PROTEIN SENSITIZATION IN SKIN DISEASES: URTICARIA AND ITS ALLIES *

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INTRODUCTION

One man's meat is another man's poison. This venerable aphorism attests the antiquity of our practical knowledge of sensitization. The first scientists to note the phenomenon with wonder were Jenner and Magendie. The first to note it appreciatively and reflectively was Richet.[1] The first to bring it into relation with cutaneous medicine were von Pirquet and Schick.[2] The only notable efforts to apply it to diagnosis were made by Smith [3] in connection with buckwheat poisoning, and by Schloss [4] in connection with egg albumin urticaria. The von Pirquet [5] test for tuberculosis suggested a method by which sensitization to various proteins could be clinically determined. Smith and Schloss, as stated, were the first to apply the procedure with results. In the meantime, White,[6] Strickler,[7] Blackfan,[8] McBride and Schorer [9] essayed in this field, but their investigations concerned chiefly eczema and, although their enthusiasm was compelling, the disease they mainly

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1. Richet: Anaphylaxis; Bligh's Translation, London, University Press, 1913.
2. Von Pirquet and Schick: Die Serumkrankheit, Leipzig, 1905.
3. Smith: Arch. Int. Med. **3**:358, 1909.
4. Schloss: A Case of Allergy to Common Foods, Am. J. Dis. Child. **3**: 341 (June) 1912.
5. Von Pirquet: Allergy, Arch. Int. Med. **7**:259 (Feb.) 1911; **7**:283 (March) 1911.
6. White, C. J.: Two Modern Methods to Be Employed in the Treatment of Chronic Eczema, J. A. M. A. **68**:81 (Jan. 13) 1917.
7. Strickler, A.: Anaphylactic Food Reactions in Skin Diseases, New York M. J. **104**:198 (July 29) 1916.
8. Blackfan: Cutaneous Reactions from Proteins in Eczema, Am. J. Dis. Child. **11**:441 (June) 1916.
9. McBride and Schorer: Erythematous and Urticarial Eruptions Resulting from Sensitization to Certain Foods, J. Cutan. Dis. **34**:70 (Feb.) 1916.

dealt with has no place in this paper, except where a liaison is established by factors common to the dermatitis and urticaria groups.

The similarity of serum sickness to urticaria is striking. Von Pirquet and Schick's work suggested that all urticaria was an anaphylactic manifestation. Osler's studies on the syndrome of toxic erythema, wheals, purpura and bronchial asthma in the later light of Richet's publications further substantiated the belief. The widely recognized fact that some foods, particularly strawberries, bivalves, and crustacea invariably provoked urticaria in certain persons, added to the growing edifice. In his case of buckwheat poisoning, Smith made percutaneous tests with the offending substance and produced local reactions. Schloss tested a patient with egg white urticaria in a like manner and with like results. The evidence for anaphylaxis seemed complete. Protein extracts of nearly all foods have been manufactured and percutaneous tests have been made with them. The purpose of this paper is to discuss whether, by means of this procedure, it is possible to detect the determining factor or factors in urticaria and kindred dermatoses.

Of fifty-three cases of urticaria, fifteen of which were chronic, studies were made in fourteen of the latter. Cases 7 and 11 were observed only as to their response to suprarenal extract. The other twelve were analyzed in this respect, as well as in relation to the cutaneous reactions. The time required for careful tests, their reading and interpretation, together with the difficulty of cooperation on the part of patients, precluded a more extensive series. Intensiveness of study is offered instead. As the work progressed, it rapidly became evident that the method was difficult to pursue and apply, and that it would offer but little to those in quest of a simple and direct means to isolate the cause or causes in individual cases of urticaria. There were numerous inconsistencies. It was not clear that allergy alone explained all cases. In short, the method proved either too much or too little, so that finally there took form in our minds certain questions. To answer these the work was and will be continued. Briefly, the problems appear to be as follows:

1. Are urticaria and allied conditions, notably angioneurotic edema, anaphylactic?
2. Do positive tests prove them to be anaphylactic?
3. If not, what may be their nature?
4. If not, what do the tests signify?
5. What is the practical value of the tests?
6. How are they to be clinically applied?

For purposes of reference, the cases studied are here recorded. Only the positive points have been noted, with a summary of its salient features after each history, and a short summing up of some general

facts necessary for practical purposes. This paper aspires to avoid the onus of being of the case report type, but rather to outline what is known and to indicate what should be studied in connection with a most important dermatosis. Only positive reactions have been mentioned, but tests were made with all other foodstuffs consumed by the patient, and in certain instances with other substances, such as serum, epidermal substances, namely, feathers, hair, etc., and bacterial proteins.

REPORT OF CASES

CASE 1.—Mr. L. A., aged 54, actor. Illness six months' duration. Sudden swelling of eyelids.

Diagnosis.—Angioneurotic edema. Supposed by patient to be due to light used in acting for screen pictures. He employed a "makeup" of a red and yellow grease paint and a brown powder.

Tests were made with the last two: red paint +++, yellow paint ++, powder —, cheese +++, coffee +++. Food tests made of substances ingested on day prior to last attack. In order to check up pathogenicity of positive substances, patient applied his make-up, and within an hour and a half his eyes began to smart and swell. Ingestion of suspected foods caused no reaction.

Therapy.—Suprarenal extract instillations in conjunctival sac to reduce swelling, and one hypodermic injection of 5 minims of this substance. Elimination of grease paint.

Result.—Cure.

Analysis.—Parenteral sensitization. Numerous positive responses checking up with suspected substances. Influence of suprarenal gland extract.

CASE 2.—H. O. B., a man, aged 54, merchant. A seborrheal dermatitis of several years' duration. Several weeks sudden swelling of eyes. As a boy eggs and veal had caused headache.

Diagnosis.—Angioneurotic edema.

Tests.—Egg yolk +++, egg white —, pork +, tomato +, veal +++, walnut +.

Therapy.—Rigid diet. Suprarenal gland extract both in conjunctiva and hypodermatically.

Result.—No severe recurrence for seven months.

Analysis.—Numerous positive tests. Effect of suprarenal extract. Group reaction between walnut and egg (?). Cure by removal. (On an ocean journey patient ate egg and veal with immediate recurrence.)

CASE 3.—D. K., a man, aged 66. Disease of four weeks' duration. Sudden swelling of eyes on Wednesday mornings; ate buckwheat cakes Tuesday evenings.

Diagnosis.—Angioneurotic edema.

Tests.—Buckwheat +++.

Therapy.—Suprarenal extract, conjunctival instillations. Elimination of buckwheat from diet.

Result.—Cure.

Analysis.—Single specific reaction. Elimination and cure.

CASE 4.—Mrs. A. B., a woman, aged 65. Recurrent attacks of urticaria for three months. Indigestion and constipation for three years. Urticarial lesions associated with facial angioneurotic edema lasting from one to three days. The urticaria comes at 2 a. m., the angioneurotic edema toward evening.

Diagnosis.—Urticaria and angioneurotic edema.

Tests.—Beans ++, beet ++, cabbage ++, pork +, potato +, onions +++, oats, rice, rye, tomato, walnut + each. Confirmatory tests on cabbage and potato.

Therapy.—Cathartics, two colon irrigations; two suprarenal gland injections. Removal of positive foods.

Result.—Improvement within ten days. Very few wheals; no itching.

Analysis.—Intestinal derangement, numerous positive tests, influence of suprarenal extract. Possibly successive sensitizations. Improvement by removal of suspected foods.

CASE 5.—Master M. C., aged 9; urticaria four years before. Annual recurrence; recent attack five days' duration. Associated by mother with eating of salmon. Marked constipation.

Diagnosis.—Urticaria.

Tests.—Salmon +; all other foods —. Salmon fed to child produced no attack.

Therapy.—Removal of salmon, but lesions had already begun to involute without treatment.

Result.—Spontaneous cure.

Analysis.—Abnormal digestion. Reacts to one food. This food apparently bears no causal relation to disease.

CASE 6.—Mr. W. F., aged 29, merchant. Disease of five months' duration, beginning suddenly after attack of acute indigestion. Spleen and glands in general enlarged since childhood. Wassermann test, blood count and search for plasmodia, all negative.

Diagnosis.—Chronic urticaria.

Tests.—Beef +++, cabbage ++, casein +++, carrots +++ and ++++, cheese +++; corn ++; lamb +++; whole milk +++; veal +++; wheat glutein ++, wheat gliadin and globulin +. Patient noticed that his attacks were precipitated only by carrots when the suspected foods were eaten serially, experimentally to corroborate the cutaneous tests.

Therapy.—Colon irrigation without improvement. Suprarenal extract injection, 7 minims every five days, for five injections. Slight improvement. Elimination of suspected foods, particularly carrots.

Result.—Now without attacks for three months with only carrots removed from diet.

Analysis.—Successive sensitization. Group sensitization; specific. Offending food corroborated by diet. Treatment of digestive tract. Influence of suprarenal extract. Cure by removal of carrots.

CASE 7.—Miss E. F., aged 21. Chronic urticaria six months' duration. Six minims suprarenal extract, complete relief at once. Well from January 25 to Aug. 6, 1917. Recurrence. Suprarenal extract injected August 6, 8 and 13. Well for two months. Not observed after this.

Analysis.—Effect of suprarenal extract.

CASE 8.—Master M. K., aged 4½. Urticaria six months.

Tests.—Barley, beef, bluefish, wheat ++++ each; whole egg and rice + each.

Analysis.—Group reaction.

CASE 9.—Mr. A. M. D., aged 22.

Diagnosis.—Recurrent urticaria for four years.

Tests.—Tomato ++++.

Therapy.—Elimination from diet of tomatoes.

Result.— Well in four days.

Analysis.—Single specific reaction. Cured by removal.

CASE 10.—Mrs. C. M., aged 31. Ill for two years; constipated.

Diagnosis.—Urticaria.

Tests.—Cod, pork, corn, coffee and tea ++ each; coco, coffee, lamb, lettuce and wheat + each.

Therapy.—Elimination of suspected articles from diet, on Jan. 21, 1920. Well for a week. Recurrence, with symptoms of acute gastritis. Diet continued. Free from urticaria for another week. March 5 slight recurrence.

Result.—Improvement but no cure on diet modified according to tests.

Analysis.—See result; also indigestion. Sensitization to several proteins. Group reactions.

CASE 11.—Mrs. H. N., aged 50. Urticaria for four weeks. One injection suprarenal extract; well for three years.

Analysis.—This case illustrates the use of suprarenal extract; the lesions vanished within five minutes after the injection.

CASE 12.—Miss E. P., aged 18. Ill for two and a half months; constipated.

