SENSITIZATION DISEASES.*

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It has become a fundamental biological truth, that the entrance of an undigested foreign protein, formed or unformed, into an animal produces profound chemical and immunological changes. The substances injected have been called antigens and the chemical biological changes have been collectively called antibodies. The number and exact nature of antibodies are only recognizable by the reactions they produce and nothing is known of their chemical structure or how they produce reactions. The mere demonstration of these antibodies in the circulatory blood is but one phase of the changes that have taken place in the treated animals and is no index to the intracellular reaction. All tissue cells suffer the most profound changes in the manufacture of immune bodies and upon this fact ultimately depend the explanation of the physiological reaction when an antigen and its antibodies are combined. This physiological cellular phenonema is a protective mechanism for the more effective assimilation and elimination of the foreign proteins that have entered and the mechanism is different when cellular and soluble proteins are injected. ¹Magendie in 1839 and ²Richet in 1902 found that the first dose of a foreign protein injected into an animal was followed by an increased susceptibility for the specific protein. The syndrome of symptoms which follows the union of the specific antibodies which are produced by a previous dose of protein and the antigen in an animal, results in shock or injury which only occur following the reinjection of the protein after a properly spaced interval. This phenonema is called anaphylaxis, hypersusceptibility, or better, allergy. If hypersensitiveness to other substances as chemicals and not protein solutions are included, allergy is the better term.

Sensitivity may be produced by injecting proteins of either animal or vegetable origin. The condition is specific for the protein injected and the hypersusceptibility develops only after the lapse of a definite interval, usually about twelve days. The interval varies to a certain extent as to the amount administered. An animal once sensitized may remain so for a long period. The condition of sensitiveness can be transmitted from one animal to another by the transfusion of blood. The sensitiveness can be made to disappear for

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a short period of time immediately after the recovery from a non fatal dose of protein. This period is called period of desensitization or antianaphylaxis and upon it is based the rationale of treatment in anaphylactic diseases.

The exact nature of the toxemia produced when an apparently harmless protein is injected perenteally into a sensitized animal has not been proven. Freidberger thought anaphylatic shock due to destruction of the blood complement. Vaughan³, Jobling⁴, Peterson and I have observed the presence of toxic protein in blood following anaphylaxis which is considered an etiological factor in the production of shock. Further ⁴Jobling, Peterson and I have observed decided blood ferment and antiferment changes during anaphylactic shock in dogs. In a recent publication⁵ I have shown by experiments upon rabbits, dogs and guinea pigs a decided reduction in the alkali reserve of the blood immediately and before the advent of other clinical symptoms of shock. Zinzer and Porges think anaphylactic shock results from a disturbance of the protective blood colloids. All these theoretical explanations fail to entirely explain this complex and violent reaction. Anyone experienced in experimental production of anaphylaxis in animals is impressed with the profound symptomatology produced by the re-injection of foreign protein into a sensitized animal.

For a long time anaphylaxis has been considered an acute phenomenon and only recently have milder allergic reactions in animals received detailed investigation and by these experiments there has developed an application of the phenomenon to practical medicine. The relation of sensitization to many diseases entities has received its greatest impetus in the last decade. Notably is the work by ⁶Von Pirquet upon tuberculin, ⁷Blackley, ⁸Schloss, ⁹Cooke, ¹¹Selfridge, ¹²Kessler, ¹³Goodale, ¹⁴Scheppegegel and others upon hay-fever, ⁶Von Pirquet, ⁷Blackley, ⁸Schloss, ⁹Cooke, ¹⁰Walker, ¹¹Selfridge, ¹²Kessler, ¹³Goodale, ¹⁴Scheppegegel, asthma, chronic bronchitis, eczema and urticaria.

Diseases now classed as some phase of allergy are:

First: Serum disease. Second: Hay-fever; seasonal and perennial. Third: Asthma; Food, Emanations and powders, Bacteria. Fourth: Skin: Urticaria, Eczema, Acne. Fifth: Conjunctivitis; Acute, Chronic. Sixth: Acute gastric collapse. Seventh: Acute gastro-enteritis, non infective. Eighth: Migraine.

