slightly reacting animal.

THE CUTANEOUS FOOD TEST

Schloss was among the first to demonstrate the possibilities of the cutaneous food test in cases of protein sensitization. Since that time the test has been developed widely both in use and in technic until today the average practitioner is as inclined to accept unquestioningly the apparent teachings of its results as he is to accept the results of the Wassermann test in syphilis. A brief study of the literature suggests that the circumstances surrounding the two are similar. Both tests lack full understanding. Both have their vagaries acting as they should not on the face of the evidence. Both are stronger on their positive than on their negative sides.

A few quotations will illustrate wherein the cutaneous food test is strong and wherein it is weak.

The cutaneous food test may be taken as an index that the body cells have been brought into contact with a certain protein and that in addition to the production of the anaphylactic state antibodies of a protective and curative nature are produced. Cutaneous anaphylaxis cannot be accepted as a direct or reliable evidence of actual immunity any more than the agglutinins in the same capacity.²¹

There is no experimental support for the theory that allergic skin reaction may be taken as an index to resistance and immunity insofar as it is possible to determine the presence of antibodies *in vitro*.²²

Walker, writing on bronchial asthma, says that since many patients were sensitive to proteins of foods not eaten every day as well as to the foods eaten regularly, it is hard to say what part the less frequently

19. Von Fenyvessy and Freund, J.: *Ztsch. f. Immunitätsf.* **22**:199, 1914.

20. Hempl: *J. Immunol.* **2**:141, 1917.

21. Kolmer and Berge: *J. Immunology* **1**:409, 1916.

22. Kolmer: *J. Immunol.* **3**:10, 1918.

eaten foods play. Furthermore, he continues, the fact that many of these patients have eczema as well as asthma complicates the interpretation of the positive skin test but does not detract from the value of the test. Speaking of the skin test as an index of desensitization, he says that usually the positiveness of the skin test decreases as the amount of protein in the treatment increases, provided the increase is slow and gradual. If the protein treatment is increased too rapidly, the skin test and desensitization cannot keep pace, so that eventually anaphylactic shock may result from the treatment.

Walker implies, in explaining the failure of the skin test in two patients, that a hyperirritable skin may give unjustified results.

That the skin test is not always positive when it may clinically be expected to be is shown by Rackemann's figures. Skin tests were done in 127 cases. One or more tests were positive in seventy-four cases (50 per cent.) and of these seventy-four positive tests, forty (27 per cent. of the cases) were compatible with the patient's history. Rackemann insists that there must be agreement between the skin tests and the patient's history before the evidence of the skin test shall be accepted as conclusive.

BIOCHEMICAL INVESTIGATION

Not only have there been many attempts to solve the question of the nature of anaphylaxis on broad lines, but much work has also been done along special biochemical lines.

In 1913, Vaughan wrote that each protein molecule is composed of two groups, a primary or poisonous group and a secondary and characteristic group. According to Vaughan it is in this second group that proteins differ and in which their sensitizing properties lie.

Achard and Flandin²³ report that they have succeeded in isolating the poison formed during the anaphylactic state. They concluded that the poison is formed more abundantly in the nervous system than elsewhere; that it is probably a lipoid substance; that the subject is not always toxic to other animals of the species; and that its active anaphylactic properties are essentially heterogeneous and, particularly, homogeneous.

Kahn and McNeil²⁴ report that the specificity of the anaphylactic reaction depends on the chemical structure of the protein molecule and that if the molecule be split, its anaphylactic specificity is lost.

To this opinion as to the catabolic nature of the anaphylactic reaction Miller²⁵ adds his testimony. He says that two or more

23. Achard and Flandin: *Compt. rend. Soc. de biol.* **83**:25, 1912.

24. Kahn and McNeil: *J. Immunology* **3**:277, 1918.

25. Miller: *J. Immunology* **1**:383, 1916.

antigens may produce the same antibody and the same antigen may produce two or more antibodies. He explains that the relation of antigen to antibody does not depend on the entire protein molecule and it so happens that various unrelated substances contain these groups and so produce a common antibody.