Diagnosis.—Urticaria.

Tests.—Lima beans ++++, wheat ++, beef, cheese, coffee, chicken, rice, rye + each.

Therapy.—Elimination of suspected foods; catharsis; suprarenal gland extract.

Result.—Remission for two days.

Analysis.—See result; effect of therapy; multiple reactions; group sensitization.

CASE 13.—Mr. D. S., aged 70. Ill four months; constipated.

Diagnosis.—Urticaria.

Tests.—Lamb and potato +++, spinach +. Patient discontinued visits.

Therapy.—None instituted.

Analysis.—Multiple or group reactions. Collapse caused by suprarenal injection administered by previous physician.

CASE 14.—Miss S. W., aged 9; ill for five years, nausea, chronic constipation.

Diagnosis.—Urticaria.

Tests.—Egg +, salmon ++. Discontinued visits.

Therapy.—None instituted.

Analysis.—Multiple reactions.

I. TECHNIC

1. *Substances and Methods Used.*—The commercial products of a large pharmaceutical firm were employed in the work. It may be assumed that these preparations are at least as conscientiously manufactured as the drugs on which physicians rely in their practice. Nevertheless, it is admitted that investigators should master the art of making their test substances themselves, as Wodehouse [10] did, in order

10. Wodehouse and Olmstead: Preparation of Vegetable Proteins for Anaphylactic Tests, Boston M. & S. J. **176**:467 (March 29) 1917. Preparation of Animal Proteids for Anaphylactic Tests, Boston M. & S. J. **177**:85 (July 19) 1917.

to be able to vouch for every aspect of their experimentation. Should it ever be shown that the commercial proteins fall short in any respect, the work herein embodied is worthless. It is impracticable both for the patient and the observer to attempt more than twenty tests at a sitting. The skin is cleansed with ether, and a minute bloodless excoriation is produced at as many points along the forearm as tests are planned. A drop of decinormal sodium hydrate solution is deposited on each excoriation, and a small quantity of the protein is rubbed in with a fresh wooden applicator for each substance. Controls are made with the alkali. At first only one control was employed, but it was noted that the controls themselves vary, those near the elbow bend being larger than those near the wrist. Thus, we decided to place four controls at equal distances from the cubital fossa to the wrist in a row parallel to those of the test. If this is not done, accurate readings are impossible, all contrary statements notwithstanding, and it will be observed that the control lesions grow progressively smaller as the hand is approached.

2. *Vagaries in the Tests.*—It might be desirable to employ emulsions of raw foods for investigation. But these would spoil, and the entire literature indicates both that foods are not absorbed through the intestine in their original physical state, and that peptones and proteoses and their parent substances interreact specifically as anaphylatoxins. What is more important is that both tests and controls exhibit numerous vagaries. At times the latter exceed the former in intensity. At times responses occur to articles never ingested. This, in itself, however, has less meaning than might be imagined, but there are certain group reactions, as in Schloss' egg albumin case, that have a definite enough explanation. In urticaria, usually, there is dermographism, a phenomenon elicited in producing the excoriations.

3. *Reading the Tests.*—Thus, the reading of the tests introduces the personal equation, and yet the tests can be read with a reasonable degree of accuracy by allowing time for traumatic irritation to vanish, and by reading carefully against the controls. The reaction shows, within from ten to thirty minutes, the following features: a wheal and a stellate erythematous zone about it. If the wheal equals that of the control, and presents no erythema, it is negative, or at the most +—; if it is half again as large as the control, it is, + positive; if twice as large, ++; if three times as large +++; or if it is but half again as large and surrounded by erythema, it is ++, and so on. A wheal twice as large as the control, with a marked erythema, is +++; and everything over the above is ++++. Of course, these standards are largely subjective, and each investigator must evolve his own scale.

Tests vary slightly in intensity from time to time, but are rarely absolutely inconsistent for a given substance. Occasionally, this is not the case, and a test which at one time is positive and a week later negative, perhaps indicates the negative or antianaphylactic phase. At times, as in Case 13, the reaction may be delayed by as much as five hours, but even in this instance, correct readings, subsequently corroborated as above, were made within fifteen minutes. Strickler and Goldberg,[11] however, considered no test positive that did not persist for forty-eight hours. They, however, used the intracutaneous method which we have not attempted. Several patients reported later developments, and so far as the percutaneous tests go, Strickler's experiences do not hold.

II. IS THE SUBSTANCE THAT ELICITS A POSITIVE LOCAL REACTION A SPECIFIC PROVOKING CAUSE OF THE DISEASE?

1. *Specificity.*—The term specific, as applied in anaphylaxis, is a trifle confusing. A distinction must be made between biologic and chemical specificity. Anaphylatoxins that are biologically unlike may be chemically similar, and thus two proteins biologically distinct, may nevertheless call forth anaphylaxis. Richet stated that when we speak of specificity, it is because the preparatory substance always coexists with the exciting substance in the organic fluids we use (see section on apotoxin, and compare with Vaughan's[12] split proteins). This fact is nicely illustrated in Schloss' case which gave positive cutaneous reactions to various egg, almond and oat derivatives. Schloss was further able to show by cutaneous tests that, related to almond proteins, were those of peach, prune and plum kernels, strawberry, pear, apple and cherry seeds, but that grape and orange seeds were not related. Related to oat were rice, barley and rye, but corn and wheat were not, etc. The implication, obviously, is a chemical identity among these numerous substances. Thus, a person sensitized to a certain protein would respond to others in a kindred chemical group, although never actually sensitized by them, as is further shown in the studies of Wells and Osborn.[13] This fact is illustrated in nearly all of our own cases by the number of foods to which the skin

11. Strickler and Goldberg: Anaphylactic Food Reactions in Dermatology, J. A. M. A. **66**:249 (Jan. 22) 1916.

12. Vaughan: Protein Split Products in Relation to Immunity and Disease, Philadelphia, Lea & Febiger, 1913.

13. Wells and Osborn: Is the Specificity of the Anaphylactic Reaction Dependent on the Chemical Constitution of the Proteids, or on Their Biological Relations, Jour. Infect. Dis. **12**:341 (May) 1913; Wells: ibid. 455 (Oct.) 1908.

responds. In Case 2, a high degree of sensitization existed against egg yolk and veal. This is consistent with the extent to which these articles figured in the man's diet. On the other hand, there are instances in which only one substance appears to be the exciting agent, as in Smith's case of buckwheat susceptibility, and in Case 3 of our series.

2. *Nonspecificity.*—Multiplicity of reactions may be explained by chemical similarities in biologically totally unrelated substances. An episode early in this study that, by its apparent absurdity almost influenced us to discontinue our investigations, may be worth citing. An orthodox Jew gave reactions to pork, oysters and sturgeon, foods forbidden by the Mosaic law. This man may have transgressed as to his observances, or may have unknowingly partaken of the forbidden foods, but it is just as likely that the inconsistency had a biochemical basis.

3. *Chemical Specificity.*—It may therefore be reasonably concluded that the substance or substances eliciting positive local reactions are the specific pathogenic agents of the disease. Specific does not necessarily mean that only one food is responsible, but indicates chemical specificity in the sense that generically unrelated substances have a chemically identical architecture. This being true, the tests seem to be clearly specific.

III. CAN THE PHENOMENON BE ANAPHYLAXIS?

1. *Literature on the Subject and Present Views.*—From the preceding it may be inferred that urticaria and allied conditions may be caused by proteins in the sense that the offenders can often be determined by eliciting a local reaction, and that removal from the dietary of the indicated foods may be curative. We are definitely, then, dealing with food poisoning of some type. Is this type of poisoning anaphylaxis? To answer the question requires an outline of the nature of anaphylaxis. Richet's conception of this phenomenon is that a specific antibody is formed for each protein substance parenterally introduced. The union of antigen and its specific antibody forms a toxic entity which Richet designates as apotoxin. The nature of apotoxin is a matter of dispute, but perhaps Vaughan's assertion that it is a split protein radical is most commonly accepted. Clinically, anaphylaxis is exhibited by a series of explosive phenomena. Wolff-Eisner was the first to include among them urticaria, a concept soon substantiated by the writings of von Pirquet and Schick. The phenomenon depends on a preparatory invasion of the body by an alien protein, an incubation period, followed by a precipitating invasion of the identical protein, whereupon promptly occur a series of objective manifestations including pruritus, dyspnea, tachycardia, convulsions, bloody movements,

involuntary micturition, urticaria, diminished blood pressure due to bleeding into the sphlanchnics, and then either recovery or death. Richet first clearly observed and described the syndrome in connection with his work with actinaria, eel and horse serum. Since that time, intensive study has been accorded the subject, and a voluminous literature has amassed itself, but in no one particular are views yet quite in unison. So far as this paper is concerned, the authors feel incapable of critical review of the subject as anaphylactologists. What follows is an impersonal exposition of the minimum that must be discussed to develop the theme at hand in its clinical aspects.

2. *Similarity of Urticaria to Anaphylactic Skin Manifestations in Animals.*—Barnathon [14] describes anaphylactic accidents as characteristically sudden in appearance, and gradual in disappearance, subject to the laws of preparation and precipitation above described; as followed by a prolonged period of hypersusceptibility, and as due to albuminoids or their derivatives. Weil [15] considers the phenomenon due to a true antigen-antibody reaction. Bronfonbrenner's [16] views merit consideration, but are too technical to be included. Pick and Yamanouchi, as cited by Hektoen,[17] found a thermolabile substance the cause, and considered it an antigen. It could not be destroyed in six hours, at a temperature of 60 C., but lost its antigenic properties in fifteen minutes at 100 C. It resists drying, age and the addition of many chemicals and digestive enzymes, notably diastase, pancreatin, invertin and pepsin. The substance is always generically specific, except the lens, which sensitizes to lenses of all species but never to any other tissue. According to Rosenau and Anderson,[18] the amplitude of the sensitizing dose has nothing to do with prolonging the incubation period, but sensitization may persist for 732 days after the initial dose. Thus, from the literature, it follows that anaphylaxis is a state produced by introducing into an animal a foreign protein which so alters the body that when, within from ten to twenty days, a minute quantity of the same substance

14. Barnathon: De l'anaphylaxie alimentaire: etude clinique et experimentelle, Thèse de Paris, 1911, No. 185.

15. Weil: Anaphylaxis and Its Relation to Problems of Human Disease, Lancet-Clinic, Nov. 19, 1913. On Antisensitization with Observations on Non-Specificity in Anaphylaxis, Ztschr. f. Immunitätsforsch., December, 1913.