Serum disease results frequently after the administration of horse serum in the treatment of hemorrhage, diphtheria and pneumonia. Large numbers of patients are naturally sensitive or have acquired

sensitiveness to horse protein. The sensitiveness may be due either to the previous injections of serum or by the absorption or inhalation of horse dander and emanations thru the mucus membrane of the nose or conjunctiva. This disease has become relatively frequent since serums are being used in the prevention and treatment of diseases and particularly in pneumonia where large doses of serum are administered. No patient should receive a dose of foreign serum without the physician having first determined if he is sensitive. This can easily be ascertained by intracutaneous injection of 0.1 minim of the protein to be used. A reaction will appear within half an hour if the patient is sensitive, and consists of an urticarial wheal surrounded with an area of erythema. If the reaction does appear small doses may be administered repeatedly with extreme caution until large doses can be given.

¹⁵MacKenzie recently published a routine to follow in desensitizing a patient. If no reaction occurs large doses of foreign protein may be given with impunity. The preliminary test upon each patient to whom serum is given is absolutely indicated. Quite a number of deaths have occurred from failure to observe this precaution and the number of deaths will increase as more foreign sera are used. One cannot depend upon a history of the previous administration of a serum to eliminate the possibility of hypersensitiveness because this may be a natural state or the patient has acquired hypersusceptibility as stated to animal emanations. The symptoms of serum diseases may be severe unto death or mild with slight urticarial rash, edema with severe itching and burning rendering the patient most uncomfortable. In serious cases a low blood pressure and dyspnea occur with purpura, cyanosis, asthma, convulsions and death.

HAY-FEVER.

Seasonable hay-fever has been definitely grouped as an allergic disease and is produced by a sensitization to pollen proteins. The disease is manifest therefore when a patient receives a second dose of pollens which occurs only when the plants pollinate. Blackley in 1865 made the first skin test to pollens for hay fever, but could not progress because little was known of immune reactions at that time. ¹²Koessler 1913, contributed much to our present day development of pollen therapy of hay-fever. The work of Goodale, Selfridge, Scheppegegrell, Walker and Cook have shown the relationship of pollens to the seasonable types of hay-fever. Cooke and ¹⁰Coca were unable to prove this relationship to be a form of anaphylaxis, however, ¹⁷Parker has recently shown that this relationship is in the form of anaphylactic shock. Hay-fever is not a local disease

of the ear, nose and throat, it is a general condition and operations upon the nose will not cure anaphylactic hay-fever. Well advised operations will give relief in those cases where there is a nasal obstruction and poor breathing space. In these cases operation is always advised but the operation will not alter the general condition of pollen sensitization.

The symptoms of hay-fever are usually manifested in the eye, ear, nose and lungs, because the pollen dusts fall upon susceptible mucus surfaces and does not effect the skin which is impervious. However, itching, redness, swelling can be produced in an open skin wound upon any part of the body if the pollens come in contact with the wound, proving the disease is a general condition and not a local disease. This principle is used in determining which pollen is responsible in each individual case. Hay-fever victims manifest general symptoms as nervousness, irritability, depression and weakness.

Pollinosis may be of the spring, summer and fall type. In the early spring it is usually a manifestation of the sensitization to the tree pollens. Pollens of many varieties of trees, grasses and plants are necessary for testing patients in order to find which is responsible. In some cases as many as fifty varieties of pollens are used before the causative one is found. When the patient has been tested, and the pollen to which he is sensitive is found, the patient is desensitized. If several pollens are responsible for the disease they are combined in the proportion to which the patient reacted, and the mixture is used in treating the case. Hay-fever during May, June and July has incorrectly been called rose cold. Roses rarely cause this condition as rose pollens are heavy and cannot be as easily transported by the wind, this is not true of the pollens of red top, timothy, orchard grass, june-grass and sheep fescue. These are the ones usually responsible for the early summer hay-fever. The August and September types of hay-fever have popularly been accredited to goldenrod pollens but this plant has been unjustly accused in the majority of cases. It has been found by testing a large number of patients that 90 per cent of the autumnal hay-fevers are due to ragweed pollens. Corn pollens are quite commonly the cause of hay-fever in farmers.

In the hay-fever clinic at The Manhattan Eye, Ear and Throat Hospital, routine tests are made for each patient at the beginning of his case using the pollens as suggested by the seasonal history of the patient. Tests are made by the cutaneous or intracutaneous application of the suspected pollen. The reaction produced, if the

patient is sensitive, appears in about 10-20 minutes and consists of an ameboid urticarial wheal and an adjacent zone of erythema. When a patient has been tested and only one pollen is responsible for the patient's disease an extract of this pollen only is used in the de-sensitization of the patient. If the patient reacts to several pollens an extract is made containing the pollens in the proportion as indicated by the reactions, and this combination is used in the treatment.

