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CONTENTS

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THE BIOLOGIC ASPECTS OF HAY FEVER AND ASTHMA[1]

The selection of hay fever and bronchial asthma for the exposition of biologic relationships may appear curious, and yet few of the many ills to which we may fall victims are as clearly dependent upon pure biological reactions. The group of so-called allergic diseases in which the biologic factors are quite similar comprise such apparently unrelated conditions as asthma, hay fever, urticaria or the hives, eczema, some cases of migraine or sick headache, of colitis and certain other less clearly defined conditions. For the sake of brevity we will devote our attention only to the first two states which are the most clearly understood.

Hay fever scarcely requires description, since the condition is so widespread that nearly every one has had some acquaintance with it. It has been fairly accurately estimated that 1 per cent. of the entire population of the United States suffers from one form or another of hay fever.

At certain times of the year, particularly the spring or early fall, some persons will experience attacks of sneezing with profuse watery discharge from the nose, irritation of the eyes and of the throat which will persist in varying intensity for weeks or months. Usually these attacks recur at the same time each year, sometimes several times during the year and occasionally at quite irregular intervals. Bronchial asthma, like hay fever, usually occurs in periodic attacks, sometimes seasonal in their distribution, separated by intervals of complete or nearly complete freedom from symptoms. The victim would describe asthma as a condition in which, beginning usually with a fit of coughing, he will rapidly become choked up, finding it most difficult to breathe either in or out. Breathing becomes labored, noisy, wheezy, the respirations become rapid, developing in a relatively short time to a state of actual air hunger which persists for a variable time. Relief comes gradually with the onset of an easier cough in which more phlegm is raised and the breathing gradually returns to normal. In the acute stages the cough is non-productive. As the patient has it, if he could only raise the mucus he would feel better, and when at last he does do so he rapidly improves.

1 Invitation address before the Virginia Academy of Science, at the College of William and Mary, Williamsburg, Va., May 4, 1928.

Not infrequently asthma and hay fever occur in the same individual. Severe hay fever is always in danger of developing into asthma.

Formerly asthma was considered a purely nervous disorder. There has perhaps been a tendency among physicians in the past, when they could not discover the reason for periodic attacks of illness in otherwise normal persons, to pass the blame on to the victim, designating the malady as nervous and unconsciously insinuating thereby that the asthmatic could control his attacks if he would. But that day has passed.

Our search for the underlying cause of these allergic diseases began with the opening of the twentieth century. The original workers, whose primary interest was a study of the mechanism by which the human body becomes immune to certain diseases, were not at all interested in asthma or hay fever. It was not until 1910 that the suggestion was made that the knowledge gained from a study of the mechanism of immunity might be successfully applied toward an understanding of the cause and relief of the allergic diseases.

At the beginning of this century some new and curious observations were being made. Guinea-pigs were being inoculated through the skin with various proteins such as egg white, horse serum, dead typhoid bacilli, the protein or rice grains and the like. These injections scarcely made the animals ill. But, curiously, if after an interval of ten days or two weeks the same amount of the same protein or even a smaller amount was again inoculated into the same animal the latter became acutely ill and died within a matter of minutes. Strange to say, the symptoms in these pigs, who died of what came to be termed anaphylactic shock, were remarkably similar to the symptoms of asthma as we see it in humans.

Something curious had happened in these animals between the first and second inoculation of the same material which on the first injection had appeared quite harmless and on the second had killed almost immediately. This curious animal experiment has been the basis for all our subsequent study of immunology and many theories have been suggested to explain the phenomenon of anaphylaxis as I have just described it. Almost as soon as one research student proposes a theory which appears to satisfactorily explain all the known facts of anaphylaxis some other worker will present new experimental evidence which the proposed theory does not satisfactorily explain. New facts are constantly accumulating and the older theories have not answered the questions which they have raised.

Just now we are in the stage of accumulation of data. Sometime a theory will be proposed which will withstand the attacks of the most critical. However, a tremendous volume of knowledge has been built up on the basis of the older theories, and our understanding of asthma and hay fever is based nearly entirely on them. Thus, even though as originally proposed they may eventually fall completely into the discard, they have been responsible for the relief of suffering of millions of humanity.

At the risk of exposing myself to the charge of unwarranted dogmatism I shall briefly present to you one of the theories of anaphylaxis which explains lucidly the biologic causes for hay fever and asthma. I will ask you to realize that there are facts which the theory does not explain and that eventually it will necessarily undergo many modifications.