16. Bronfenbrenner: Specific Parenteral Digestion and Its Relation to the Phenomena of Immunity and Anaphylaxis, J. Lab. & Clin. Med. **1**:573 (April) 1916. The Nature of Anaphylatoxin, J. Exper. Med. **21**:480 (May) 1915.

17. Hektoen: Allergy or Anaphylaxis in Experiment and Disease, J. A. M. A. **58**:1081 (April 13) 1912. Precipitation Production in Allergic Rabbits, J. Infect. Dis. **21**:279 (Sept.) 1917.

18. Rosenau and Anderson: Further Studies on Anaphylaxis, Hyg. Lab. Bull. **45**: (June) 1908. Further Studies on the Phenomenon of Anaphylaxis, Hyg. Lab. Bull. **50**: (April) 1909.

is introduced, a definite syndrome is provoked. The underlying mechanism is not entirely understood, but depends on one factor or on a combination of the factors outlined. The body cells are altered to become most susceptible to a substance not inherently poisonous. The sensitization may persist for two years, as Rosenau and Anderson have shown, and the provoking substance is highly resistant to physical, chemical and digestive agents.

3. *Allergy, Idiosyncrasy, Susceptibility and Hypersusceptibility.*—After a body has been sensitized, its cells are temporarily or permanently altered in such a manner that they have become susceptible to formerly harmless proteins. In other words, their reactive powers have undergone a subtle metamorphosis. Pirquet designates this fact by the term allergy. Allergy indicates, practically, a cell hypersusceptibility to foreign proteins demonstrable by exposing the cells to small amounts of a sensitizing substance, whereupon a local, visible, inflammatory reaction arises. Pirquet called the local excitant allergen, and considered it analagous to Detre's antigen. Both in anaphylaxis and allergy periods develop in which, for reasons needing no elaboration at this point, sensitized organisms fail to respond to the precipitating substance. This phase of nonreactibility is called anergy. Antianaphylaxis is the state of desensitization.

In the preceding paragraph the word hypersusceptibility was employed. Hypersusceptibility, as Hektoen explains, is not synonymous with anaphylaxis. In a given animal a peculiar toxic reaction, depending on uniformity of the offending protein, is hypersusceptibility. In anaphylaxis, which is the result of sensitization, no matter what proteins are employed the symptoms are constant. Von Behring,[19] who noted anaphylaxis in horses against the bacillus of Nicolaier, and of various animals to diphtheria antitoxin, termed the phenomenon hypersusceptibility. This is untechnical usage in the modern sense. Anaphylaxis, then, is an artificial and restricted form of induced hypersusceptibility—a condition *sui generis*. Hypersusceptibility cannot be transmitted artificially to normal animals (it is a congenital characteristic), while anaphylaxis is transmissible. Idiosyncrasy is a broad and ill-defined term. It signifies an unusual body response to a substance. A person rendered restless by morphin, or one who gets an erythema from arsenic, has an idiosyncrasy to these substances. So, too, one who is nauseated by a given food without sensitization. Susceptibility signifies the normal tissue response to given substances, such as increased vascular tone, perhaps, to digitalis. Hypersusceptibility

19. Von Behring: Allgemeine Therapie der Infektionskrankheiten, Lehrbuch der Allgemeinen Therapie, Wien., 1899. Von Behring and Kitashima: Ueber Veminderung und Steigerung der ererbten Giftempfindlichkeit, Berl. klin. Wchnschr. **38**:157 (Feb. 11) 1901.

is an idiosyncrasy when not anaphylactic. When anaphylactic, if the word hypersusceptibility may be employed at all, it signifies an acquired characteristic due to artificially induced, definite body alterations. Hair splitting as these distinctions must seem, since in technical usage they have acquired definite significance, their definition must be understood.

4. *Anergy.*—To revert to the question of anergy alluded to above: If a sensitized animal, as Besredka, Nicolle and Otto and numerous others have amply demonstrated, be reinjected before the incubation period is complete, anaphylaxis does not take place. Also, shortly after anaphylactic shock, if animals are reinjected, the phenomenon fails to appear. Thus, by injecting at too short intervals for anaphylactic manifestations to recur, the animal can be rendered immune. In other words, it has become desensitized, and it is widely accepted that immunity and anaphylaxis are one in mechanism and significance. The state after anaphylaxis which is free from reactability to the alien protein is what von Pirquet designated as anergy.

4. *Nonprotein Substances and Anaphylaxis.*—Curiously enough, substances not proteins are capable of producing a condition at least simulating anaphylaxis. It is too fresh in the minds of physicians to need emphasis that arsphenamin is one of these, as pointed out by Homer Swift. Adercco [20] found a similar state of affairs in animals in the experimental use of cocain. The possibility of cumulative effect, however, must not be overlooked. On the other hand, it is conceivable that chemicals may alter body proteins of the host in such a manner as to convert these, in effect, into alien proteins capable of producing anaphylaxis. No experimental evidence of this exists.

5. *Humeral and Cellular Theories.*—The final scene of the anaphylactic phenomenon is the cell, but it has not yet been positively decided whether the entire action takes place there, or whether its earlier phases occur in the body juices, subsequently to be transferred to the cell for the dénouement. Thus, two schools exist, one favoring the cellular, the other the humeral theory. There is a third which records the entire process as physical. We do not pose as arbiters in the debate. As a matter of fact, so far as our theme is concerned, it makes no difference which view is academically correct, for in the final analysis, it is the cell that is affected.

6. *Clinical Mechanism of Sensitization: The Portal of Entry Intestinal.*—Thus far, mainly abstract questions of anapyhlaxis have been discussed. If urticaria is an anaphylactic phenomenon due to food sensitization, the question arises whether alimentary sensitization can

20. Adercco, V.: Action plus intense de a cocaine quand on en répète l'administration a courte intervalle, Arch. Ital. de Biol. **20**:32, 1896.

take place. Normally, only amino acids permeate the intestinal wall; peptones and proteoses do not. Amino acids cannot cause anaphylaxis. Peptones and proteoses can, and they react biologically specifically with their parent substances, or chemically specifically with related substances, as brought out in Schloss' work. Thus, it is necessary to inquire whether peptones and proteoses ever enter the circulation through the intestine. If they do, can they accomplish this through a normal intestine, or must there be an organic or functional derangement to permit this? Obviously, foods in their original chemical state are rarely assimilated. For such absorption, however, the proteins must be in solution, or at least partly hydrolyzed. Hektoen states that sensitization has been experimentally produced in guinea-pigs by the "inhalation of a fine spray of foreign serum." It is possible that some of the inhaled protein may have reached the stomach; it is also likely that some inhaled pollens reach the stomach in asthmatics and in victims of hay fever. But the supposition generally held in the latter conditions is that the protein is absorbed through the bronchial mucosa. Since there are no ferments in the latter, we may assume, with reason, that the protein is absorbed in its natural state. The inference, as it relates to the gastro-intestinal mucosa, is obvious. Furthermore, sensitization can be accomplished by rectal injection in animals, indicating absorption of unchanged protein through the alimentary mucosa.

Barnathon has exhaustively analyzed these considerations. He points out, assuming the possibility of intestinal sensitization, that patients presenting the condition are habitually troubled with constipation, or enteritis, or enterocolitis or diarrhea, and that even small amounts of precipitating doses enterally absorbed, cause the phenomenon precisely as in experimental parenteral anaphylaxis. He was able to cure urticaria in a young woman whose attacks were caused by shell fish and accompanied by vomiting and diarrhea, when he prescribed pepsin and hydrochloric acid for her achlorhydria. Arthus, cited by Barnathon, introduced antigen rectally into a rabbit, and seventeen days later elicited anaphylaxis by injection. Bouteil[21] injected the preparatory dose into the portal and mesenteric veins of dogs and rabbits, and produced anaphylaxis after a suitable incubation period. Nobecourt[22] sensitized rabbits to egg white by gastric and rectal injection. Barnathon concluded that alimentary sensitization could occur and was due to absorption of proteins incompletely hydrolyzed because of some disturbance of the digestive juices. In dogs, previously sensitized to egg white, he was unable to obtain toxic effects

21. Bouteil: Des voies d'introduction des substances anaphylactisantes, Thèse de Paris, 1910.

22. Nobecourt, P.: Mortalité des lapins sounis a des injections de blanc d'oeuf, Compt. rend. Soc. biol. **66**:850, 1909.

by injecting that substance, digested for forty-eight hours by pancreatin in an incubator. Van Alstyne,[23] experimenting with dogs, proved that egg albumin introduced into the stomach or intestine (except the duodenum) passed into the blood. With proper controls, she obtained anaphylactic shock with a dog's blood (so prepared) in guinea-pigs sensitized to albumin. She duplicated these results by feeding egg white by gavage, thus not injuring the alimentary tract. In her first series of experiments she had ligated the intestine to form a cul de sac. With milk, and horse and beef serum she reproduced both series of experiments. Ligation of the duodenum gave no consistent findings, nor did edestin give consistent results. She concluded that protein was absorbable unaltered through intact alimentary epithelium, but that trauma favored the phenomenon. She decided that conditions interfering with digestion increase absorption of unaltered protein, and applied her views particularly to urticaria. Ganghofer and Langer [24] showed that in animals under eight days old, in massive doses, the gut was permeable to alien proteins, and in two debilitated infants undigested egg white was demonstrated in the blood by precipitation tests. In this connection, be it particularly noted for future reference, that Cannon [25] observed that the alimentary canal is highly adaptable in its function. Experimentally he found that the saliva of dogs feeding on a rich carbohydrate diet acquired marked amylolitic powers, and that animals, when enraged, showed diminished intestinal peristalsis.

Uhlenhuth [26] found that prolonged feeding of egg to rabbits produced specific precipitins in their blood, and Ascoli [27] was able under the conditions mentioned to determine its presence in the blood within three quarters of an hour after ingestion. Vaughan, Cummings and McGlumpy [28] demonstrated by anaphylactic tests, that rabbits absorb incompletely digested protein through the alimentary tract. Schloss and Worthen,[27] by applying the facts recited, determined that such

23. Van Alstyne, E. V.: The Absorption of Protein without Digestion, Arch. Int. Med. **12**:372 (Oct.) 1913.

24. Ganghofer and Langer: Ueber die Resorption genuiner Eiweisskorper im Magendarmkanal Neugeborener Tiere und Säuglinge, München. med. Wchnschr. **51**:1497, 1904.

25. Cannon, W. B.: Recent Advances in the Physiology of the Digestive Organs, Am. J. Med. Sc. **131**:563 (April) 1906.

26. Uhlenhuth: Neue Beiträge zur Spezifischen Nachweiss von Eierweiss auf biologischem Wege, Deutsch. med. Wchnschr. **26**:734, 1900.