The modern accepted way to treat these patients is by de-sensitization and immunization against the exciting pollens. The rationale of this is based upon the following fundamental biological fact. A protein sensitive animal when injected with a sublethal dose of protein will manifest mild symptoms of shock and if it does not die will not react to subsequent larger doses of the same protein. This refractive period has been called period of desensitization and anti-anaphylaxis. This period is temporary only as the animal again becomes sensitive after an interval of time. This occurs in hay-fever treatments, the patient will experience a brief period of relief from the injections. For this reason the treatments should be scheduled so that a patient is getting injections up to the time of the hay-fever season. If this brief period of relief were the only value of the injections it would hardly seem worth while. A dual effect is obtained from the injections and this is in the nature of a permanent immunization to the pollens, as about 7% of the hay-fever cases are permanently cured with one series of treatments while in the remaining number there is a decreased sensitization to the protein and the patient can receive much larger doses in the treatment the second or third year.

Pollen extracts are prepared in the laboratory for the treatments and diagnosis of the hay-fever cases. The technic used in preparing the pollens is briefly as follows:

In the treatment of cases 1-100 dilution is the weakest solution used. This is done by employing a tuberculin syringe, giving .01—.03—.05—.07 and upwards to 1cc. All injections are given in the same anatomical location, *i. e.*, arm or thigh. I have noted a distinct local tolerance to the extracts from the injections and large doses can be endured without reaction if this rule is followed. If large doses are given in areas not previously desensitized severe reactions may occur. Treatments are given intravenously to those cases that have been under treatments for some time and which have received the maxim dosage of 1cc. of 1-100 dilution subcutaneously.

The first dose intravenously being .02cc. of 1-100 dilution and the dosage increased as indicated by the reactions of the patient. The

intravenous method is not without some reactions in some cases but the results in the cases so treated have been gratifying. This is a preliminary report of the intravenous injection upon a limited number of cases. The intravenous administration of antigens in desensitization treatment should not be generally advocated, and further experimentation is necessary with this method of treatment.

The following results have been obtained in 130 cases of treatment as above indicated:

	Total relief	Some relief	No relief.
First year	7%	63%	30%
Second year	16%	64%	20%
Third year	23.6%	69.4%	7%

Perennial hay-fever Some patients give no history of seasonal periodicity, suffering at irregular intervals thruout the year. It requires real detective ingenuity to determine the cause in these cases. The causes are many some are due to foci of infection particularly of the intestinal tract. Endocrine disfunction is the etiological factor in some cases while others are due to protein sensitization. The proteins responsible for this variety of hay-fever must be sought for in food, bacterial proteins and animal emanations. Sometimes it is necessary to visit the patient's home in search of possible animal emanations as occurs in rugs and furs and pillows. Occupation frequently gives a clue to the etiology. This is illustrated in the case of a man, age 35, who had been suffering from sneezing and itching, conjunctival and asthmatic attacks for years without seasonal recurrences. His occupation was that of a baker, but he had been unable to do his work for a year. The mere passing of a baker-shop would precipitate an attack of hay-fever. With this history food proteins were used in testing him. The patient reacted violently to wheat, rice, barley, rye flour, oats and corn meal. The mere testing the patient by the cutaneous method precipitated a violent attack of hay-fever. In the above case search for the etiology was simple enough but not so in all cases, and not infrequently the cause is never found. Many cases of rhinorrhea are tested at the hospital with sensitization apparently responsible for about 10 per cent of cases.

ASTHMA.

Pulmonary asthmatic attacks are of three distinct types.

First: Anaphylactic spasmodic contraction of the bronchial musculature.

Second. Bacterial infective asthma.

Third: Combination of sensitization and infection.

