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A CASE OF ALLERGY TO COMMON FOODS *

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The idiosyncrasy of certain individuals to common foods has been recognized for many years, but until recently our knowledge has depended mainly on isolated clinical observations, and the essential causes of the condition have remained obscure.

Through the courtesy of Dr. Eli Long of this city I have had the opportunity to investigate a case of pronounced idiosyncrasy to eggs, almonds and oats in a child 8 years old, the data from which furnish the basis of this communication. At the very outset I wish to acknowledge my great indebtedness to Dr. Long for the privilege of observing the case and for a number of valuable suggestions.

I. HISTORY

Family History.—The maternal grandmother is affected with ichthyosis; with this exception the family history is irrelevant.

Personal History.—The patient, an only child, was born at term, May 10, 1904. Delivery was by low forceps and the infant was entirely normal. He was breast-fed for eighteen months and received no supplementary food until over a year old. The first teeth erupted when the patient was ten months old; he walked at the age of 18 months.

Previous Illness.—Beginning at the age of 3 months the patient was affected with seborrheic eczema of the face, head and limbs, which showed periods of improvement and recrudescence during the first year. At the age of 9 months he had a very severe attack of coryza. During the first 3 years of life the patient had a number of general convulsions, the first of which appeared at the age of 18 months. During this period there was evidence of a mild grade of rickets.

The patient has been subject to rather frequent attacks of inflammation of the respiratory tract. At the onset the symptoms resembled hay fever—frequent sneezing, lachrymation and coryza with a clear mucoid discharge. Attacks resembling bronchial asthma have been frequent, usually during the course of an infectious cold.

For a number of years the child has had a chronic scaly skin eruption which is most pronounced on the hands and arms but which has at various times affected the entire body. This rash is usually associated with itching. The severity and extent of involvement varies greatly from time to time. At times the rash has improved greatly and has almost disappeared, usually when he was on a restricted diet.

The patient has been free from all of the common infectious diseases.

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Idiosyncrasy to Egg.—The child was first given egg when 10 days old, at which time he was suffering from a slight attack of diarrhea. The white of an egg was administered in barley water and caused no symptoms whatever. The next time egg was given the patient was 14 months old, when he showed the characteristic symptoms of egg intolerance. The attempt was made to feed a soft boiled egg, of which the child took only a few tastes, cried, and refused more. Almost immediately he began to claw at his mouth and the tongue and buccal tissues swelled until they reached a size many times greater than normal. Around the mouth a distinct crop of urticarial wheals appeared. Subsequent to this experience the child refused to eat soft boiled egg.

Toward the end of his second year the action of egg on the skin was noted. The child would frequently play with empty egg shells, which always gave rise to an urticarial rash over the hands and arms.

When 22 months old egg was administered the third time. About one-eighth of an egg-white was given in milk. The child vomited immediately, the lips, tongue and inner surfaces of the cheeks became swollen and a general urticarial rash appeared.

When 2 years old, in order to determine the exact effect of egg, he was given a small quantity of partially coagulated egg-white between slices of bread. Only a very small amount was swallowed and almost immediately he began to gag and vomited profusely. The child became extremely ill. The lips, tongue and buccal tissues became enormously swollen and urticarial wheals appeared around the mouth. His face was flushed, the respirations were rapid and the mental condition dull. He soon fell into a restless sleep from which he awoke in a few moments and vomited several times. He went to sleep again and awoke after two and a half to three hours apparently well.

The next experience with egg occurred eight months later when the child ate a few small cakes in the preparation of which egg was used. Within a few moments he began to vomit and the characteristic swelling of the lips and tongue appeared. The swelling subsided within an hour.

From this time the patient was carefully guarded from all food which might contain egg, but in April, 1910, he ate a small portion of a roll the top of which was glazed with egg. The lips and tongue swelled and hives appeared around the mouth.

Idiosyncrasy to Almonds.—Two years ago the patient was given an almond for the first time. Very soon he complained of a queer feeling in his throat and within a few moments the characteristic swelling of the tongue, lips and mouth appeared. Other nuts had been eaten at various times with no ill effect.

Idiosyncrasy to Oatmeal.—During an attack of gastro-enteritis at the age of 22 months the patient was given a single feeding of oatmeal jelly from which no symptoms were observed. Oatmeal caused symptoms similar to but much milder than those due to eggs or almonds. Usually urticarial wheals appeared around the mouth and on one occasion vomiting occurred.

Examination.—Physical examination disclosed nothing of importance beyond the skin rash noted in the personal history. The skin of the hands and arms, and, to a lesser degree, of the trunk and lower extremities was dry and covered with fine scales. The individual scales were quite small and at most times the condition amounted to nothing more than a roughening of the skin. When the rash was at its maximum it was accompanied by itching.

The blood was examined twice with the following result: May, 1911: Hemoglobin 70 per cent. (Sahli), red cells 4,800,000, white cells 10,000. The differential count of 1,000 cells showed, polynuclear neutrophil cells, 70 per cent.; mononuclear cells, 18.6 per cent.; eosinophil cells, 10.1 per cent.; mast cells, 0.7 per cent. Oct. 7, 1911, the differential count was as follows: Polynuclear neutrophil cells, 68.1 per cent.; mononuclear cells, 19.2 per cent.; eosinophil cells, 11 per cent.; mast cells, 1 per cent. An examination of the urine at this time disclosed nothing abnormal.

DISCUSSION

The main problems for investigation in this case are indicated by the history. The patient exhibited an idiosyncrasy toward eggs, almonds and oatmeal, foods which are entirely harmless to the normal individual. It seemed of importance to ascertain, if possible, the constituents of the foods which were responsible for the toxic symptoms. The underlying cause of the patient's allergic condition, and a means to overcome it, seemed also problems for investigation.

II. THE REACTION

At the very outset it was necessary to devise some test other than actual feeding by which the toxic substances could be identified. Owing to the decided and at times alarming symptoms produced by the ingestion of the toxic foods, this method of investigation was considered unjustifiable.

Cutaneous inoculations on the basis of the von Pirquet tuberculin test were tried. The "borer" devised by v. Pirquet was used to produce a uniform abrasion of the skin, into which the substance to be tested was gently rubbed. The active substances produced a distinct urticarial wheal at the site of inoculation, which appeared within five to fifteen minutes after the test was made.¹ The intensity of the reaction varied but with the more active substances a wheal 1.5 to 3 cm. in diameter, which was elevated 1 to 5 mm. above the surrounding skin, was often produced. In stronger dilutions the active substances caused typical urticarial wheals by mere contact with the unbroken skin. The reaction was always immediate and always disappeared within one-half to one hour. After this time the skin abrasion only marked the site of inoculation.²

1. In a case of buckwheat poisoning observed by Smith (*Arch. Int. Med.*, 1909, iii, 350), a cutaneous inoculation of this substance caused a large urticarial wheal to appear at the abraded surface. A general reaction also occurred.