27. Ascoli in Schloss and Worthen: The Permeability of the Gastro-Intestinal Tract of Infants to Undigested Protein, Am. J. Dis. Child. **11**:342 (May) 1916.

28. Vaughan, Cummings and McGlumpy: The Parenteral Introduction of Proteids, Ztschr. f. Immunitätsforsch. **9**:16, 1911.

substances appeared in the urine. In normal infants they found that imperfectly digested proteins were absent from the urine, but were present in infants with gastro-intestinal disturbances which evidently favored assimilation of incompletely digested proteins.

As to clinical medicine, the practical inferences to be drawn from the statements made above are numerous. The intact intestine, as shown by Van Alstyne, may be capable of assimilating unaltered protein, and as shown by Arthus, is capable of assimilating altered protein. Abnormal intestinal mucosa, as indicated by Barnathon, is capable of this, and he includes in his conception of disturbances, those which are functional as well as anatomic. Bouteil's findings confirm this, as do those of all other authors cited. Schloss and Worthen, by their studies of infants, bring the work on animals into relation with human problems of sensitization, and Van Alstyne specifically applies her results to urticaria. It is perhaps speculative to remark here that the flora of the intestine, biliary disturbances, the free consumption of alcohol, spices and acid substances, may so influence the alimentary mucosa as to alter its permeability, or so influence the function of digestion as to alter the character of the proteins. By either means, or a combination of them, sensitization is as likely to occur in human beings as in animals. Herein lies probable clinical substantiation of experimental evidence. In this connection, emotional and nervous instability or strain may, in man, produce the digestive disturbances mentioned by Cannon as occurring in animals. Thus, may be accounted for practically the frequent occurrence of urticaria in neurotic and vagotonic persons.

So far as it is possible to translate human statements and physical signs into terms of morbid biology, with special reference to sound clinical medicine, many of our patients present features consonant with the ideas expressed in the foregoing paragraphs. Intestinal disturbances occurred in Cases 4, 5, 6, 10, 12, 13 and 14, a total of seven in fourteen. As a rule, the complaint was constipation. At times, nausea, vomiting, or diarrhea were found. In a woman, not included in this series, mucous colitis had existed for ten years, and the urticarial attacks began with vomiting.

7. Clinical Mechanism of Sensitization: The Portal of Entry Parenteral.—In experimental anaphylaxis it has been shown that the portal of entry may be either enteral or parenteral, and in human anaphylaxis it is clear that, when not artificially produced, as by serum injections, it is mainly enteral. Can it be parenteral? Pirquet and Schick state that guinea-pigs may be sensitized by inhaling sprayed foreign serum. In Schloss' patient, mere contact of egg with the lip produced urticaria. It is conceivable, however, that substances entering the mouth might have to be swallowed before being absorbed. In this connection it may

be remarked that such small amounts of alien protein may sensitize (1/1000,000 gm. egg white; Wells working with guinea-pigs), that sensitization through injured integument is conceivable. This entire question has not yet been adequately investigated.

If Case 1 of our series actually is an example of allergy, sensitization must have been parenteral, for the offending substances had been applied mainly to his eyelids. These substances gave positive local reactions percutaneously, and when, for purposes of corroboration, he applied the pigments to his lids, itching, burning, and slight swelling appeared within an hour and a half. Nothing is known of sensitization through normal integument, but it is possible that the skin at these sites always presents microscopic injuries, particularly in people applying cosmetics. This patient will receive further study.

8. *Clinical Mechanism of Sensitization: Hereditary, Congenital and Spontaneous Occurrence; Transmission Through Maternal Milk.*—Longcope [29] believes that hypersusceptibility is hereditary and at times spontaneous. Pirquet has shown that it may be congenital, for it is found in the offspring of anaphylactic animals shortly after birth. This, however, is merely an example of passive sensitization. Barnathon cites Hutinel's [30] observation of sensitization transmitted passively through human milk to nursing infants. The concept of hereditary anaphylaxis is difficult to grasp, unless acquired characteristics are transmissible. If the peculiarity was congenital in the first generation, it could be transmitted via the chromosomes, but this would be an example of hereditary transmission of a congenital variation, a concept conforming to our knowledge of the laws of heredity. If congenital in the first generation, and not acquired, the phenomenon would not be anaphylaxis, but hypersusceptibility or idiosyncrasy; for, having started spontaneously, it could not be construed strictly as anaphylaxis. Transmission of sensitization to offspring, or through the milk, are sound examples of the passive form, but are transitory, and the former variety has nothing to do with heredity.

9. *Influence of Drugs and Chemicals on Anaphylaxis.*—Banzhaf [31] and Steinhardt have shown that chloral inhibits anaphylactic shock, while lecethin does not. Stokes pointed out the value of atropin as a prophylactic in acute arsphenamin reactions, particularly of the type designated anaphylactoid by Swift. It is, of course, not quite clear how arsenic can cause anaphylaxis, but a discussion of this problem appears in an earlier passage (III, 4), and need not be repeated. The

29. Longcope: Susceptibility of Man to Foreign Proteids, Am. J. Med. Sc. **152**:625 (Nov.) 1916.

30. Hutinel: Intolérance pour le Lait, La Clinique, April, 1908.

31. Banzhaf and Steinhardt: Vaughan's Split Products and Unbroken Proteins: A Comparative Study of Their Effects, J. Med. Res. **23**:5, 1910.

usefulness of suprarenal extract in inhibiting anaphylaxis is widely known, and will again be alluded to in an entirely different phase, particularly in its special application to urticaria. As Sâmberger [32] points out, the wheal is primarily due to a dilatation of vessels, and suprarenal extract narrows them. The chemical mechanism of this will be further explained later. Undeniably, suprarenal gland extract usually limits individual outbreaks of wheals, and at times controls urticaria completely. In our experience, the calcium salts are utterly valueless.

Suprarenal gland extract is most efficacious when employed hypodermatically. Its administration by mouth seems futile, for it does not survive alimentary digestion as an efficacious substance. In employing it, the possibility of cardiac collapse must be remembered, and if results are not obtained after one or two injections, they will not be obtained. H. Miller's suspension in olive oil is less toxic and seems no less efficacious than aqueous solutions. Its absorption is more gradual, and hence smaller amounts of the drug may be employed, with practically no risk to the heart. Instillation into the conjunctival sac promptly reduces the swelling of the eyelids in angioneurotic edema of these organs. This was observed in Cases 1, 2 and 3 of our series. In Cases 4, 6, 7, 10, 11 and 12, it was used with uniformly good results. In Cases 5, 8, 9, 13 and 14, it was not employed, either because of the youth of the patient, or because our studies had not sufficiently advanced, or, as in Case 13, because the drug was known to act badly. The patient in this instance, a man of 70, had been given an injection of the gland extract by another physician and had collapsed. Cases 7 and 11 were included in our series to illustrate the effect of the drug. The patient in Case 7 was a young woman whose first relief in six months immediately followed an injection. She remained well thereafter, as the history shows, for seven months. The second patient was a woman of about 50 who, after constant urticaria for four weeks, was cured within ten minutes of her injection, and has since remained well for a period of three years. Knowing that suprarenal gland extract curbs anaphylaxis, and that it often curbs urticaria, have we here evidence that urticaria is an anaphylactic phenomenon? Have we here the elements of axiom one? Have we a syllogism or a sophism?

10. *The Nature of the Anaphylatoxin.*—Proteins in their original state as ingested may be anaphylatoxic, and furthermore, parent substances react specifically with their derivatives, as repeatedly stated. What, then, are these products? Magendie noted the egg phenomenon in 1839, but could not explain it. Rosenau and Anderson, working

32. Samberger: Die Entzündliche und Urtikarielle Hautreaktion, Dermat. Wchnschr. **61**:739 (July) 1915. Weitere Erfahrungen über die lymphatische Hautreaktion, Dermat. Wchnschr. **65**:623, 1917.

with horse serum, noted that its toxic properties disappeared when heated at 100 C. for an hour, but could not confirm Besredka's observations that this substance lost its sensitizing properties through age. Fleischmann [33] digested beef serum with trypsin until the Biuret test failed. Such serum loses its precipitins, and this was further substantiated by Moreschi, Neisser and Sachs by means of the Bordet-Gengou test. However, in the course of digestion, preceding the loss of the Biuret reaction, substances capable of producing anaphylaxis exist. Werbitski [34] thus was able to elicit shock in guinea-pigs sensitized to serum by reinjecting peptones derived from like serum by digestion. Richet corroborates this in the statement "as long as the albuminoid molecule is not completely destroyed, even when it is broken up by tryptic digestion, it remains capable of producing anaphylaxis." Zunz [35] proved that primary proteoses could cause both active and passive anaphylaxis, but not thio-albuminose, or other so-called proteoses, Siegfried's pepsin, fibrin, peptone-beta, or any abiuret products of peptic, tryptic or ereptic digestion. Animals sensitized to heteroproteose, protoproteose or synalbuminose (the primary proteoses) develop anaphylactic shock on reinjection with the original serum, hetero-albuminose or proto-albuminose. This does not occur with synalbuminose, thio-albuminose, or any abiuret products of any form of digestion. Hetero-albuminose and proto-albuminose sensitize and precipitate anaphylactic shock, while synalbuminose only sensitizes. It follows, therefore, that sensitization and the production of anaphylactic shock are due to different groups in the protein molecule. Pirquet long before, in the early days of anaphylaxis, stated that not all albuminoids were allergens, but that peptones acted weakly and leucin and tyrosin not at all.

Thus original proteins and their digestive derivatives, up to a certain point, are admittedly capable of intersubstitution, in the anaphylactic sense. After a certain point in cleavage, however, this no longer obtains. Moreschi, Neisser and Sachs, as quoted by Fleischmann, proved that amino acids could not be antigens. Pirquet's observations as to leucin and tyrosin apply here, as do Zunz's regarding any protein cleavage products beyond the biuret stage. Barnathon states that proteins of advanced decomposition, particularly leucin and tyrosin, do not cause anaphylaxis. Schloss and Worthen say "it has

33. Fleischmann: Ueber die Prazipitogens Eigenschaft trypsinverdaute Rinderserum, Ztschr. f. klin. Med. **59**:515, 1906.

34. Werbitski: Contribution à l'étude de l'anaphylaxie, Compt. rend. Soc. de biol. **66**:1084, 1909.

35. Zunz: Contribution a l'étude de la digestion et de la resorption des proteins dans l'estomac et l'intestin grêle chez le chien, Mém Curonnés **20**:3, 1908.

been demonstrated that specificity is lost in protein cleavage products lower than the peptones." Saunders [36] implies all of the foregoing with regard to the effect of egg albumin and milk.