The first is due to the deposition of the protein upon the respiratory tubes of an animal sensitive to a protein. Spasmodic asthma is true anaphylactic asthma and is a local manifestation of a general condition the same as hay-fever. In fact hay-fever patients will suffer with asthma if the pollens to which they are sensitive reach the bronchial passages. The proteins responsible for this form of asthma are various, animal emanations, food and bacterial proteins, various powders and dusts. The animal emanations most commonly responsible for the spasmodic asthma are from horse, dog, rabbit, chicken and goose. The foods responsible for most of the asthmas of children are wheat, rice, flour, eggs and milk. Bacterial protein sensitization asthma has been rare in our clinic, in fact we seriously doubt if sensitization to bacterial protein exists. This phase of our work has been most unsatisfactory and we are inclined to think bacteria are responsible for asthma as infective agents only. There are a multitude of powders which at times cause asthma and the one responsible is most illusive and difficult to find in some cases. The age of the onset of asthma is very important. The younger it develops the more likely it is a sensitization asthma. If the asthma has developed later in life the more likely it is of the infective type. The treatment of anaphylactic asthma consists of elimination of the offending protein or the de-sensitization and immunization of the patient to the extracts made from the toxic substances. Operations upon the nose and throat will have little value when a patient has asthma of the purely anaphylactic variety.

Second: Infective bronchial asthma. Classically a pyogenic inflammatory infection of the bronchi mucosa, lymphoid tissue and musculature of the bronchi by bacteria. These bacteria and their toxins periodically irritate the vago-constrictor mechanism of the bronchiles producing a spasmodic obstruction of respiration. The infective type also produces a chronic obstruction to the bronchi by inflammatory thickening of the mucosa of the passages. In the infective types and mixed forms, the treatment consists of drugs, non-specific proteins, vaccines, operative procedures, climatic and general supportive measures. Vaccines are of frequent aid in the infective types, while procedures relieving foci of infections in the teeth, sinuses, tonsils and gastro-intestinal tract will entirely relieve some of the cases. Autogenous vaccines are given in strong solutions and in large doses. The vaccines are made fresh every four weeks and treatment continued over a long period of time. A combination of the sensitization and bacterial invasion frequently exists. The sensitization asthmas are prone to become infected. It fre-

quently requires long study and patience to get at the fundamental facts in an asthmatic patient.

ECZEMA.

Some forms of eczema particularly in children have resulted from sensitization to food. The foods responsible are the cereals, eggs and milk. Eczema in adults is also due to sensitization in a limited number of cases. Eczema has been observed in several hay-fever patients. I have had two patients who would have large areas of eczema upon the hands and face during the entire time they suffered with hay-fever. Walker has previously reported the frequency of eczema associated with asthma in children. Immunization of eczema associated with asthma in children. The explanation for the eczematous tendency in sensitive animals has received considerable scientific support. Auer has recently shown that sensitized rabbits will more easily develop an eczematous condition of the ears after application of the skin irritant than nonsensitized rabbits.

URTICARIA.

Urticarial and angioneurotic edema have also been classed as protein sensitizations. I have treated 18 of these cases and have found 7 of them sensitive to some form of protein, chiefly food proteins. Quite a number of my hay-fever cases have developed urticaria during the desensitizing treatments. This is particularly likely to occur if the dose is too rapidly advanced. Experimentally rabbits when injected subcutaneously by a protein to which they are sensitive frequently show urticarial manifestations which may advance to a stage of suppuration and abscess formation. This was first described by ¹⁹Arthus. The differential diagnosis of all sensitizations by means of the precutaneous or intracutaneous tests depends upon the development of an urticarial wheal at sight of the test, this wheal rapidly disappears and the skin becomes normal in from 1-24 hours. Rarely do they suppurate and ulcerate, however it appears that multiple furunculosis is an evidence of the sensitization in some individuals.

CHRONIC CONJUNCTIVITIS.

Chronic conjunctivitis and frequently recurring acute attacks with itching have given sensitization to proteins. I have upon record one case sensitive to salmon and one sensitive to orris root and face powders she was accustomed to using. In both instances the avoidance of these factors have prevented up to this time any recurrence of conjunctival symptoms.

ACUTE GASTRIC COLLAPSE.

My experience with three cases of gastric collapse has convinced me that many patients suffering with acute indigestion of the past