Unicellular animals, such as the ameba, paramecium or the typhoid bacillus, derive their food supply from their immediate environment. Carbohydrate is used for fuel, to keep the engine going, as it were, and the animo-acids, those relatively simple nitrogenous units which when linked together form proteins, are assimilated by the living cell for the purpose of growth and reproduction and protoplasmic repair. A single living cell in a medium where there is an abundance of appropriate amino-acids and of carbohydrate or energy producing substance will grow and reproduce. But not infrequently the available amino-acids in the immediate environment are chemically bound together into more complex substances, such as peptones, proteoses or even actual proteins. Every protein consists of a combination of amino-acids. Each different kind of protein represents a different combination of the amino-acids. There are not more than twenty amino-acids to be found in native proteins and yet these may be combined in so many different ways as to produce an almost limitless number of distinct proteins very much as the twenty-six letters of our alphabet may be so combined as to produce an endless variety of words. Different proteins may contain different types of amino-acids or they may contain the same amino-acids in varying proportions, or again these units may be combined into the protein molecule in different chemical groupings or locations. The protein of colon bacillus differs from the protein of ameba in the quality, relative proportion and intramolecular placement of the constituent amino-acids. In order that the ameba may build the amino-acids of colon bacillus into its own structure it must first digest the colon bacillus, breaking apart the constituent amino-acids, discarding any that it does not itself possess or require and utilizing the remainder. In the case of ameba the disruption probably occurs within the digestion vacuole, after which the amino-acids are absorbed and built into the protoplasmic structure of the living cell.

According to the theory it is a fundamental biologic law that whenever a living cell comes into contact with a foreign protein it will elaborate an enzyme or ferment which will digest and destroy the foreign protein so that its constituent amino-acids will be available for the nutrition of the living cell.

Living cells appear to possess proteolytic ferments which will readily digest a large variety of proteins. These ferments may be likened to keys which unlock the combinations in which the proteins are bound together. In every protein the combination is different, but there are master keys which will unlock many combinations. On the other hand, the living cell sometimes finds in its environment a protein which the general proteolytic ferment or master key will not unlock. Stimulated by the presence of this foreign protein the cell will then build a new key which will fit the combination. The cell elaborates an enzyme or ferment, specific for that particular foreign protein which will digest that protein and none other. Time is required for this enzyme production. There is evidence that ten days or two weeks are necessary before the living cell will produce the new enzyme in large amounts. After it has once learned to elaborate the enzyme it continues to retain this ability and the enzyme will be poured out whenever the cell is again stimulated by contact with the specific foreign protein.

So much for unicellular organisms. The same biologic principles appear to hold when large numbers of cells are aggregated together, as in the guinea-pig or human being. In complex organisms such as these groups of cells take on special functions. The individual cells become specialists. The cells in the gastro-intestinal tract secrete the general proteolytic ferments or the master keys. This no longer becomes a necessary function of the tissue cells within the body, whose environment is always essentially the same, that is, the blood and lymph, in which foreign proteins do not normally appear, for they have already been broken down in the process of normal digestion.

But if you will inject a foreign protein such as egg albumin or egg white into a guinea-pig, thus sidestepping normal gastro-intestinal digestion, the foreign protein appears in the blood and lymph, thus changing the immediate environment of the tissue cells.

According to the theory, the body cells so stimulated by the presence of a foreign protein and lacking in their high specialization any considerable degree of general proteolytic ferment immediately set to work to manufacture a specific enzyme which will digest and destroy this one specific protein, egg albumin. This is the change that has taken place in the guinea-pig, following the first injection of egg white. Now, why does the pig die immediately after the second injection?

There is evidence that as protein is being digested, as the constituent amino-acids are being chopped off one by one, we may say, or in terms of organic chemistry, as the uncombined or free valences are being greatly multiplied, a stage is reached in which the remaining portion of the molecule becomes extremely poisonous. We might say that the unsatisfied valences of the partially digested protein molecule become so numerous and in view of their number so strong that they will tear off amino-acids from the living cells in the neighborhood. This is pure hypothesis.

At any rate, proteins may be partially digested in the test-tube and divided into two parts, one poisonous and the other non-poisonous, the former of which, when injected for the first time into guinea-pigs, will produce typical anaphylactic shock with its asthmatic symptoms followed by rapid death.

Following the first introduction of egg white the body cells manufacture the specific enzyme slowly, the foreign protein is digested slowly, and too little poison is liberated at any one time for symptoms to become manifest. Upon the second injection the cells immediately pour out large amounts of enzyme or the enzyme may be already present in large amounts in the blood and lymph with the result that destruction of the foreign protein takes place rapidly and such a great volume of protein poison is liberated almost at once that the serious symptoms of anaphylactic shock rapidly ensue.