2. Schmidt (*Beiträge zum Studium der cutanen Allergien*, *Arch. f. Kinderh.*, 1910, liii, 349) has made cutaneous tests with food substances on children of different ages. He used for this purpose "puro," which consists of egg white and beef extract, and a milk preparation. The positive reaction as described by him was an area of redness or a raised papule which appeared eight to twenty-four hours after the inoculation and was analogous to the reaction to tuberculin. The positive reactions bore no relation to the disease with which the children were affected but Schmidt observed that the percentage of reactions increased with age. So far as I am aware these observations have not been confirmed and out of a great number of cutaneous tests with food substances I have never observed a clearly positive reaction of this variety. In some instances the site of inoculation would show a slight redness after twelve to twenty-four hours which at times was a trifle greater perhaps than the control. But in no instance was the redness sufficiently marked to be conclusive and the formation of a distinct papule was never observed.

Itching was a frequent accompaniment but was not constant. Usually it was present with the more pronounced reactions, and always when urticarial wheals were produced by the contact of active substances with the unbroken skin.

In order that this reaction could be used as the basis of experimental work it was necessary to show that it was specific and to determine whether it could be produced by chemical or mechanical irritation alone. Pursuant of this, numerous control experiments were made.

The mechanical irritation produced by the borer alone, or by inoculation of inert substances into the abrasion, always caused a slight swelling at the abraded surface. This traumatic reaction was slightly greater, perhaps, than that present in normal persons, but was never sufficiently marked to cause any confusion. The abrasion gave rise to a perfectly circular papule about 1 to 2 mm. in diameter and identical with the slight reaction which sometimes appears immediately after a v. Pirquet tuberculin test.

On a number of occasions tests were made to ascertain if the patient was subject to factitious urticaria, but always with negative results. Inoculation of acids in different strengths (acetic, formic, picric, sulphuric, nitric, hydrochloric, oxalic and citric) gave no evidence of the true reaction. Alkaline substances in varying dilution (carbonates and hydroxids of sodium, potassium and ammonium) were also inactive. Numerous tests were made with solutions of salts (copper sulphate, ammonium chlorid and sulphate, sodium chlorid and citrate, uranium acetate, ferrous sulphate, etc.), all of which gave negative results. Tests were also made to determine whether the various reagents used in the preparation or extraction of the different substances to be tested might cause or inhibit the reaction. In no instance could such action be demonstrated.

These experiments showed that the cutaneous reaction was not the result of chemical or mechanical irritation. Other experiments to be described later showed that the cutaneous reaction was caused only by certain food substances and to a marked degree only by those to which the patient had exhibited a pronounced idiosyncrasy.³

The occurrence of an urticarial lesion from cutaneous inoculation of the toxic foods was directly comparable to the more striking effects produced by their ingestion—urticaria and swelling of the tissues with which they had come in contact. The swelling was strictly analogous to angioneurotic edema which is closely related to urticaria if not identical with it. The symptoms due to ingestion occurred immediately, the cutaneous

3. Control tests with preparations of eggs, almonds and oats to which the patient showed a marked reaction, were made on twenty children—from two to eight years of age—and on four adults. In no case was a reaction produced.

neous reaction was also immediate. The cutaneous reaction was considered therefore as direct evidence of the toxic nature of the substance tested.

III. EXPERIMENTS WITH HEN'S EGGS

A. Egg-White

General.—Egg-white liquefied by cutting and diluted with distilled water produced a cutaneous reaction in the dilutions shown in Table 1.⁴

TABLE 1.—EGG-WHITE DILUTED WITH DISTILLED WATER

Dilution	Reaction*	Dilution	Reaction
1 to 200	—	1 to 50	+
1 to 150	±	1 to 20	+u
1 to 100	+	1 to 10	+u
1 to 75	+		

* + and — indicate positive and negative reactions, respectively; ± indicates a reaction which was suggestive or at one time positive and at another negative; u indicates urticaria by contact with the unbroken skin. These symbols will be used throughout the paper.

Experiments were then undertaken to determine the nature and properties of the toxic substance (or substances) in egg-white.

1. Dialysis of egg-white through a collodion membrane against distilled water for varying periods up to seventy-two hours showed that the active substance was not diffusible. The dialysates when tested plain or after concentration to a small volume were incapable of causing a cutaneous reaction.

2. Alcohol (95 per cent.) and ether extracts and the residues obtained by complete evaporation of the solvents were inert. The residues insoluble in alcohol and ether were capable of causing a marked reaction.

3. The active substances were completely precipitated by saturation with ammonium sulphate. The filtrates freed from ammonium sulphate by dialysis, or by heating with barium carbonate, were inert. The precipitate was extremely active.

4. Egg-white was coagulated by heat and acetic acid. The filtrate was concentrated to a small volume and freed from protein by precipitation with alcohol. The protein-free filtrate was inert.

These experiments indicated that the toxic action of egg-white was due to the protein substances or to some substance intimately connected with them.

Experiments with Proteins Isolated from Egg-White.—Despite the vast amount of study devoted to the separation and properties of the

4. Throughout the experimental work a control test was made with each series of experiments, using distilled water or some substance previously found to be inert. All of the experiments were made at least twice; a number were repeated many times.

proteins of egg-white, the exact relationship and nature of some of the substances isolated by different workers is not clearly established.⁵

It is not my intention, nor is it within the province of this paper to discuss the unity or the chemical relationship of the various proteins separated from egg-white. The attempt has been made to isolate protein substances which are apparently distinct in order to ascertain if possible the protein fraction — or fractions — responsible for the patient's symptoms.

Five proteins were separated — ovomucin, ovoglobulin, ovalbumin, ovomucoid and conalbumin. These terms refer only to the substances isolated by the methods followed. Ovalbumin was obtained in crystalline form by the method of Hopkins⁶ and was purified by recrystallizing three times. Ovomucin was prepared by diluting egg-white with four volumes of distilled water, dissolving the precipitate in a weak solution of sodium hydroxid and reprecipitating with dilute acetic acid. This procedure was repeated four to five times, the precipitate being thoroughly washed between each precipitation.

The fractions called ovoglobulin were obtained as follows: Egg-white was precipitated by half saturation with ammonium sulphate, the precipitate mixed with a small amount of distilled water and dialysed against running water for twenty-four hours. A rather heavy precipitate in mucin-like threads and flakes settled out. This precipitate was thoroughly washed with water, pressed between layers of filter paper and dried in a current of air from an electric fan. This fraction was called Ovoglobulin 1.