Thus sensitization is produced by proteins down to, but exclusive of, the amino acid stage. The conception depends on two factors as illustrated in the split protein conception of Vaughan, Zunz and others. According to Hektoen, in sensitization, bodies of the general nature of amboceptors are formed which are specific, and after uniting with complement and antigen, produce anaphylactic symptoms and lesions. This action depends on protein digestion, as seen after the injection of Witte's peptone, a split protein. Vaughan thinks a ferment exists in the organs of sensitized animals, capable of splitting protein. Bruck's [37] experiment practically substantiates all of this. He passively sensitized a guinea-pig with human serum of a person reacting to pork and produced anaphylaxis by a second injection of hog's serum.

Anaphylatoxins are proteins capable of withstanding heat of 100 C. for an hour, or peptones, or proteoses derived from these, or split proteins such as Witte's peptone. But no protein derivatives are among these that no longer give the Biuret reaction. The parent substances, and their derivatives, obtained by any type of digestion whatever, or chemical splitting, interplay in producing sensitization or precipitation, and are capable of provoking active or passive anaphylaxis. One element of the split protein acts generically, and the other specifically, and so far as the body is concerned it is conceivable, as Vaughan states, that in the last analysis anaphylaxis depends on protein-splitting ferments in the sensitized body.

11. *Demonstration of Sensitization by Local Reactions.*—Schloss' case of egg albumin urticaria, Wolff-Eisner's impression of this disease, Smith's case of buckwheat poisoning, amply illustrate the fact that allergy exists in the tissues of sensitized persons. These authors further show that it is demonstrable by local tests. As Vaughan indicates, the higher mechanism of immunity and anaphylaxis are identical, and in a similar fashion it is clear that all nutrition and immunity being in the same category, sensitization must bear a relation to nutrition equivalent to its relation to immunity. The curious fact remains that since urticaria is anaphylactic, local reactions may be elicited by so many substances in each case. This is explained by facts outlined earlier. In the first place, a person may be actually sensitized to more than one food, just as an animal may experimentally be sensitized to several substances. Second, specificity is chemical, as well as biologic,

36. Saunders: Serum Disease as a Clinical Manifestation of Anaphylaxis, Interstate M. J. **15**:576, 1908.

37. Bruck: Experimentelle Beiträge zur Aetiologie und Pathogenese der Urticaria, Arch. Dermat. u. Syph. **96**:241, 1909.

and proteins fall into related groups as has been shown by Schloss (II, 1) and as follows from the studies of Banzhof and Steinhardt. As a matter of fact, in our series, Cases 2, 4, 6, 8, 9, 10, 12 and 13 responded to several proteins, but always with greater intensity to two, as in Case 2 (egg yolk and veal), or only one, as in Case 4 (onions), Case 6 (carrots), Case 9 (tomato), and Case 12 (lima beans). Case 8 responded intensely to barley, beef, bluefish and wheat. It will be a problem of the future to try to work out these group relationships in anaphylaxis, as only such a solution will increase the clinical value of cutaneous tests.

Perhaps the greatest practical light is thrown on multiple reactions and chemical and biologic specificity by the work of Wells and Osborn. These writers found that wheat and rye interreacted. Zein (corn) does not react to wheat gliadin, while hordein (barley) does. They continue:

> The specificity of the anaphylaxis reaction is determined by the chemical structure of the reacting proteins, rather than by their biological origin. The most reasonable explanation of these results is that both gliadin and glutein contain common groups which react with one another, and that the specificity of the anaphylaxis reaction is not dependent on the chemical makeup of the entire protein molecule.

Hordein reacts with gliadin, gliadin with glutein, but glutein does not react with hordein. Thus, probably, glutein and gliadin contain common groups. "Animals sensitized with proteins will, as is well known, react with either, and after recovery from reaction to one protein, the reaction given with the second protein is less severe."

12. *Summary.*—Different animals, as shown by Richet, present varying syndromes under anaphylactic shock, each species always presenting the same symptoms, whatever the protein used. Among symptoms of anaphylaxis in human beings, as shown by the writings of Schloss, White, McBride and Schorer, Wolff-Eisner, Pirquet and Schick, and others, may be included urticaria. Even in lower animals cutaneous manifestations, such as pruritus, occur. Anaphylaxis produces changed tissue reactions, or allergy, in the sense of Pirquet. Thus the skin may reasonably be included among the allergic tissues. It is compatible with our knowledge that sensitization may occur enterally, as well as parenterally, and thus, in human beings, incomplete products of protein cleavage may be absorbed by an abnormal intestine and sensitize the person. Sensitization of this sort is subject to the same laws as is the parenteral variety; namely, incubation, precipitation and desensitization after the shock. Even active and passive sensitization (Bruck) can be demonstrated by the serums of anaphylactic people, by means of the milk of sensitized women. The anaphylatoxin has distinct physical properties, and is both biologically and chemically

specific, the latter specificity being clinically as important as the former. It follows, since the skin is allergic, and since urticaria in general is an allergic phenomenon, that urticaria is probably an anaphylactic manifestation.

DO POSITIVE SKIN TESTS PROVE THAT URTICARIA IS ALWAYS ANAPHYLACTIC?

It is admitted that urticaria may be an anaphylactic manifestation, and that sensitization is demonstrable by local reactions or tests. Does it follow from this that positive tests prove that urticaria always is due to allergy? To discuss this we must take up several questions. 1. What is the nature of urticaria clinically, pathologically and pathogenically? 2. Is there anything in these conditions indicating anaphylaxis? 3. What is the nature of tissue reactions in general to pathogenic agents?

1. *The Nature of Urticaria Clinically, Pathologically and Pathogenically.*—Urticaria is an acute or chronic dermatosis characterized by the sudden appearance in crops of wheals. The duration of the disease may be indefinite, although the individual wheals are usually evanescent. Chronic varieties in which papules form are known and are related to prurigo. Bullous varities are related to Duhring's disease. The two last have been interpreted by Johnston and Schwartz [38] as anaphylactic manifestations. There is no substantiation of the belief. More important is the relation of urticaria to toxic dermatoses caused by drugs, unascertained factors, or appearing in general infectious diseases. The last might well be anaphylactic and of bacterial origin, but equally well might be more like drug eruptions and due to bacterial or metabolic toxins. The relationship of toxic rashes, purpura and erythema multiforme to anaphylaxis is strongly suggested in Osler's studies. An analogy between urticaria and hay fever is strikingly indicated in the writings of Robert Cooke and I. Chandler Walker, and a common bond between hay fever and urticaria is the asthma emphasized in Osler's group of diseases. That angioneurotic edema and urticaria are allied is clear from the frequency with which the former appears as a participant in the latter.

Pathologically, urticaria narrows itself down to an understanding of the wheal. Brun,[39] with egg albumin and milk, produced swellings in the ears of sensitized rabbits. True, they were not wheals, but such lesions do not develop in these animals. Undoubtedly, Schloss, Smith, Pirquet and Schick, and Longcope produced wheals locally by trauma,

38. Schwartz: Studies in the Metabolism of Dermatitis Herpetiformis, J. Cutan. Dis. **31**:994 (Dec.) 1913.

39. Brun: Contribution a l'étude de l'anaphylaxie, Thèse de Montpellier **81**: 1905.

and the application of suitable protein in poisoning by egg albumin, buckwheat and serum. Thus in urticaria, specific wheals can be produced by specific toxins. On the other hand, dermographism exists nonspecifically in urticaria, and thus excoriations alone may excite wheals. It is for this reason that specific are compared with nonspecific wheals, as controls, in making and reading the tests.

According to Kreibich,[40] wheals are due to the irritation of sympathetic cells through sensory irritants. The sympathetic ganglions are not diseased, but pathologically overfunctionate. He quotes Török [41] and Philipson, however, who considered wheals the result of toxins, and Quincke's edema is included in his generalization. More important than Kreibich's views are those of Sâmberger. He agrees with Török and Philipson to some extent, and also with Kreibich, but believes that a vasodilatation alone can produce no inflammation. Bier [42] amputated a hog's leg below a tourniquet. After removing the latter, and in spite of free hemorrhage, there was hyperemia. The explanations of Török, Kreibich and the Unna school would be inadequate to a situation in which hyperemia existed where there was a free flow of blood, as from the cut surface of the hog's amputation stump. Sâmberger, himself, thinks that the cells in the involved area have been asphyxiated, and that their oxygen hunger calls for an increased blood supply (hence, hyperemia) in order to bring more oxygen to the asphyxiated cells. Thus he concludes that capillary dilatation has this purpose. In addition, leukocytes bring nourishment to affected cells, and favoring this function is the lowered circulatory rate in hyperemia. These phenomena determine the first step in exudation, and an exudate shows the local need of cells for nutrition. In health, enough oxygen and nourishment are derived from the normally circulating blood. Exudation determines a hypersecretion of vascular endothelium, notably that of the lymphatics; and the endothelial cells, which are capable of an ameboid movement, locate themselves near disturbed tissue cells that require more oxygen and nourishment.

Hyperemia of the skin is observed in injuries by the sun, heat, mechanical agents and toxins, not through their direct influence on vasodilators, but because they thus subserve the increased need of the exposed cells for oxygen and nourishment. He regards urticaria in this category and explains the wheal on this basis. The edema of the collagen is caused by dilatation of the lymph spaces, and the wheal is not an angioneurosis but the result of an endothelial proliferation dependent on an attempt to oxygenate and feed asphyxiated and starv-

40. Kreibich: Die Angioneurotische Entzündung, Wien., 1905.

41. Török and Hari: Experimentelle Untersuchungen über die Pathogenese der Urticaria, Arch. f. Dermat. u. Syph. **65**:21, 1903.

42. Bier: Mares Physiology, Part 3, Division 2.

ing cells. The presence of mast cells proves this, and a wheal represents a compensatory hypertrophy of tissue and an increase of function designed to satisfy an imperative local need. He characterizes the wheal as a "secretory anomaly of lymph" or what he calls "a lymphatic hypersecretory efflorescence." He makes his classification more extensive than this paper requires, even including therein pemphigus. He distinguishes between ordinary and urticarial inflammation, stating that the same cause may incite in one person the former, and in another the latter, and that this rule applies to all injurious substances and traumas.