Anaphylaxis does not occur in normal enteric digestion, because this is really taking place outside of the body, in the stomach and intestines, and while the protein poison is probably formed at one stage in the digestion, it is still further broken down into its harmless constituent amino-acids before absorption through the mucous membrane of the intestines takes place. This is the theory of anaphylaxis that has been developed by Dr. Victor C. Vaughan.

And now we come to asthma as we see it in humans.

We speak of an animal which has been rendered sensitive to the repeated introduction of a foreign protein as being sensitized. Diseases in which the phenomenon described plays a part are termed sensitization diseases. The curious phenomenon which occurs on the second injection or reinjection of an experimental animal is termed anaphylaxis, derived from the Greek and meaning *without protection,* just as prophylaxis means *for protection, favoring protection.* The analogous human diseases, hay fever, asthma, some cases of hives, eczema, migraine, colitis and a few other conditions, are termed allergic diseases. Allergy means literally *altered energy* or activity or altered reactivity. This is rather a happy appellation, for it indicates an alteration that has occurred in the tissues of the body without attempting to explain it more precisely in terms of any theory which would be sure to require subsequent change.

There are several points of divergence in the similarity between experimental anaphylaxis and clinical allergy, as it is seen in humans. Some of these divergences are so definite that it is still a question whether the experimental disease and the natural disease are dependent upon identical processes. But all our progress in treatment has been made on the basis of an assumed relationship or identity and it is not within the province of this presentation to enter into the minutiae of this and similar unsettled questions.

Some persons will develop attacks of sneezing or asthma after riding behind horses. Others develop these symptoms after inhaling the pollen of certain plants, particularly weeds and grasses and sometimes trees. Among still others the symptoms become manifest after the eating of certain foods, such as clams, strawberries, chocolate, eggs or wheat.

The purified proteins from horse hair or horse dander, the epidermal proteins from a host of other animals, the proteins of the pollen grain from all the important pollinating plants, the proteins of nearly all foods eaten and of a rather large miscellaneous group of other substances have all been separated out in relatively pure state and are used for testing allergic persons. The test is very simple. A small amount of the protein solution is either applied to a minute scratch in the skin or injected into the skin with a hypodermic needle. If the patient is not sensitized no reaction occurs. If he is allergic to the particular protein, a small urticarial wheal or hive occurs at the site of testing. This lasts some minutes, then gradually fades. The protein has come in intimate contact with the body cells at the cut in the skin and the hypothetical protein poison has been liberated but in such small amounts that only a local reaction occurs.

The first function of the examiner is to find out to what proteins the patient is sensitive, for sensitization is usually multiple. Following this relief is obtained either by avoidance of the particular food, pollen or other substance or through gradual desensitization or immunization by repeated injections of small amounts, of increasing size so that the victim will eventually tolerate many times the dosage or exposure that would otherwise have given rise to acute symptoms.

We do not know precisely why repeated injections of increasing amounts of the poisonous protein will eventually relieve the symptoms. The most popular explanation suggested is that with the continuous or quasi-continuous introduction of foreign protein the velocity of the chemical reaction is slowed up so that the protein poison is liberated more and more slowly and less explosively, while the body cells themselves become increasingly resistant or impervious to the action of the poison itself.

While other factors play a part the basic cause for hay fever and asthma appears to be the inhalation or ingestion of some foreign protein and its absorption through the mucous membrane of the respiratory tract or the gastro-intestinal tract. There is evidence that once having become sensitive to the protein of a food an individual's barriers against the subsequent absorption of this protein are let down to a degree, so that the protein passes through the intestines or respiratory mucous membranes and into the circulation without being completely digested, as it should be.

Among the inhalants which produce asthma or hay fever we should mention the pollens; animal epidermal emanations, such as horse dander; the dust from feathers, as in feather pillows; or rabbit hair, which is a constituent of felt and is found in one form or another in nearly every home; orris root, the dried and powdered root of the iris, a constituent of most face powders and various cosmetics, and some dusts. Among the less common causes of inhalant allergic attacks I might mention as examples the protein from dried glue in furniture; pyrethrum, a constituent of insect powders; the furs of wild animals found in fur coats or mounted as trophies of the chase, and feathers from sparrows nesting just outside open windows. Often the search for the causative protein is a long-drawn-out affair. A patient may be sensitive to almost any known food. Not infrequently it is necessary to test him with a hundred or more different proteins before all the possible causes for allergic manifestations have been eliminated.