To the filtrate was added three-eighths volume of a saturated solution of ammonium sulphate, the resulting precipitate mixed with water and

5. Two protein fractions can be separated with a considerable degree of sharpness, ovalbumin and ovomucoid. The former can be obtained in crystalline form. The latter, owing to the fact that it is not coagulated by heat and is precipitated by alcohol without losing its solubility in water, can be obtained free from coagulable protein. There is some uncertainty concerning the relationship of ovoglobulin and ovomucin. The ovomucin of Eicholtz (*The Hydrolysis of the Albumins*, Jour. Physiol., 1898, xxiii, 163) was obtained by diluting egg white with water and is considered by some to belong to the globulin fraction. Osborne and Campbell (*The Protein Constituents of Egg-White*, Jour. Am. Chem. Soc., 1900, xxii, 423) used the term ovomucin for a considerable portion of the fraction precipitated from egg-white by one-half saturation with ammonium sulphate. They considered that their ovomucin was identical with that of Eicholtz. Langstein (*Ueber die gerinnbaren Stoffe des Eierklars*, Beitr. z. chem. Phys. u. Path., 1902, i, 83) objects to the term ovomucin and with Corin and Berard (*Beitrag zum Studien der Albumenstoffe Eierweiss*, Jahresb. d. Fortschr. d. Tier-Chem., 1888, xviii, 13) believes that there is more than one globulin in egg-white. A non-crystalline albumin with a lower coagulation temperature than the crystalline form has been described by Osborne and Campbell, and later by Langstein. This substance has been termed conalbumin.

6. Hopkins: On the Separation of a Pure Albumin from Egg-White, Jour. Physiol., 1900, xxv, 307.

filtered. A considerable portion of the precipitate remained on the filter. The insoluble residue was washed with water and dried in the same manner as Ovoglobulin 1. This fraction was called Ovoglobulin 2.

The opalescent filtrate was dialysed against running water for twenty-four hours. No precipitation occurred. The solution was precipitated by one-third saturation with ammonium sulphate, the precipitate redissolved in water and again dialysed. This dialysed solution was used for the cutaneous test as Ovoglobulin 3.

Ovomucoid was prepared by the method of Mörner.⁷ Liquefied egg-white was poured into boiling water acidulated with acetic acid. The mixture was heated in the presence of a sufficient quantity of acetic acid to precipitate all of the coagulable protein. The filtrate was concentrated on the water-bath and the ovomucoid precipitated by pouring into four volumes of alcohol. Purification was effected by redissolving in water and reprecipitating by alcohol several times, solution in water, dialysis for twenty-four hours, and final precipitation by alcohol.⁸

TABLE 2.—TESTS WITH PROTEINS ISOLATED FROM EGG-WHITE

Solution	1-20,000	1-15,000	1-10,000	1-5,000	1-1,000	1-500	1-100	1-10
Ovomucin dissolved in 0.5 per cent. sod. carb.	—	—	—	+	+	+	+u	+u
Ovoglobulin 1 dissolved in 0.5 per cent. sodium carbonate solution	—	—	—	+	+	+	+u	+u
Ovoglobulin 2 in 0.5 sodium carbonate solution	—	—	—	+	+	+	+u	+u
Ovoglobulin 3	—	—	—	—	—	—	—	—
Ovalbumin, dissolved in distilled water	—	—	—	—	—	—	±	+
Ovomucoid dissolved in distilled water	±	+	+	+u	+u	+u	+u	+u
Conalbumin dissolved in 1 per cent. sodium carbonate solution	—	—	—	—	—	—	—	—
Conalbumin liquefied by artificial gastric juice	—	—	—	—	—	—	—	—

Conalbumin was prepared by the method of Langstein (see note 5). These protein fractions were used for the skin test with the results shown in Table 2.

These tests show that ovomucoid was the most active protein and was capable of causing a cutaneous reaction constantly in dilutions of 1 to 15,000 and frequently in dilutions as high as 1 to 20,000. Ovomucin and the fractions called Ovoglobulin 1 and 2 were next in activity. According to our present knowledge these three fractions are identical

7. Mörner: Ueber ein im Hühnereiweiss in reichlicher Menge vorkommende Muzinsubstanz, *Ztschr. f. physiol. Chemie*, 1894, xviii, 525.

8. I am indebted to Dr. Eddy (On the Synthesis of Some Protein Salts, Dissert. Columbia Univer., 1909) for a considerable quantity of very pure ovomucoid which he had carefully prepared for use in previous experiments.

(Osborne and Campbell, Eicholtz). Conalbumin and the fraction called Ovoglobulin 3 were incapable of causing a reaction. Ovalbumin was active only in a comparatively concentrated solution. In consideration of the fact that the first separation of ovalbumin takes place in a liquor rich in ovomucoid, and owing to the activity of ovomucoid in high dilution, it was considered possible that the reaction produced by ovalbumin was dependent on a small amount of ovomucoid mechanically incorporated in or adherent to the crystals. That such was true is indicated by the following experiment:

A concentrated solution of ovalbumin was coagulated by heat and acetic acid. The coagulum, thoroughly washed with distilled water and liquefied by the action of artificial gastric juice or dissolved in 1 per cent. sodium hydroxid solution, caused no reaction.⁹

The toxic action of egg-white was due, therefore, to the protein ovomucoid and to the fractions called ovomucin by Osborne and Campbell and Eicholtz.

*B. Experiments with Egg-Yolk*¹⁰

Egg-yolk was capable of producing a cutaneous reaction in the dilutions shown in Table 3.

TABLE 3.—EFFECT EGG-YOLK DILUTED WITH DISTILLED WATER

Dilution	Reaction	Dilution	Reaction
1 to 50	—	1 to 10	+
1 to 20	—	1 to 5	+
1 to 15	±		

The activity of egg-yolk was shown to be about one-tenth as great as egg-white.

Experiments demonstrated that the active constituents of egg-yolk were completely precipitated by saturation with ammonium sulphate, were insoluble in alcohol or ether and were not diffusible through collodion membranes. These properties would seem to indicate that the toxic substances belonged to the protein constituents.

9. Control experiments with the active proteins showed that the action of gastric juice for several hours or even days, was incapable of preventing the reaction. The same was true of the action of sodium hydroxid.

10. To obtain the yolks entirely free from egg-white the following procedure was used: The yolks were first washed as free as possible from the white by the method of Pennington (*A Chemical and Bacteriological Study of Fresh Eggs*, Jour. Biol. Chem., 1909, vii, 109) and then treated with 95 per cent. alcohol which served to harden the vitelline membrane and to coagulate any trace of white adherent. The alcohol was poured off and the remaining traces removed by gently blotting with filter paper. A fine pointed pipette was passed through the vitelline membrane into the center of the yolk mass. The fluid yolk was aspirated into the pipette and blown into suitable receptacles, the first and last portions in the pipette being discarded as a further precaution.