In his second paper he continues with the idea that the angioneurotic reaction, better called the "lymphatic skin reaction," is primarily due to anaphylaxis. He analyzes, in case reports, the relation between urticaria, diarrheas, weakness and asthma and discusses the rôle of vagotonia and sympathetic disturbances to the disease. Thus, he allies the mechanism to the ductless gland system. He calls anaphylaxis vagotonia acutissima, and serum sickness vagotonia acuta. In this sense he regards urticaria as an endocrine disease in which the vagus dominates the sympathetic system. In the final analysis anaphylaxis causes local asphyxia and malnutrition; wherefore, hyperemia, exudation and an endothelial hyperplasia develop. In other words, because of sympathetic paralysis as artificially produced by Claude Bernard, who elicited sympathetic ischemia by extirpating the cervical gland, the blood is locally squeezed out of the tissue in urticaria. Hence, an increased demand for oxygen is registered in the form of a final hyperemia and wheal formation. Administration of suprarenal gland extract in urticaria cured several of Sâmberger's cases. Gradinescu extirpated suprarenal glands in animals and found that the lymph flow from the thoracic duct was increased. Sâmberger thus concludes that since suprarenal extract increases the circulatory rate by narrowing the capillaries, it prevents anaphylaxis, and causes involution of wheals by the resultant increase of oxygen content in the asphyxiated cells.

Sâmberger's theory may be overnice, but it is so far in conformity with experience that his objective observations are correct. The wheal is due to the exudation. The mast cells definitely indicate the need for hypernutrition. The collagen is swollen. Suprarenal gland extract causes the wheals to involute. Whether the entire process depends on asphyxia or not, we cannot state, but whatever Sâmberger's explanation, there is something fundamental in his concept.

2. *Indication of Anaphylaxis.*—Consensus of opinion favors the belief that suprarenal gland extract inhibits anaphylactic shock. Its place in urticaria is established beyond doubt. Does this indicate that urticaria is anaphylactic? Sâmberger holds that any agent, physical, chemical, or toxic, can produce cell asphyxia, that cell asphyxia determines the wheal, and that the wheal disappears when oxygenation is

re-established, as by the effect of suprarenal gland extract. If these views are correct, wheals can be produced otherwise than in anaphylaxis, an suprarenal gland extract, because of its utility in urticaria, would not necessarily prove that the latter is anaphylactic. The effect of suprarenal gland extract in our cases, both of angioneurotic edema and urticaria, has been recorded (III, 9).

Unquestionably dermatitis venenata, some forms of which have groundlessly been considered anaphylactic, does not respond to suprarenal gland extract. Neither do these forms give positive cutaneous reactions, and nevertheless, some confusion exists as to this group. Urticarial elements, small lesions suggesting wheals, have been seen in all types of acute dermatitis. Urticarial lesions have been described in syphilis, particularly by Hazen and Sutton, and nevertheless no percutaneous responses exist in this disease, nor does suprarenal extract cause their involution. Wechselmann thought his case of satinwood dermatitis anaphylactic. The urticaria caused by the nettles is apparently not anaphylactic, and the exciting agent in primrose dermatitis, as shown by Simpson, is not a protein. In short, syphilis, nettle, primrose, rhus, and other forms of dermatitis venenata may have urticarial lesions, but these are not anaphylactic in causation. They do not respond to suprarenal gland substance, and, so far as our experience goes, no type of urticarial lesions, except those of presumably anaphylactic origin, give cutaneous reactions, or respond to suprarenal extract.

3. *Nature of Tissue Reactions in General to Pathogenic Agents.*—Whereas, in general, urticaria is perhaps justifiably considered anaphylactic, it is reasonable to suppose that other pathogenic agents, as shown above, may cause similar tissue responses. It has already been noted that wheals at times are seen in syphilis and various forms of acute dermatitis of known and unknown causation. Thus the wheal alone does not indicate anaphylaxis. On the other hand, a dermatosis characterized by wheals and giving a percutaneous protein reaction may be reasonably certainly regarded as anaphylactic, for such reactions are not encountered save in diseases due to sensitization. No toxin of any sort, of itself, causes disease. Disease is just as much a matter of tissue response, as of a pathogenic agent, and depends on an interplay of the two. Thus, no disease can arise without tissue hypersusceptibility. In this sense there is nothing peculiar about urticaria; but it is peculiar to urticaria that the special mechanism is one of general sensitization, a condition registered in given cells as allergy which can be demonstrated by a special test, not known except as to allergy. In other words, in urticaria a tissue reaction is provokable by the local application of small doses of chemically or biologically specific toxins. Without dogmatizing then, although wheal-like lesions exist in diseases not urticarial, and clearly not due to anaphylaxis, that

disease which is called urticaria may be regarded as being so, among other reasons, because evidence may be adduced of its anaphylactic origin by means of cutaneous tests.

V. SIGNIFICANCE OF THE TESTS

Numerous controls, the combined observations of numerous writers, indicate that positive reactions reveal a peculiarity of the person, otherwise every one would react to all protein, or no one would react to any. It need no longer be reiterated that at least in the majority of cases a percutaneous reaction indicates sensitization, while a negative test does not rule this out. This statement is not to be regarded as dogmatic. Amazing possibilities of confusion exist.

1. *Variations in the Reactions.*—A test may be negative in a sensitized person, perhaps because he has become desensitized, as has been pointed out by Longcope, or after serum sickness. Or it may be positive, as in the case of the orthodox Jew. Mechanical problems also arise. The excoriations may be too superficial, or too deep, introducing fortuitous elements into the wheal. But nevertheless the significance of tests is amenable to some criteria. If a substance indicated by the tests is eliminated from the diet and the patient recovers, as in Case 2 caused by veal and egg yolk, Case 3 caused by buckwheat, Case 6 caused by carrots, the test indicates a great deal. If the suspected substance is ingested, as were carrots in Case 6 and urticaria reappears, the evidence obtained by the tests seems significant. Every one is familiar with instances in which simple foods cause urticaria and on numerous occasions their pathogenicity has been proved by cutaneous tests, notably in buckwheat poisoning and in egg urticaria.

2. *Inconsistencies.*—Inconsistencies depend on mechanical data, as mentioned above, ignorance of foods ingested, as people reacting to substances they deny having eaten, and perhaps, congenital variations making them susceptible or spontaneously sensitized (III, 2, 3 and 8). Perhaps the most important consideration, however, is involved in questions of specificity and group reactions (II, 1 and 2, and III, 10).

VI. PRACTICAL VALUE OF THE TESTS

Other things being equal, and with an understanding of the possible limitations and variations in the test, a positive test, subject to conditions analyzed above, and exceptions to be indicated below, signifies sensitization to a given protein.

1. *Indications of Specificity.*—As Longcope states, and as the work of Schloss and Smith indicates, the tests may be absolutely specific. In serum sickness, however, Longcope found that the test disappeared after the onset of the disease. Unquestionably, a specific test is

obtainable, as Cases 1, 2 and particularly 3, and 6 of our series indicate. In Cases 2, 3 and 6, removal of the indicated articles determined the end of the disease. In Case 4, a large number of foods was implicated, and these foods had been included in diet especially prescribed for the patient's condition. Her first improvement dated from the elimination of the prescribed articles and the substitution of a diet consisting of substances to which she had reacted negatively. The same is true of Case 9, in which tomatoes caused the outbreak. This patient was not observed long enough to have ruled out recurrence.

On the other hand, removing the suspected substances sometimes is without result. In Cases 10 and 12 there was recurrence after improvement. Of the remaining seven cases, Case 1 was not due to food sensitization, but to vegetable substance in cosmetics. The patient recovered when he discontinued the use of these cosmetics. The patients in Cases 7 and 11 were not tested. The remaining four showed features already mentioned, or to be mentioned, but on the whole prejudicial to the value of the tests. Eight of the twelve cases tested, however, support its value.

2. *Limitations of the Test.*—The limitations of the test are perhaps better described as the limitations of our understanding of the test. Nevertheless, we may justifiably conclude that the tests themselves still present some inherent imperfections. In the first place, the proteins used are not those we eat. On the other hand, what we eat is by no means what we absorb, or what sensitizes, but must be some hydrolyzed or cleavage product resulting from digestion. We know, however, that these derivatives inter-react specifically with their parent. We further know, as nearly all our cases reveal, that there is usually sensitization to more than a single substance. The explanation of this has already appeared. In short, it is a matter of group reactions and factors inherent in the concept of split proteins. Moreover, alimentary sensitization depends on anatomic or functional disturbances, and sensitization may continue through introducing chemically like though biologically unlike substances when we attempt to modify diet with regard to suspected foods. In such an eventuality, the disease would necessarily continue. Thus no patient, until more is known of the actual facts, should be given a suspected food, without being observed for attacks of urticaria, and no cure can be expected without adequate treatment of the gastro-intestinal tract, or the latter will continue its rôle as portal of entry.

Some forms of urticaria may not be anaphylactic. This seems unlikely, although possible, as Case 5 shows. A weakly positive response to salmon was elicited in this patient, but ingestion of the suspected substance provoked no attacks. All other food substances gave negative reactions. It is probable that we did not find the right protein in this case.

3. *Value of the Tests.*—The value of the tests may be summed up as follows: Positive reactions indicate sensitization to a protein or certain proteins, as in Cases 2, 3, 4, 6, 9, 10, 11 and 14. In seven of these, the removal from the diet of the single, or the most strikingly reactive of several substances, determined a cure, and in two more, improvement, albeit with recurrence. The significance of negative tests was summed up in the last paragraph of the section preceding this.

4. *Clinical Application of the Tests.*—The limitations of the test are embraced in the newness of the method which requires improvement, in the fact that the urticarial skin is inherently irritable and may give false reactions, and in our ignorance of the clinical significance both of anaphylaxis in man and its demonstrability by local reactions. In addition to this, it requires time and perseverance on the part of both physician and patient, and a great spirit of cooperation on the part of the latter. No more than two dozen tests can be made at a sitting, and thus about seven visits are required, four to complete the series, and two or three more to corroborate the findings. But the method should be pursued, because it promises practical aid in diagnosis and therapy, as our cases show. We do not subscribe at all to Strickler's pessimism, for he worked with too few proteins to justify his condemnation of the procedure. Had it aided us less than it did, we should be loathe to relinquish the method until convinced of its worthlessness. We are convinced of precisely the opposite, and the faintest praise we can accord it is that it at least tends to elide guess work in explaining the cause of urticaria, and in treating the disease.

VII. CONCLUSIONS

1. Are urticaria and allied conditions, notably angioneurotic edema, anaphylactic manifestations? The answer is affirmative, with certain possible exceptions, and sensitization mainly occurs through an anatomically or functionally deranged intestine.

2. Do positive tests prove them to be anaphylactic? This question, too, is answered affirmatively. Sensitization can be demonstrated by local reactions. The qualifications have been discussed.

3. If not, what may their nature be? Possibly, but not probably, they may indicate susceptibility or idiosyncrasy (III, 3 and 4; IV, 3).