Obviously, if these statements are true, the explanation of such multiple sensitization by unrelated substances as seen in the second clinical case, and as has been so frequently encountered by others, may lie therein.

Jobling²⁶ stated in a discussion of anaphylaxis before the Society of Immunology that the lipoids, which some accuse of being actively concerned in the production of the phenomena of anaphylactic shock, can cause shock but are not able to sensitize. Wilson confirms the statement.

Saula says that there is a marked increase in soaps, fatty acids and lipoids subsequent to sensitization. He suggests that anaphylaxis may be due to increased saponification. Peterson and Jobling found that soaps injected intravenously into guinea-pigs in proper doses produce the symptoms and postmortem findings of anaphylaxis.

It has been asserted from time to time that kaolin broths, starch broths, guinea-pig serum after treatment with chloroform and ether and iodized guinea-pig serum were capable of causing anaphylactic shock and that their injection was an adequate method of studying the phenomena.

Loewit denies that these substances are capable of causing anaphylactic shock and that they furnish an adequate method of study. He finds that symptoms resulting from the kaolin and starch preparations are purely mechanical effects caused by large particles of the kaolin or starch being carried into the vessels by the injection and there producing thrombi. Likewise, the fatal effect of chloroform and ether serum is not due to anaphylaxis but to thrombi. True anaphylactic death Loewit says may occur in one of two forms—suffocation arising from bronchospasm with secondary inflation of the lung or by peripheral or central paresis of the breathing apparatus with more or less edema and hyperemia of the lungs and more or less acute pulmonary dilation. The thoracic breathing always ceases before the abdominal.

Kleinschmidt²⁷ found that guinea-pigs can be sensitized per os by boiled or unboiled cow's milk and that the active factor was the milk albumin, the casein merely causing a condition of hypersensitiveness.

Weil says that in the guinea-pig anaphylactic death is due to a cellular reaction and that the serum changes play no part in it but, on the other hand, in prolonged or delayed shock in the dog striking

26. Jobling: *J. Immunol.* **1**:491, 1916.

27. Kleinschmidt: *Monatschr. f. Kinderh.* **11**:664, 1913.

alterations occur in the chemical composition of the blood. Weil has himself contributed largely to our knowledge of anaphylactic serums by his widespread researches. He states that immune serum consists of two substances, one thermolabile (precipitin), the second thermostabile (sensitizin). Heated precipitin will unite with the antigen but has lost its power of precipitating. It has lost its ergophore group and retained its haptophore. Moreover, Weil has found that precipitating serums which give a voluminous precipitate with certain concentrations of the antigen may fail to give any precipitate with still higher concentrations. This zone of absent precipitation he calls the prozone.

Disassociation of the precipitate, which probably occurs within the body, sets free antibody in a form which sensitizes passively but fails to give a precipitate reaction; but as has been stated in another place and connection, the antigen and precipitating antibody do not coexist in the same fluid without union.

The precipitate represents a complex of both factors, antigen and antibody; neither very largely destroys the other if, indeed, any destruction occurs. In this the anaphylactic process resembles the precipitation reaction in the test tube which is not accompanied by the chemical destruction of either factor. It is immediate. It proceeds in the absence of complement. It requires relatively large amounts of antibody and relatively minute amounts of antigen.

This rapid survey of the field of protein sensitization is far from complete. Many articles have of necessity been passed over, many special researches omitted. Yet it is hoped that the broad lines have been drawn so fairly as to give an honest view of the field as a whole.

SUMMARY

1. Protein sensitization is now an accepted fact.
2. Theories as to its meaning and its mechanism differ.
3. Much that has been published concerning the process lacks confirmation.
4. Much work is still necessary in allied fields, such as the diatheses and the intoxications, before full use can be made of the new cult.
5. In the meantime while accepting the principles of the cutaneous food test, interpretation must await fuller, better defined understanding of the process of protein sensitization before it can attain its greatest efficiency.