Ovovitelline was prepared by the method of Weyl,¹¹ dissolved in 0.5 per cent. solution of sodium carbonate, and tested on the patient. No reaction occurred.

IV. EXPERIMENTS WITH ALMONDS

General.—An emulsion of ground almonds produced a marked cutaneous reaction and the following experiments were undertaken to determine the nature of the toxic constituents:¹²

1. A substance capable of causing the reaction was diffusible through both collodion and parchment membranes. This activity of the dialysate was dependent on a protein substance which gave positive tests for proteose. About 10 gm. of finely ground almonds were dialysed through collodion against 100 c.c. of distilled water. The separate dialysates for each twenty-four hours were concentrated to a small bulk on the water-bath and used for the skin test. The results are shown in Table 4.

TABLE 4.—DIALYSIS OF AN EMULSION OF ALMONDS THROUGH COLLODION

Period of Dialysis	Cutaneous Reaction	Biuret Reaction
First 24 hours	+	+
Second 24 hours	+	+
Third 24 hours	+	+
Fourth 24 hours	+	+
Fifth 24 hours	+	+†
Sixth 24 hours	*	—
Seventh 24 hours	—	—

*Suggestive. †Very faint.

At the conclusion of the experiment the contents of the bag gave a positive cutaneous reaction and a strong biuret test.

2. Aqueous and 10 per cent. saline extracts of almonds were freed from protein by treatment with heat and acetic acid, concentration of the filtrate and complete precipitation of the remaining protein by alcohol. The precipitate in each instance was quite active, the protein-free filtrate was inert.

3. Saturation of an aqueous or a 10 per cent. saline extract of almonds with ammonium sulphate precipitated all of the active constituents. The filtrate when tested plain, or when freed from ammonium sulphate, was entirely inert.

4. The active substances were not soluble in alcohol (95 per cent.) or ether.

These experiments indicated that the active constituents of almonds belong to or were intimately connected with the proteins.

11. Weyl: Abderhalden's Handb. d. Biochem. Arbeitsmeth., 1910, ii, 381.

12. The almonds used in the experiments were freed from the brownish outer skins by drenching for a few moments with boiling water, since it had been found by previous experiment that these skins were incapable of causing a cutaneous reaction.

Experiments with Proteins Isolated from Almonds.—The globulin amandin¹³ was extracted by treating finely ground almonds with 10 per cent. sodium chlorid solution for twenty-four hours. The extract was saturated with ammonium sulphate. The precipitate, dissolved in 10 per cent. sodium chlorid solution, was dialysed through collodion. The amandin was precipitated as a viscid, semiliquid mass which settled to the bottom of the bag. The crude amandin was washed with water, dissolved in 10 per cent. sodium chlorid and again precipitated by dialysis. The precipitate was washed thoroughly with distilled water, increasing strengths of alcohol and absolute alcohol, and then dried in a warm room.

A considerable quantity of amandin is extracted from almonds by distilled water. A small portion thus dissolved is precipitated by dialysis and is probably extracted by the neutral salts contained in the almonds. The greater portion of the amandin dissolved in an aqueous extract, however, does not separate on dialysis but is precipitated by dilute acetic acid and is probably extracted in the form of a salt. After precipitation it shows the same gross chemical and physical properties as the amandin extracted with salt solution.

A proteose was obtained from almonds by two methods: (1) A saline or aqueous extract, which gave no further precipitate on dialysis, was dialysed against increasing strengths of alcohol and precipitated by pouring into four volumes of 95 per cent. alcohol. This crude material was purified by solution in water and reprecipitation by alcohol, which procedure was repeated three times. This method gave only a very small yield of proteose, which was explained by the fact that the proteose itself was to a great extent diffusible, in consequence of which a considerable portion was lost during the dialysis against water. (2) The second method was similar to that used in preparing ovomucoid. An aqueous extract of finely ground almonds was completely precipitated by heat and acetic acid, the filtrate concentrated and precipitated by alcohol. Purification was effected in the usual manner.¹⁴

13. Osborne: Conglutin and Vitellin, *Amer. Chem. Jour.*, 1896, xviii, 609; *The Vegetable Proteins*, 1909.

14. The different preparations of the proteose gave a distinct biuret reaction in dilutions of 1 to 10,000 to 1 to 15,000. A positive reaction was given to the Liebermann, Millons, xanthroproteic, Molisch and Hopkins-Cole tests. The proteose was precipitated from an aqueous solution by picric acid, potassium ferrocyanid and acetic acid, phosphomolybdic acid, phosphotungstic acid and nitric acid. The precipitates were soluble on warming the mixtures and reappeared on cooling. Tannic acid also caused a heavy precipitate, but it was not soluble on warming. Precipitation was not effected by half saturation with sodium chlorid alone but was induced by the addition of acetic acid. Acetic acid alone caused no precipitate. Partial precipitation occurred on half saturation with ammonium sulphate. The proteose was diffusible through both collodion and parchment membranes but not completely so. Prolonged dialysis always left a non-dialysable portion which responded to the proteose tests.

The results obtained with the isolated proteins from almonds when used for the cutaneous test are shown in Table 5.

TABLE 5.—TESTS WITH THE ISOLATED PROTEINS FROM ALMONDS

Solution	1-20,000	1-15,000	1-10,000	1-5,000	1-1,000	1-100
Amandin in 10 per cent. sodium chlorid or 0.5 per cent. sodium carbonate solution*	—	—	—	+	+	+
Proteose in distilled water†	±	+	+	+	+	+

*Separate tests made with preparations of amandin obtained by dialysis of a saline extract, by dialysis of an aqueous extract, or by precipitation of an aqueous extract with acetic acid gave the same results.

†Preparations of the proteose obtained by direct dialysis of ground almonds, and by methods 1 and 2, gave the same results.

The proteose from almonds was therefore capable of producing a cutaneous reaction in approximately the same dilutions as ovomucoid. The diffusible nature of the proteose explains the results shown in Table 4.

The activity of amandin was less than the proteose and was comparable to the ovomucin-globulin fraction from egg-white.

V. EXPERIMENTS WITH OATS AND OATMEAL

General.—An aqueous suspension of oatmeal or finely ground oats gave a distinct cutaneous reaction which was much less marked, however, than that obtained with almonds. The general properties of the constituents of oats on which the cutaneous reaction depended were as follows:

1. Ether and alcohol (95 per cent.) extracts of oats or prepared oatmeal applied directly or after evaporation of the solvent were inert.