4. If not, what do the tests signify? They may indicate merely a tissue reactability required for response to any pathogenic agent, but this is unlikely, for no other diseases except bacterial ones, react in a manner suggesting allergy (IV, 3).

5. What is the practical value of the tests? The practical value of the tests is far reaching. First (V) positive tests indicate sensitization. Second (VI, 1), they show sensitization to certain definite proteins, either singly or in groups.

6. How are they to be clinically applied (VI, 4)? The suspected articles are to be removed from the diet. One by one they should be given to the patient. Those provoking recurrences should be permanently eliminated. Desensitization is to be practiced only as to important foods, and particularly in infants and children in whom the diet is necessarily restricted. No cures can be expected unless the abnormal digestive tract, which is the avenue of sensitization, is treated.

Certain other conclusions that cannot be incorporated in the answers to the six problems must be mentioned.

7. Of sixty-three positive reactions, thirty-seven were to vegetable, twenty-six to animal proteins.

8. Reactions to more than one protein occurred in eleven cases of twelve tested.

9. Reactions to both vegetable and animal proteins occurred in ten cases. In Case 3, however, only buckwheat was tried.

10. Suprarenal extract was of benefit in eight cases, not employed in five, and caused collapse in one.[43]

INDEX

43. In addition to the references already given, the following may be of interest:

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. TOWLE AND HIGHMAN AND MICHAEL

DR. HARTZELL was much pleased by the conversation of the gentlemen who discussed protein sensitization. It was one not only of scientific and academic interest, but of extreme practical importance. Many of the so-called special discoveries and advances in medicine spread from centers like this out to the general practitioner and he did not always use them as they might be used, but abused them. He had recently seen a number of such instances, and within a few weeks had heard a pediatrist state that infantile eczema was nothing but an anaphylactic phenomenon. Dr. Hartzell did not believe this. He had seen for some time past infants and children from 10 to 12 years of age who did not get enough to eat, and their physicians told him they were afraid those children could not digest certain proteins. Dr. Hartzell believed all would agree that urticaria was in the main a phenomenon of anaphylaxis, but was it always so? All had heard of the classic case reported years ago by Hebra in which urticaria could be produced by passing a uterine sound. It was rather difficult to explain this on any theory of anaphylaxis. One of the gentlemen had stated that dermographism was frequently associated with this trouble. Two of the most pronounced examples of dermographism that Dr. Hartzell had seen were associated with pediculosis corporis. In a case seen recently with a most extraordinary dermographism, with the disappearance of the pediculosis the dermographism disappeared promptly.

To return to the question of eczema as an anaphylactic phenomena, one was back to the old question, what is eczema? Dr. Hartzell would not deny that certain types of dermatitis might resemble eczema, but he did not believe that eczema and chronic dermatitis, which we regard as eczema, were of anaphylactic origin.

DR. FORDYCE said one of the most striking examples of the so-called anaphylactic or anaphylactoid reaction to a foreign protein was the case of a man who could not eat shell fish. If he touched the fish with his fork and put the fork in his mouth he would immediately have an outbreak of generalized urticaria. He had repeated this test many times and always with the same result. A young woman developed an outbreak of erythema iris after eating lobster. After three months she ventured again to eat lobster and had an outbreak of bullous erythema involving her face, arms and thighs.

Dr. Fordyce thought attention should be called to the sensitization of the skin that sometimes followed repeated injections of arsphenamin. He had a patient who was treated over three years ago and who developed after his fourth injection of arsphenamin a generalized exfoliative dermatitis. Three years after the dermatitis he was given a small injection of the drug, which was followed within twenty-four hours by an erythematous rash that progressively involved the entire body. His experience had taught him never to repeat the arsphenamin if the patient had previously developed an exfoliative dermatitis following its use. Sensitization to drugs was not alone confined to their internal administration. Analogous conditions have been seen after exposure to liquor formaldehydi. He had recently seen a generalized case of exfoliative dermatitis following the prolonged application of a hair dye which was chemically a paraphenylendiamin compound. This woman suffered for two months from the dermatitis and during part of this time she had an irregular rise of temperature sometimes as high as 103 degrees. She had a leukocytosis of 30,000

and an increase of eosinophils to 30 per cent. Dr. Fordyce desired to emphasize especially the skin allergy after the development of the generalized exfoliative dermatitis from arsenic.

DR. SMITH, apropos of Dr. Fordyce's remarks on sensitization to arsphenamin, recalled the case of a gentleman who was seen by Dr. White and a probable diagnosis of mycosis fungoides made. There were certain syphilitic manifestations and a positive Wassermann reaction; rather small doses of arsphenamin were given. Before this he had received a certain amount of roentgen-ray treatment for his supposed mycosis. Several months after receiving the arsphenamin, he was given Fowler's solution and became sensitized. He then disappeared for approximately two years and returned showing definite late manifestations of syphilis and received 0.3 gm. of arsphenamin. The fact that he had been sensitized to Fowler's solution three years before was overlooked. He promptly developed a severe arsphenamin dermatitis especially over the areas treated before with the roentgen ray. Dr. Smith thought it was surprising that this sensitization had persisted for such a long time.

DR. HOWARD FOX spoke of his work in conjunction with Dr. J. Edgar Fisher during the past six months with the protein skin tests. In fifteen cases (other than eczema) of urticaria, erythema multiforme, angioneurotic edema and a few other skin diseases, the practical results had been unsatisfactory. Their experience in sixty cases of adult eczema had also been disappointing. The cutaneous tests with commercial proteins had been used, following the technic of Walker of Boston. Of the sixty cases, nineteen gave positive reactions to one or more proteins. It was rather surprising to find that most of these reactions were given by the proteins of vegetables and cereals.

As most of the patients were private patients it was not feasible, as a rule, to withhold all treatment for several weeks to watch the effect of a modified diet. A striking result occurred in one case in which no treatment was given and merely the reacting foods eliminated from the diet. This patient gave a strong reaction to cabbage and several other foods. After omitting these articles from his diet, his eruption of eight years' duration cleared up for the most part in a short time. It later recurred when, on request, he again ate cabbage. In some cases the results were contradictory. Patients reacted to certain foods, but failed to improve when they were removed from the diet. Dr. Fox said that he and Dr. Fisher finally concluded that the skin tests might ultimately prove of value in a small number of cases of adult eczema.

DR. SCHAMBERG said that an attempt had been made by certain students of this subject to clarify the atmosphere by assuming two different processes, one an anaphylaxis and the other allergy or hypersensitiveness to nonprotein substances. How much scientific basis there was for this differentiation, it was impossible to say. As Dr. Highman said, certain drugs combine with proteins of the blood and then acquire the properties of proteins; especially was this so with arsphenamin. As soon as it is introduced into the blood it combines with the globulin or protein of the serum. There was a strong parallelism between dermatitis venenata and pollen catarrhs. Many persons suffer with plant poisoning, especially ivy poison, a much greater percentage perhaps than suffer with hay fever. It is impossible to speak with positiveness concerning the nature of the substance that produced the ivy poisons. We know that there is a great variety of antibodies which may be produced in response to the introduction of various antigens into the system. Some are doubtless of the nature of antitoxins. There are two types of cutaneous reactions, one exemplified in the

von Pirquet test and the other in the Schick test. A positive von Pirquet reaction means that a specific antibody in the body has reacted with the antigen injected into the skin. With the Schick test it is to determine whether the subject has natural diphtheria antibodies in his body. A positive reaction indicates that there is no antitoxin in the blood to neutralize the injected toxin, whereas a positive reaction with the von Pirquet test means that there are antibodies in the blood. It must be remembered that a positive result in the two tests lead to quite opposite deductions.

As to the practical value of cutaneous food tests, in his experience he had found that in a few instances they have given information of the greatest possible value. In the majority of instances they have proved great disappointments. The type of local reaction varies greatly according to the method employed. If the abrasive method is used the resultant reaction is a wheal, which develops in fifteen minutes, whereas if the intradermal puncture is used the resulting reaction is a nodule, which appears within twenty-four hours.

Dr. Wile said that he would like to inject a little question of doubt into much that had been said in the previous discussion. He thought there had been a loose use of the terms "anaphylaxis" and "sensitization." As he understood anaphylaxis it was not only individual inability to metabolize certain substances, but the term included the ability to transfer similar reactions to laboratory animals passively, by injection of the offending substance and the patient's serum.

Dr. Wile had had the opportunity of discussing with Dr. Schloss, at great length, some years ago the classic case of Dr. Schloss referred to. It was only after the latter was able to produce passive anaphylaxis in laboratory animals, with ovomucoid, the offending substance in egg white, and the patient's serum, that Schloss was satisfied that he had proved out anaphylaxis. The mere percutaneous tests on the skin with various protein substances that might react positively was to his mind not even presumptive evidence that such substances were necessarily anaphylactic to the person. They might suggest occasionally accurately a hypersusceptibility, but, as Dr. Engman had shown, a positive test could occur with certain substances in persons who did not and had never shown idiosyncrasy to such substance.

Dr. Hazen thought it was impossible to study this phenomenon without considering the vegetative nervous system. He remembered a child who had urticaria and this was combined in many instances with bronchial stenosis and asthma. The history, according to the child's mother, was that after riding behind a horse, and after eating eggs and chicken these attacks would come on. Dr. Hazen saw the child in one attack and found that he had a dermatitis, a true bronchial asthma, a true pyloric stenosis, a spastic colon and classic eye changes, and on examination he found that he reacted to the skin tests of horse dandruff, egg albumin and chicken. These had produced an effect on the vagus nerves and the things found clinically were due to vagotonia. At the same time Dr. Hazen did not think one was justified in thinking all these were due to allergy or hypersusceptibility.

A well-known man in Washington had three children, one of whom Dr. Hazen saw a number of years ago because of a dermatitis. Associated with this was pyloric stenosis, bronchial asthma and a spastic colon. A few days before another boy put a dog on him and the father came along and scolded the boy. Within a few minutes the boy had developed all the signs of a vagotonia. In the same family other children developed attacks absolutely similar in every respect, and these attacks could be controlled promptly by the

use of atropin. In other words, some of the attacks unquestionably are due to a vagus irritation and this is not always due to a hypersusceptibility or an allergy; in some instances they are due to marked mental irritation. This would explain some of the cases of urticaria when a patient was in a doctor's office, and when a uterine sound was passed. In a case of scabies it was possible that the absorption of the parasite would explain it, due to absorption of the protein, but not necessarily through the food tract.