We rarely attempt desensitizing injections for the foods, since they are more easily avoided. Likewise asthma or sneezing due to feather sensitization is sometimes relieved by the simple procedure of changing from feather pillows to silk floss or kapok and removal of dust from the bedroom. A horse asthmatic need but avoid horses to remain free from symptoms. But he is a poor risk for serum treatment for other diseases, such as diphtheria or pneumonia, for most serums used in medicine are horse serums. But dust, pollen granules and orris root are not so easily avoided. Nowadays, wherever women are, there also in the dust is an abundance of orris root from cosmetics. Churches, theaters, schools, stores and homes are rarely free from orris root. Its avoidance is difficult, indeed. Ragweed pollen may be carried on the wind for ten miles, and during the pollinating season its avoidance is impossible. Those who can afford it may take an ocean voyage or sojourn at the seashore where the prevailing wind is from the ocean or go to the woods where ragweed is less abundant, but the majority of hay fever sufferers must depend upon desensitization for relief. Fortunately, this method of treatment has been so perfected that in expert hands from 75 to 100 per cent. relief may be had in most cases. Unfortunately the so-called serum treatment for hay fever and asthma has been inefficiently given by physicians who have not made a special study of allergy, with the consequence that the results have not been good and the patient has denounced the method as a failure, whereas had it been properly supervised it would have been more successful.

Not all people develop allergy. Conservatively put, about 10 per cent. of the general population is predisposed. The remainder never develop the disease. Curiously enough, the tendency appears to be hereditary. There are several diseases in which we find evidence of an hereditary predisposition, and allergy is one of them. Among the others I might mention hemophilia, some forms of insanity, certain rather rare diseases of the bones and of the spinal cord, gout, and probably rheumatism and high blood pressure. The list is not complete.

There is a record of a family in France in which members of four generations were sensitized to egg. But this is not the usual case. It is not the specific sensitization which is inherited, but the tendency to become sensitive. In one generation there may be a sensitization to timothy pollen, in another to strawberry protein and in yet another to chicken feathers. It is probably only the tendency that is inherited. Not only this, but the allergic explosion does not necessarily manifest itself in the same way in the various members of the family. One may have asthma, another hay fever, another migraine or sick headache and yet another eczema. In my own work I have made a careful study of an interesting family. The boy, sensitive to wheat, chocolate and strawberry, has asthma. His brother has had the hives. His mother, sensitive to wheat, had suffered in the past from eczema. The maternal grandmother was a victim of migraine, while the paternal grandmother was subject to hay fever from exposure to the pollen of daisy, and acute colitis or gastro-intestinal upset which always followed the ingestion of clams. She would also develop hives after taking quinine. An uncle developed hives after eating strawberries.

The evidence so far indicates that the inheritance of allergy follows the Mendelian law probably as a dominant characteristic. Where the inheritance is bilateral the symptoms usually become manifest earlier and in more members of the family than when it is unilateral.

The biologist will be especially interested in pollens as the cause of asthma and hay fever. Roughly there are three hay fever seasons in which pollens are causative factors, an early spring period during which tree pollens are in the air, early summer when the grasses are pollinating and late summer or early autumn when the compositae, particularly the ragweeds, are shedding their pollens. Formerly it was thought that goldenrod was a chief malefactor, while the more drab and less noticeable ragweed next to it remained unsuspected. As a general principle we may say that the brightly colored plants are far less important than are those without brilliant flowerings. The colorful plants usually possess heavy sticky pollens which are carried from plant to plant on the bodies of insects and never reach a high concentration in the air, certainly not at any great distance from the plants. Goldenrod, rose, apple blossoms, daisy, sunflower and the like fall within this group of insect pollinated plants. They may and do cause symptoms when the sensitive individual stays for some time within, say, a hundred yards of the plant but rarely otherwise. With a sunflower sensitive patient it is only necessary to destroy these plants in the immediate neighborhood and desensitizing injections are rarely needed.

But the drab plant without brilliant colors to attract insects possesses much lighter pollen grains, which are wind-borne. It has been estimated that a single ragweed plant will shed millions of pollens in twenty-four hours. As I have said, on a dry windy day they are carried many miles. At my pollen station on the roof of the Medical Arts Building in the heart of Richmond I obtained practically the identical pollen count that I did at my other two stations, one in the residential district and one in the town of Ashland. These pollens one can not avoid, and desensitization is necessary.