2. The active constituents were completely precipitated by saturation with ammonium sulphate.

3. Oatmeal and oats were dialysed through collodion against distilled water. The dialysates for each twenty-four hours were concentrated on the water-bath and used for the skin test. The dialysates for the first five days gave a positive biuret test coincident with a distinct cutaneous reaction. The dialysates for the sixth and seventh days caused no reaction when tested on the patient and were negative to the biuret test.

4. Aqueous and 10 per cent. saline extracts of oats and prepared oatmeal were freed from protein by heat and acetic acid and by precipitation of the concentrated filtrate with alcohol. The protein-free filtrate was inert.

Experiments with the Isolated Proteins from Oats.—The globulin avenalin was extracted and purified in the same manner as amandin from almonds. Owing to the considerable amount of starch in oats a different procedure was necessary to obtain the proteose. It was prepared by two methods: (1) Oatmeal was dialysed against distilled water until the dialysates no longer gave a positive biuret test. The dialysates were

mixed, concentrated to a small bulk on the water-bath and precipitated by 95 per cent. alcohol. Purification was effected in the usual manner. (2) The proteose was found to be soluble in 50 per cent. alcohol while but a small amount of starch was removed by this menstruum. Based on this property the following procedure was used: Oatmeal or finely ground oats were extracted with 50 per cent. alcohol for twenty-four hours. The alcohol was evaporated and the remaining aqueous extract was concentrated to a very small bulk and precipitated by 95 per cent. alcohol. The resulting precipitate was purified in the usual way by dissolving in a small amount of water and reprecipitating by alcohol.

On evaporation of the 50 per cent. alcohol extract a considerable amount of the alcohol-soluble protein, *prolamine*,¹⁵ separated out. This material was dissolved in hot 65 per cent. alcohol and precipitated by allowing the alcohol to evaporate. The precipitate was again dissolved in hot alcohol and reprecipitated by pouring into a large volume of water. This precipitate was well washed with water and 95 per cent. alcohol and dried before an electric fan. The prolamine was also obtained by extracting oats with 70 per cent. alcohol and purifying by the method given above. The three proteins from oats were used for the cutaneous test with the results shown in Table 7.

TABLE 7.—TESTS WITH THE PROTEINS ISOLATED FROM OATS OR OATMEAL

Solution	1-20,000	1-15,000	1-10,000	1-5,000	1-1,000	1-500	1-100
Globulin dissolved in 10 per cent. sodium chlorid or 0.5 per cent. sodium carbonate	—	—	—	+	+	+	+u
Proteose obtained by alcohol extraction..	—	—	±	+	+	+u	+u
Proteose* obtained by direct dialysis	—	±	+	+	+u	+u	+u
Prolamine† dissolved in 0.5 per cent. sodium carbonate or 0.5 sodium hydroxid	—	—	—	—	—	—	—

*The difference in the activity of the proteose prepared by alcohol extraction and that prepared by direct dialysis is probably due to the fact that the latter was in a purer form. It was found that the former contained some starch, while the latter was almost starch free.

†Uniform results were obtained with several different preparations of this protein.

The experiments with oats have practically the same significance as those with almonds. The active substances were closely associated or identical with the proteins. An active substance (proteose) was diffusible. The prolamine from oats was incapable of causing a cutaneous

15. Osborne: The Proteids or Albuminoids of the Oat Kernel, Amer. Jour. Chem., 1891, xiii, 327; The Vegetable Proteins, 1909.

reaction, the globulin was active in approximately the same dilutions as the globulin from almonds. The proteose from oats was slightly less active than the proteose from almonds.

VI. TESTS WITH OTHER FOODS

Various foods were used for the skin test as control experiments and also to determine whether certain substances biologically related to the toxic foods were capable of causing a reaction. The results are given in the accompanying tables.

TABLE 8.—RESULTS OF SKIN TESTS WITH VARIOUS FOODS, BLOOD SERUMS, ETC.

Food substances related to almonds (Rosaceae)	Tests with various nuts	Miscellaneous food substances
Peach kernel +	Brazil nut —	Peas —
Prune kernel +	Pecan —	Beans —
Plum kernel +	English walnut —	Cabbage —
Strawberry seed +	Black walnut —	Sweet potato —
Apple seed +	Chestnut —	Irish potato —
Pear seed +	Butternut —	Parsnips —
Cherry seed +	Hazelnut —	Carrots —
	Peanut —	Cauliflower —
	Skin tests with chicken and related blood sera	Tea —
Other fruit seed	Chicken—	Coffee —
Grape —	Hen +	Milk —
Orange —	Rooster +	Sugar —
	Duck +	Bananas +
	Turkey +	Tests with proteins chemically related to the active proteins from eggs, almonds and oats
	Goose +	Witte's peptone (proteose) —
Food substances related to oats	Tests with miscellaneous blood sera	Bence Jones protein* —
Rice +	Lamb —	Nucleoalbumin —
Barley +	Horse —	Salivary mucin —
Corn —	Calf —	Ovomucoid from shad roe† —
Wheat —	Pig —	Tendomucoid‡ —
Rye +	Fish (whole blood) —	

*Obtained through the courtesy of Dr. J. Rosenbloom of this Laboratory. "A Contribution to the Study of the Nature and Origin of the Bence-Jones Protein." Dissertation, Columbia University, 1909.

†This preparation was kindly supplied by Dr. Eddy and was prepared during previous experimental work, "On the Synthesis of Some Protein Salts." Dissertation, Columbia University, 1909.

‡One of the many preparations Prof. Gies has used in previous researches on glycoproteins.

These experiments show that the cutaneous reaction was only relatively specific and was caused by substances biologically related to eggs, almonds and oats. The reaction was produced not only by the blood-serum of the chicken, but also by that of the turkey, goose and duck. The serums of creatures not biologically related (sheep, horse, pig and cow) caused no reaction. Certain plant substances which belong to the

same family, as almonds, also caused the reaction. The results with foods related to oats were somewhat though not quite similar. Rice, barley and rye were capable of producing a mild reaction, but wheat and corn were apparently inert. On the other hand seeds of fruits and various vegetable foods which were not related to almonds or oats were incapable of causing a reaction. Bananas, however, furnish a striking exception for they caused a pronounced skin reaction. It is interesting to note that although rice, barley, rye and bananas were capable of causing a skin reaction, yet they had been eaten at various times without the production of definite symptoms.