DR. GRINDON thought it was possible that urticaria might be due to two causes, one anaphylactic and the other nervous in origin. To the latter group probably belonged the case of the girl mentioned by Leloir who developed urticaria whenever she was kissed. While true anaphylaxis differed from sensitization to nonprotein drugs, yet there was a certain relationship between these phenomena. If a person was subject to the one he was probably subject to the other. In a family under his observation for a number of years, a certain lady had urticaria every time she took quinin. A sister was similarly affected. She enjoyed most excellent health except that she was subject to hay fever. On one occasion Dunbar's pollantin, which was a horse serum, was used with considerable relief of the symptoms. Some years later during an attack, a drop was placed in each eye sac and a drop in each nostril. Within a few seconds she became dyspneic, the conjunctivae swelled so that they protruded from the eye clefts and the cornea could be seen at the bottom of a cup. The symptoms were most alarming, but passed off within a few minutes. One of this lady's children was given an immunizing dose of diphtheria antitoxin. Three years later the same child ran a rusty nail into its foot and was given a dose of tetanus antitoxin. Within a short time it was enormously swollen, with the eyes closed tight, the hands and fingers much swollen, and the lips everted. That condition continued off and on for three weeks; it would entirely disappear and then return. After this had been going on for two weeks the child one day suddenly became dyspneic. Epinephrin was at once administered and within a few minutes the respiratory symptoms disappeared, although the skin symptoms continued. This family group showed undoubted sensitization, both to proteins and nonproteins. This might be explained by the protein combination of which Dr. Schamberg has spoken. Another of the children in this family was subject to urticaria from a wide variety of foods.

DR. CARMICHAEL recalled the case of the infant of a prominent physician in Cincinnati. The child was breast fed for six months without any trouble. At that time the mother became ill and the child was put on bottled milk in small amounts, when it promptly developed urticaria and convulsions and almost died. It was then suggested that goat's milk be substituted for cow's milk. This was procured and the child remained on this diet for eighteen months. It was then brought to Washington and at Dr. Carmichael's suggestion cow's milk was again tried. The child was given one teaspoonful of cow's milk and within a short time a severe urticaria resulted. The child had been tested and now the only positive reactions were for cocoa and grape juice. The child could take cocoa and grape juice.

DR. VARNEY thought that desensitization, as the term was being used in the discussion, was the removal of the specific food or sensitizing substance rather than what he understood as desensitization. To desensitize a person would be to render him able to assimilate that article of food without symptoms of sensitization. Infantile eczema probably presents the most definite sensitization picture of any dermatosis. This particular form of dermatitis of

infantile eczema is fast being taken from the dermatologist by the pediatrician, largely because of our percentage of failures through, probably, lack of definite methods of determining the specific food or foods that cause the trouble.

Dr. Varney had been interested in attempts at desensitizing infants with chronic eczema of the face by administering small rectal injecions of milk every two or three days. The effect, clinically, within twenty-four hours is first a marked aggravation of the eczema, and then a prompt improvement in about 50 per cent. of the cases.

Dr. Engman said that what he meant by desensitization was the hypodermic injection of extremely small quantities of the offending protein, so that the patient could afterward use that article.

Dr. Hartzell asked whether the gentleman who referred to a dermatitis following arsphenamin thought the dermatitis was evidence of sensitization. Was such a dermatitis never the result of arsenical poisoning?

Dr. Fordyce was of the opinion that the case in which the eruption occurred after three years was due to drug sensitization.

Dr. Stokes had a way of suspecting an external factor in connection with eczema. If the patient started from home with a dermatitis and was nearly well when he arrived at Rochester they studied his environment. An interesting example of this was the case of a man from Tennessee who arrived in pretty bad shape but promptly recovered. He then went home and relapsed. It was found that the dermatitis was due to the ground bone mixture he fed his chickens. He got rid of the dermatitis by getting rid of this brand of chicken food.

Dr. Stokes wished to have Dr. Highman explain the observation of which he thought there were two recorded cases, in which raw egg white caused symptoms, whereas boiled eggs did not. Dr. Stoke's eldest son was an example of this. On the first occasion on receiving a spoonful of egg nog he immediately became cyanotic and greatly swollen, and had alarming symptoms. Since that time he had twice been the victim of raw egg white anaphylaxis. The second time was when some of the nurses went up to his house and decided that the boy had a cowlick which was not becoming and applied egg white in an attempt to improve his appearance. The boy at once developed the most alarming symptoms, a hurry call was sent to his father and when he reached home he found the boy cyanotic, the face tremendously swollen with the lower lip hanging down on the chin and giant wheals over the forehead and in the scalp. This boy could eat hard boiled eggs all the time and have no trouble, but if they were soft boiled he had a prompt response in the form of urticaria.

Dr. Stokes thought the work of Bruno Bloch was interesting in that he reported the transplanting of skin hypersensitive to trichophyton to the varicose ulcer of a patient who was not sensitive. It was found that even after the skin continued to grow on this foreign soil it still retained its sensitiveness to trichophyton.

Dr. Schamberg's mention of a tendency to distinguish between allergy and anaphylaxis reminded him that there was evidence that hypersensitiveness of the skin was not necessarily associated with systemic hypersensitiveness and that accordingly the findings in cutaneous tests could not be interpreted too literally or specifically in regard to the body at large. It was possible to demonstrate that *Spirochaeta pallida* had nothing to do with the positiveness of the luetin test and that the allergy of late syphilis might be imitated in a nonsyphilitic merely by injecting into his skin emulsions of his own skin.

Some recent experimental work by Meyers and his collaborators had tended to show that systemic egg white anaphylaxis in guinea-pigs is not necessarily associated with cutaneous hypersensitiveness to egg white.

DR. PUSEY thought that in this Friday night experience meeting the members had, in their engrossment in giving their own experiences, failed to comment sufficiently on the excellent character of the two papers that opened the discussion, for which he thought the Association was much indebted to the writers. They not only covered the subjects in an exhaustive way, but temperately and wisely. They had, in fact, epitomized all sound information on the subject up to the present. Dr. Pusey gathered that the experiences of most of the gentlemen agreed with his; that specific sensitization tests had not thus far proved of as great practical value as we had hoped they would. He, however, felt that the subject was founded on sound premises and that small as were the practical results at present, there were possibilities of much usefulness in the future.

DR. TOWLE (closing) thought the situation could be summed up very well in a phrase—"He damned it with faint praise." He had found great difficulty in writing his paper, in trying to put it in positive terms rather than indefinite terms, and the discussion had corroborated his difficulties.

Dr. Hazen spoke of the vegetative nervous system and tried to draw a sharp line where no sharp line was possible.

Dr. Schamberg spoke of the close relationship between a hypersensitive skin and anaphylaxis. Where does the one begin and the other end? That was the difficulty—they had not stopped to consider what was doing. This was not to deny that anaphylaxis did not exist, but the other also existed and always had. A good example of similar conflict of opinion is found in hysteria. Can it of itself cause actual physical signs? Some authorities say that it can and others that it cannot. A rather illuminating act is that of a Boston man specializing in food testing who has abandoned preparing a special specific substance and has adopted the practice of preparing a single immunizing substance which he gives alike to all patients, and gets equally good results. He labeled it "341" and all the patients got it.

As to the intestinal tract, it is well known that the intestinal tract becomes more permeable in the presence of pathologic conditions. Putrefaction favors congestion, congestion interferes with the normal function of the mucosa, and that favors absorption. The only question that remains to be settled is why patient "A" becomes sensitized to pork and patient "B" refuses to be sensitized. It is evident that there is a foundation somewhere and the profession must find that foundation and then determine what building should be erected on that foundation. The fact should be accepted that physicians know the pros and cons but are utterly ignorant of what goes on between the two.

DR. HIGHMAN (closing) said there was so much to be said that had been inspired by the adequate discussion that it was hard to know where to begin.

As to Dr. Wile's theory, he participated with him in his doubts as to the relationship of anaphylaxis and sensitization in a great many instances, and thought further experimentation was necessary. One experiment by Bruck was significant. He had a patient who was sensitized to pork, so he sensitized a guinea-pig to pork and then injected some of the patient's serum into the guinea-pig and produced anaphylactic shock. That showed how closely in this patient the entire complex held together.

As to the question of Dr. Stokes in regard to the egg white, he thought he could explain that. Anaphylatoxin was destroyed at 100 degrees, which was required to boil an egg hard. He did not know why the eggs would affect some children when they were boiled and some when they were raw, but so far as he was familiar with the literature, hard boiled eggs were not assumed to produce anaphylactic shock.

The question brought up in connection with the relation of hypersusceptibility to anaphylaxis was, Dr. Highman thought, a matter of academic distinction. He believed one should use the term anaphylaxis in a restricted sense as applying solely to protein poisons, and that the types of irritability of the skin seen in response to mercuric chlorid or rhus did represent something in another category. As a matter of fact, even these conditions have the elements of the cutaneous sensitization, because people who were sensitive to ivy or mercuric chlorid or any of the other substances, obviously responded in a manner somewhat similar to what occurred in some forms of food poisoning. The relation of anaphylaxis and the relation of cutaneous sensitization to anaphylaxis were not clearly understood, and, finally, the relation of cutaneous tests to the whole affair was not clearly understood, so we were venturing in a field that as yet had scarcely been explored. For this reason all scientific notions must still necessarily be vague. The whole thing must be considered with a sort of optimistic skepticism. In a series of twelve cases, which he analyzed, eight were illuminated by the test both as to the etiology and therapy. In the next series of twelve this might be reversed. Twelve swallows did not make a summer and twelve cases in a series did not constitute a thesis. We must approach the subject with an open mind. If it proved of value the value would be great, and if it had no value there was certainly no harm in traveling this uncharted sea.

DR. ENGMAN (closing) said that in egg white sensitization, bread toast could frequently be used, as could hard boiled eggs, when egg white could not be used. He thought words rather than the fundamental principles were being discussed. Was there something in which they could take the offending article which might enter the system and come in contact with the skin? There was, and if not all cases of urticaria were due to it, or all cases of eczema, some undoubtedly were. As men who limit their work to the realm of skin diseases, Dr. Engman felt that dermatologists should thoroughly investigate the subject as others were doing in other branches. The test was very delicate and had to be performed with great care, and it did not always have the same effect on a patient. Findings might be obtained at one time and none the next, and the offending element might not be recognized.

DR. MARKLEY (closing) said that it was well known that the epidermal products of certain animals may cause general sensitization with the production of asthma or hay fever as well as skin manifestations; under such circumstances the nature of the disorder is usually recognized, but if the skin alone is sensitized it presents a more difficult problem. If the skin is sensitized in local areas the skin test will, of course, be positive in these areas but negative in unsensitized areas, the result being therefore obscure unless multiple tests be made, as pointed out.