were simply acute manifestations of anaphylaxis. I wish to describe the following case:—A married woman, age 28, in perfect health, became violently ill one morning at 10 a. m. after having eaten ham for breakfast at 8:30. The symptoms manifest were restlessness, vertigo, nausea, vomiting, diarrhea, acute abdominal pain, cynosis, muscular twitching, rapid respiration, collapse and asthmatic symptoms. At 11 a. m. her blood pressure was 95, pulse 140 and barely perceptible, extreme pallor, dyspnea and exhaustion. Temperature 97.5, leucocyte count 9,000 and .05 per cent polymorphonuclear leucocytes. Blood count repeated in eight hours, 8,000 leucocytes with neutrophils 80 per cent. Urinalysis negative. Patient was given adrenalin and strychnine subcutaneously with a rapid response and recovery. The patient was tested for food sensitization with a marked reaction to pork. She was told to eliminate this element of food and so far has not had any further manifestations of the sensitization. This patient became seriously ill in a brief period of time with symptoms approaching death due to an absorption of an almost lethal dose of protein to which she was highly sensitive. Sensitizations to foods absorbed thru the intestinal tract is somewhat obscure and undoubtedly is due to poor digestive secretions of an excessively permeable intestinal mucosa. Experimental data seems to show that a protein molecule sufficiently hydrolyzed to the peptone or amino stage will not sensitize. Normally the digestive tract should so completely hydrolyze its foods, but in pathological states of the intestines undoubtedly some molecules of the undigested protein is absorbed and acts the same as when artificially introduced intravenously. In children suffering from enterocolitis, ¹⁰Schloss has shown that proteins may be absorbed in an unhydrolyzed state which undoubtedly accounts for more frequent occurrences of sensitization diseases in children.

The prognosis of sensitization diseases has been decidedly more favorable since the discovery of their etiology. In every case where there is a probability of a shock factor in the patient, he should have well advised tests made for sensitization. If positive the line of treatment is evident and consists of either elimination and avoidance or an attempt at the active desensitization and immunization to the proteins responsible.

In the treatment of allergic diseases with the etiological protein one must bear uppermost the danger of producing acute shock. The symptoms of shock come on so rapidly and are so alarming to the patient and doctor that they should always be carefully avoided. Several deaths have been reported from the treatment of

these cases. The action of adrenalin in restoring these cases is instantaneous and miraculous in most instances. Treatment of these cases is essentially one of responsibility and the success of treatment and safety of the patient depends upon the care taken. There is a happy medium dosage which is desensitizing and is not alarmingly anaphylactic. I feel, however, that the production of mild symptoms is essential to the successful treatment of these diseases.

CONCLUSION.

There is probably no line of medical research more interesting or more promising than the study of allergy. Practical medicine has again been enriched by fundamental biological studies and simply by the practical application of the fundamental biological truth of anaphylaxis to the etiology and treatment of allied diseases. Diseases whose etiology remained for decades obscure, which offered barren results therapeutically.

CONCLUSION.

1. MAGENDIE, F.: *Vorlesungen Uber das Blut.*, 1839.
2. RICHET, C., et PORTIER, P.: *C. R. de la Soc. Biol.*, 1902, LIV, 170.
3. VAUGHAN, V. C.: Philadelphia and New York, 1913.
4. JOHLING, J. W., WM. PETERSON, AND A. A. EGGSTON: *Jour. Exp. Med.*, Vol. XXII, No. 4, 1915.
5. ANDREW A. EGGSTON: *Jour. Lab. and Clin. Med.*, Vol. VI, Nos. 9-10.
6. VON PIRGUET: *Berl. Klin. Woch.*, XX, 1907; *Med. Klinik*, XL, 1907.
7. BLACKLEY, C. H.: *Exper. Researches on Causes and Nature of Hay-Fever*, 1873.
8. SCHLOSS, O.: *Amer. Jour.*, Dis of Children, 1912-13, 341.
9. COOKE, R. A.: *THE LARYNGOSCOPE*, 1915, 25-108.
10. WALKER, I. C., AND ADKINSON, JUNE: *Jour. Med. Res.*, 322, 277.
11. SELFRIDGE, GRANT: *Calif. State Jour. Med.*, 13, 308, 1918.
12. KESSLER, K. K.: *Ill. Med. Jour.*, 1913, XXIII, 66.
13. GOODALE, J. L.: *Boston Med. and Surg. Jour.*, 1916, 175-181.
14. SCHEPPEGREL, WILLIAM: *M. Rec.*, 92, 230, 1917.
15. MACKENZIE, G. M.: *Jour. Amer. Med. Assoc.*, 1921, p. 1563.
16. COCA, A. F.: *Tice Practice of Med.*, Vol. I, p. 107; *Jour. Immunology*, 1920, 5, 363.
17. PARKER, J. T.: *Soc. Exper. Biol. and Med.*, 18: 237, 1921.
18. SCHLOSS, O.: *Amer. Jour. Dis. Child.*, 11, 342.
19. ARTHUS: *Compt. rend. Soc. de Biol.*, 1903, LV, 817.