VII. EXPERIMENTS WITH THE ACTIVE SUBSTANCES

It was demonstrated by experiments previously described that the cutaneous reaction was caused by various proteins from eggs, almonds and oats. These results indicate that the reaction was dependent on the protein substances themselves or on some substance intimately connected with them. It seemed desirable, therefore, to ascertain if possible whether the reaction was caused by the proteins themselves, or whether it was due perhaps to some contaminating substance which, though distinct from the proteins, was inseparable by the ordinary methods of preparation.

Effect of Heat.—In the preparation of the proteoses from almonds and oats and of ovomucoid, a considerable degree of heat was used which had no apparent influence on the cutaneous reaction. To determine definitely if heat had any power of impairing the reaction, the following experiments were made: Solutions of 1-to-10,000 ovomucoid and the proteoses were placed in test-tubes and immersed in boiling water for three hours. Any loss by evaporation was made up, and the solutions tested on the patient, using a part of the original (unheated) solution as a control. There was no perceptible difference in the reactions.

Dialysis.—Ovomucoid and the globulins from oats and almonds did not pass through a collodion membrane and the dialysates, though concentrated to a very small bulk, did not cause a cutaneous reaction. The proteoses from almonds and oats were to a great extent diffusible through collodion and parchment membranes and the patient reacted to the dialysates as long as they gave a positive biuret test. When the dialysates no longer contained protein, no cutaneous reaction was given. At this time, however, the contents of the bag still contained a non-diffusible residue which responded to the proteose tests and was capable of causing a cutaneous reaction.

Fractional Precipitation with Ammonium Sulphate.—Aqueous solutions of ovomucoid and the proteoses from almonds and oats were precipitated by the graduated addition of ammonium sulphate. The demarcation of the different precipitates was not sharp, but from four to six fractions were obtained for each protein. Each fraction caused a cutaneous reac-

tion in dilutions of from 1 to 14,000 to 1 to 8,000.¹⁶ The final filtrates which had been saturated with ammonium sulphate caused no reaction.

Precipitation with the Alkaloidal Reagents.—Aqueous solutions of ovomucoid and the proteose from almonds were precipitated by phosphotungstic and phosphomolybdic acids, by potassiomeric iodid, potassium ferrocyanid and acetic acid and tannic acid. The mixtures were filtered and the filtrates used for the skin test. In no instance was a cutaneous reaction produced.

TABLE 9.—THE EFFECT OF TRYPTIC DIGESTION UPON THE ACTIVITY OF OVOMUCOID AND THE GLOBULINS AND PROTEOSES FROM ALMONDS AND OATS

Duration of Digestion, Days	Ovo-mucoid		Globulin Oats		Proteose Oats		Globulin Almonds		Proteose Almonds	
	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction
7	+	+	+	+	+	+	+	+	+	+
11	+	+	+	+	++	+	+	+	+	+
13	+	+	+	+	—	+	+	+	++	+
15	+	+	+	+	+	+	—	+
19	+	+	—	+	++	+	—	+
24	+	+	—	+	—	+	..	—
46	+	+	—	+	—	+
56	+	+	—	+	+
74	—	+
80	—	+

*Faint.

Adsorptive Properties.—If the active substances were chemically distinct from, but mechanically adherent to, the proteins, it was considered possible that this adsorptive tendency might be manifested by other proteins. In the effort to ascertain whether this was true, the following experiments were made:

Ten c.c. of horse's blood-serum was mixed with an equal volume of 1 to 10,000 solutions of ovomucoid and almond proteoses. The mixtures were acidulated with acetic acid and coagulated by heat. The well-washed coagulums, plain, or liquefied by artificial gastric juice, caused no reaction on the patient. The experiments were repeated using sheep instead of horse blood-serum. The results were also negative.

Effect of Tryptic Digestion.—Ovomucoid and the globulins and proteoses from almonds and oats were digested by means of an active pancreatic extract. The proteins were dissolved in 0.5 per cent. sodium carbonate solution in dilutions of 1 to 500 and 1 to 1,000 and digested at 37° C. Toluol was used as a preservative. From time to time portions of the material were removed and used for the skin test, the results of which are given in Table 9.

16. All of these precipitates contained ammonium sulphate, which accounts for the fact that they gave the reaction only in more concentrated solution than the pure proteins.

These experiments showed that the activity of the proteins was destroyed by tryptic digestion and that the cutaneous reaction disappeared before the proteins were completely hydrolysed. It seemed, therefore, that the cutaneous reaction was dependent on some grouping of the protein molecule higher than the peptones. In order to determine this point with greater accuracy the globulins from almonds and ovomucoid were subjected to tryptic digestion for fifteen days, at which time the mixtures were capable of producing a marked reaction. No precipitate was produced by neutralization with hydrochloric acid. The substances precipitated by saturation with ammonium sulphate produced a marked skin reaction; the filtrate gave a distinct biuret reaction but produced no effect when tested on the patient.¹⁷

These experiments demonstrate that the substances responsible for the cutaneous reaction partook of the general properties of the proteins and that it was impossible to obtain an active substance distinct from the proteins. On gradual hydrolysis of the active proteins with trypsin the cutaneous reaction disappeared before the biuret reaction. So far as one can judge from these experiments it seems probable that the cutaneous reaction was dependent on some definite grouping in the protein molecules.

VIII. THE NATURE OF THE PATIENT'S HYPERSUSCEPTIBILITY

The next problem of importance concerned the nature of the patient's idiosyncrasy. Obviously his hypersusceptibility to the food proteins was due to one of two causes. Either he lacked some protective substance which is present in normal individuals, or he was sensitized in some way to the food proteins.

A number of experiments were undertaken in the effort to demonstrate the presence of a protective substance in normal individuals. Four specimens of human blood (citrate) and human blood-serum were mixed with different dilutions of the active proteins and tested on the patient immediately or after incubation at 37 C. In no instance did these solutions give a less active cutaneous reaction than the controls which were of the same dilution but did not contain blood or serum. Moreover, the minimum dilution of the active substances necessary to induce the cutaneous reaction was entirely independent of the presence of human blood or serum in the solutions.¹⁸

17. Results obtained by hydrolysis with 25 per cent. sulphuric acid were practically identical with those obtained by tryptic digestion.

18. The attempt was also made to determine whether the patient's blood contained some substance which by its action on or combination with the active proteins was capable of producing urticaria. Mixtures of the patient's blood and blood serum in different proportions with varying dilutions of ovomucoid and the proteoses from almonds and oats were tested on normal individuals. The tests were made immediately after mixing and also after varying periods of incubation at 37 C. In no instance was urticaria produced.