While there are quite a number of tree pollen sensitive individuals it has been thought that since the pollinating season for trees was of but two or three weeks' duration desensitization was not necessary. But, as I have said, sensitization is usually multiple, and with sensitization to several trees which pollinate at different times tree pollen sensitization may become quite a problem. Indeed, one may be sensitive to several varieties of one tree. There are said to be some sixty-five varieties of oaks in the United States, and these do not all pollinate simultaneously. Furthermore, some trees have a relatively long pollinating season. Mountain cedar in parts of Texas sheds enormous quantities of pollens from before Christmas to mid-February, and it has been discovered that in this section the so-called winter cold is much more often a winter hay fever. Persons have been found sensitive to maple, willow, alder, birch, hawthorn, oak, walnut, ash, cottonwood, box elder, sycamore, hickory, elm, cedar, pecan, pine and apple. And the list is not complete, for, as pollens from other trees are being obtained and patients are being tested to them, still other positive reactions are being observed.

The most important grasses are timothy, orchard grass, red top and June grass, but there are many others.

As might be expected, the plants responsible for symptoms vary in different sections of the country, depending upon the predominating local flora. The physician treating allergy in Texas selects a slightly different group of pollens from one who is working in Oklahoma or California or Virginia or the New England states. Indeed, for best results in relieving the victims of hay fever and asthma a botanical survey of the local section must be made. One of the most comprehensive local surveys of this sort so far as I know is that made under the direction of Ray M. Balyeat, of Oklahoma City, covering the state of Oklahoma. As a result of these studies Balyeat finds that even in different sections of the one state different plants are chiefly responsible for symptoms. And since success in treatment depends upon finding the chief causative pollens it is obvious that good results will be directly proportional to our knowledge of the nature, distribution and abundance of the local flora.

I trust that in this survey of a part of the field of allergy I have been able to establish my conception that the study and treatment of allergic diseases is primarily a biologic problem in the strict sense of the term and might well be designated a branch of applied biology in which the subject of investigation happens to be the human being. The allergist who delves deeply into his field must necessarily become a student of the activity of living matter, for in the last analysis the basis of anaphylaxis and of allergy is the vital activity of the living cell and its reaction to environmental alterations.

Warren T. Vaughan

Richmond, Va.

EDGAR FAHS SMITH

On the evening of Thursday, May 3, 1928, Dr. Edgar Fahs Smith, thirteenth provost of the University of Pennsylvania, died in the university hospital, following an illness contracted only a few days previously.

The announcement of Dr. Smith's death came as a thunderbolt to his many friends, as he had been in apparent good health. Within a few hours men in every part of the world were mourning his loss. Thousands of the alumni, the faculty and the student body felt that they had lost one of the staunchest of friends and counsellors. The people of the city of Philadelphia, where he lived and labored for half a century, recognized him as one of their foremost citizens. The flags upon the municipal buildings were lowered to half-mast as a tribute to his memory. From every part of the United States messages of sympathy were received, testifying in the highest terms to the esteem and admiration in which he was held.

His fifty years with the University of Pennsylvania, which he faithfully served as teacher and administrator, will always be referred to as one of the most important periods in the history of the institution; his contributions to science during that period won for him the highest tributes of the scientific world.

In his chosen field he was invariably referred to as one of the most eminent American chemists and some of his investigations and discoveries have been of the utmost value to the industrial world. As a result of his researches, which were generously contributed for the advancement of science, he made himself a true benefactor of mankind.

As a teacher he was interesting and inspiring, always patient and painstaking; his advice was freely sought and generously given; no wonder that he should be *Beloved of Pennsylvania Men.*

As a man he was deeply religious, unassuming, easily approachable, companionable, sympathetic, of quiet and lovable disposition and always generous.

Dr. Smith was born at York, Pennsylvania, May 23, 1854. His early education was received in the York County Academy, and in 1872 he entered the junior class of Pennsylvania College at Gettysburg, from which he was graduated in 1874 with the degree of bachelor of science. While a student at Gettysburg, his interest in the study of chemistry and mineralogy attracted the attention of Dr. Samuel P. Stadtler, who urged him to specialize along those lines. This was the beginning of an eventful career. He entered the University of Göttingen, Germany, where he studied under the celebrated Frederick Wöhler, and was graduated in 1876 with the degrees of A.M. and Ph.D. In 1926 the University of Göttingen again honored Dr. Smith by renewing his doctor of philosophy degree for his "fifty years of science as a teacher and investigator."

Upon returning to America he was appointed instructor in chemistry at the University of Pennsylvania, which position he held until 1881, when he accepted the Asa Packer professorship of chemistry at Muhlenberg College; he remained here for two