These experiments being entirely negative, the attempt was made to sensitize passively guinea-pigs to egg my means of the patient's blood-serum. The results of the experiments are shown in the following protocols:

1. A 260 gm. guinea-pig was given 6 c.c. of partially inactivated¹⁹ blood-serum from the patient by intraperitoneal injection. Twenty-five hours later 150 mg. of ovomucoid by intraperitoneal injection. The development of symptoms was as follows: 15 minutes after injection, coat roughened, animal uneasy. Twenty minutes: cough, stridor, recession of sides on inspiration, slight diarrhea. Twenty-five minutes: dyspnea increasing, tendency to lie on side. Forty-five minutes: body limp, respirations labored. Apnea and death 82 minutes after injection. Autopsy: Lungs whitish and enormously distended leaving but a small triangular area of the heart uncovered, petechial hemorrhages in intestinal wall. Heart continued to beat over 10 minutes after the thorax was opened.

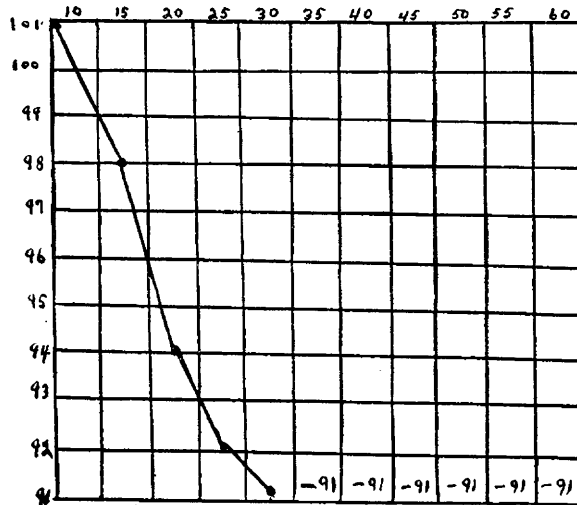


Chart 1.—Temperature Curve of Guinea-Pig 1. Figures at the left indicate the temperature F. The thermometer was not graduated below 91 F. The figures at the top indicate minutes after the injection.

2. Weight 290 gm.; 6 c.c. of partially inactivated blood serum from the patient by intraperitoneal injection; twenty-nine hours later 150 mg. of ovomucoid by intraperitoneal injection.

19. In the first experiments the attempt was made to inject the blood-serum in active form. The active serum was extremely toxic for guinea pigs, 3 c.c. being sufficient to cause the death of a 250 gm. pig within eight to ten hours. The serum was then partially inactivated by heating at 53 to 54 degrees C. for sixteen minutes. After this treatment the serum still caused the animals to become slightly ill (roughening of coat, lachrymation, slight dyspnea), but they recovered completely within a few hours. The toxic action of normal blood-sera has been studied by Uhlenhuth, Pfeiffer (Ueber die nekrotisierende Wirkung normaler Seren, *Ztschr. f. Hyg. u. Infektionskr.*, 1905, li, 183; *ibid.*, *Wien. klin. Wchnschr.*, 1909, xviii, 465; *Das Problem der eiweiss Anaphylaxie*, etc., 1910) and others and is considered due to a definite antibody, probably hemolytic. According to Pfeiffer the symptoms due to the injection of toxic foreign sera are practically identical with those of anaphylaxis.

coid (in normal saline) by intraperitoneal injection. Fifteen minutes: animal uneasy, roughening of coat; 25 minutes: Dyspnea, recession of sides on inspiration, cough; 45 minutes: body limp, lying on side; respirations slowed and labored; began to improve about an hour after the injection and had recovered completely in about five hours.

Controls.—Four guinea-pigs about 250 gm. in weight each, were given 6 c.c. of normal human serum (partially inactivated) by intraperitoneal injection. Twenty-four hours later three were given 150 mg. of ovomucoid by intraperitoneal injection. Beyond a fall of temperature of 1 to 3 degrees F. they developed no symptoms. The remaining animal was given 2 c.c. of inactivated horse serum by intraperitoneal injection. No symptoms developed.

These experiments demonstrate that the patient's blood-serum contained some substance which was capable of sensitizing guinea-pigs to ovomucoid. It seems justifiable to assume therefore that the allergic condition of the patient — to egg at least — was due to protein sensitization or anaphylaxis.²⁰

IX. IMMUNIZATION. THE RELATIONSHIP OF THE PATIENT'S ALLERGY TO EGGS, ALMONDS AND OATS

The next, and the most important problem from a practical standpoint, was that of immunization.²¹ The patient's marked idiosyncrasy to egg was, to say the least, a great inconvenience. A vast amount of care was required in the preparation and supervision of his food and a number of palatable and nutritious food preparations were excluded from his dietary. With the problem of immunization was also connected several points of scientific interest.

The history of the patient indicates that his idiosyncrasy to egg was not congenital but was acquired at some time when he was between the ages of 10 days and 14 months. It seems possible that sensitization occurred at the time egg was first administered. In reference to oatmeal the history is similar. The first administration of oatmeal when the patient was 22 months old caused no symptoms; subsequently the ingestion of oatmeal caused characteristic urticarial lesions.

On the other hand, so far as can be ascertained from the history, toxic symptoms occurred the first time almonds were eaten. To explain his

20. These experiments have a close analogy to those of Bruck (*Experimental Beiträge zur Aetiologie und Pathogenese der Urticaria*, Arch. f. Dermat. u. Syph., 1909, xevi, 241). The patient was susceptible to urticaria from the ingestion of pork. Bruck was able to sensitize guinea-pigs to pig's serum by means of injections of the blood-serum of the patient. The experiments were admirably controlled and were conclusive in every way.

21. The only recorded instance of immunization in a case of idiosyncrasy to egg that I have been able to find is that of Scofield (*A Case of Egg Poisoning*, Lancet, London, 1908, i. 716) whose patient suffered from disturbances practically identical with those of my own patient. Scofield began by administering minute quantities of egg in pills (1-10,000 part of a raw egg), gradually increased the dose and later gave foods containing small amounts of egg. By this means the patient was cured of the idiosyncrasy.

hypersusceptibility to almonds three possibilities were suggested: (1) The condition may have been congenital; (2) the patient may have been sensitized by eating a small amount of almonds, which circumstance escaped the observation or memory of the parents, though this seems most unlikely; (3) the sensitization to eggs or oats may have in some way rendered him hypersusceptible to almonds. There would be no means of ascertaining whether the first or second hypothesis was correct. From the results of immunization, however, evidence could be obtained which would serve to show the correctness of the third hypothesis.

It seemed preferable therefore to use a single protein for immunization rather than any one or all of the three foods, as by this means it could be ascertained whether the patient's hypersusceptibility to the different proteins and foods was in any way related. If, for example, immunization to one protein from the egg also induced immunity to the other active

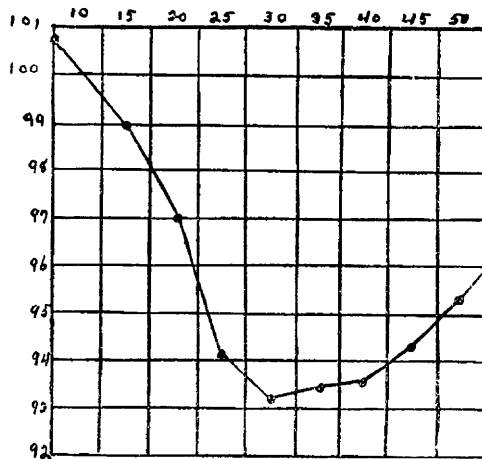


Chart 2.—Temperature curve Guinea-Pig 2. The figures at the left indicate the temperature F. The figures at the top indicate the numbers of minutes after the injection.

protein from this source, it would show that the patient was not sensitized to the distinct proteins but to some constituent group common to both. If immunity to almonds and oats also occurred, proof would be ample that the patient's allergic condition was specific neither for the protein molecule as a whole nor for the proteins of a single source, but to some group common to the active proteins of all three foods.

On the other hand, if immunity was induced only to the protein administered, or to proteins of the same source, a separate sensitization to each protein, or to each food, must be assumed.

Ovomucoid was selected as the protein for immunization, as it was one of the most active and could be prepared easily and in a state of comparative purity.

Treatment was begun Oct. 28, 1911, by the administration of 2 mg. of ovomucoid in capsules three times a day. The dose was increased at first gradually and then more rapidly. At first the quantity was increased at the rate of 2 mg. a day and on November 19 the daily increase was raised to 6 mg. Subsequently the daily increase was as follows: from November 26 to December 5, 12 mg.; from December 5 to December 14, 24 mg.; from December 14 to December 23, 48 mg.; from December 23 to January 1, 78 mg.; from January 1 to January 14, 190 mg.; from January 14, 380 mg. Toward the end of immunization the patient was taking over 7 gm. of ovomucoid a day.

The progress of immunization was determined by means of the cutaneous reaction. About the first of December the reaction began to decrease and was induced only by comparatively strong dilutions of ovomucoid, 1 to 500 and stronger. On January 8 the reaction had decreased greatly and on January 11 a small amount of egg-white was touched to the patient's lips. No disturbance occurred and on January 12 the patient ate about one-sixth of an egg with no ill effect.

From this time foods containing egg, and also soft boiled or raw eggs; were fed each day. The foods containing egg caused no symptoms. At first the patient complained that soft boiled egg caused his mouth to sting or itch but these sensations were accompanied by no objective disturbances and later disappeared. During the immunization the patient was in comparatively good health and presented no symptoms referable to the administration of the ovomucoid. The larger doses of ovomucoid, however, produced a fall of temperature which was most pronounced after a marked increase in the dose and at times amounted to 1.8 F. This fall of temperature would gradually become less pronounced. When the dose was again greatly increased the fall of temperature would recur.

The cutaneous reaction to egg and the proteins from egg has entirely disappeared. The proteose from oats causes no reaction in dilutions as great as 1 to 50 and oatmeal has been eaten a great number of times with no resulting symptoms. A distinct cutaneous reaction is still given to a 1 to 500 dilution of almond proteose. A 1 to 100 dilution is capable of causing urticaria by contact with the unbroken skin. Dilutions weaker than 1 to 1,000, however, cause no cutaneous reaction. The decrease in the patient's reaction to this substance is shown by comparison with the results in Table 5. Almonds have been eaten several times; in most instances the patient complained of itching of the tongue or throat, but usually nothing was visible on examination. On two occasions, however, urticarial wheals appeared on the inner surface of the lower lip. This disturbance appeared to be less than that which occurred previous to immunization. A differential blood count on February 7 was as

follows: polynuclear cells, 64 per cent.; mononuclear cells, 27.3 per cent.; eosinophils, 8.1 per cent.; mast cells, 0.2 per cent.

The above experiments showed that the administration of ovomucoid by mouth completely immunized the patient to egg. It is therefore apparent that he was not sensitized to the distinct proteins of the egg but to some constituent group common to the toxic proteins. At the same time the patient became entirely immune to oatmeal and less sensitive, though not immune, to almonds. Judging from these results it would seem that the patient's allergic condition to the three dissimilar foods was in some way related. Our present knowledge of the subject is too meager, however, to interpret these results as proving that the original sensitization to egg or oats also sensitized the patient to almonds. Moreover, the results from a single case are insufficient data on which to base this view, which is not in accord with the current ideas of the specificity of anaphylaxis.²² Another possibility which must be considered is that the sensitization to egg and oats, although not the direct cause of the patient's idiosyncrasy to almonds, may have served in some way as a predisposing cause.

X. SUMMARY

In a boy now 8 years old marked urticarial lesions were caused by the ingestion of eggs, almonds and oatmeal. The idiosyncrasy to egg was not congenital but was acquired at some time between the ages of 10 days and 14 months. Symptoms due to the ingestion of oats appeared some time after the child had first eaten oatmeal when he was 22 months old. As far as can be ascertained, the idiosyncrasy to almonds was manifested the first time this food was eaten.

It was found that cutaneous inoculation of these and certain related food substances produced an urticarial wheal at the site of inoculation. The cutaneous reaction was produced only by the protein constituents of eggs, almonds and oats. Different proteins from the same source varied in activity, some being incapable of causing a reaction. Some of the active proteins caused urticaria by mere contact with the unbroken skin.

It was possible passively to sensitize guinea-pigs to ovomucoid (one of the active proteins from eggs) by intraperitoneal injections of the patient's blood-serum.

22. Our present knowledge of anaphylaxis, however, is derived almost entirely from animal experiments and there is no proof that the specificity of the phenomenon is the same for all species. It is quite possible that the reaction in man is not specific, and other cases of food allergy which are under observation at the present time support this view. On the other hand, it is also possible that there is some fundamental condition present in certain individuals which may predispose to sensitization by food substances. If this were true the individual may be sensitized separately to each food to which he reacts and the non-specificity of anaphylaxis in the human being may be only apparent and not real.

By feeding ovomucoid in gradually increasing doses the patient became immune to egg. At the same time immunity to oatmeal and an apparently decreased susceptibility to almonds occurred.

I wish to acknowledge my deep indebtedness to Professor Gies for his kindness in placing the facilities of his laboratory at my disposal, and to him and his associates for much assistance. It is a pleasant duty to express my thanks to the parents of the patient not only for their patience and cooperation during ten months of tedious experimentation, but also for a number of valuable observations.

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