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Asthma

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A thesis presented to the faculty of the University of Nebraska College of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine

July 1934.
INTRODUCTION

For my senior thesis, I have chosen the subject of "Asthma" for two reasons: (a) I became interested in the physiology of the lungs while working on a research fellowship in physiology. (b) Asthma is a common disease and every practitioner of medicine should know something of it. The subject is exceedingly large, and the literature is voluminous. To write on every phase of the subject would fill several volumes. To attempt such a task in a paper of this kind would neither be wise nor desirable. I have tried to limit myself to: (a) The things of special interest to me. (b) The basic principles of the disease. I have purposely omitted such material as the skin tests for sensitization to proteins, methods of desensitization, seasonal treatments, the use of such medicines as epinephrine and ephedrine, and other material of such nature. This has been left out, not because it is unimportant but because they have become routine procedures which are familiar to every worker in allergy. The use of epinephrine is familiar to every physician, it being used in many cases of asthma without an attempt in many instances to find the exciting factor of the disease. Such treatment is a mistake, yet no other means is possible without a thorough understanding of the mechanism of the disease.

That the disease is difficult to treat and unsatisfactory results are obtained in many cases is shown by Rackeman(33) in a study of 1,074 asthma patients. Of this number 213
remained "cured" for two years and 131 remained "cured" for six years. The old dictum of "Once an asthmatic, always an asthmatic" contains a lot of truth. Some patients have such a capacity to develop hypersensitiveness to foreign proteins, that a permanent cure is improbable. This tendency to react is deeply rooted in the biologic inheritance of the individual.
ASTHMA

DEFINITION.....The term "asthma" is sometimes used to designate a symptom, being confused with the symptom of dyspnea. The term "cardiac asthma" is sometimes used to designate a type of dyspnea which is primarily of cardiac origin. The term "renal asthma" is sometimes used to designate a type of dyspnea produced by a renal insufficiency resulting in an accumulation of fixed acids within the body, producing difficult respirations.

The term "asthma" should be used only to designate a specific disease produced by a narrowing of the lumen of the bronchial tubes, by the combined action of the exudative and bronchomuscular systems, characterized by dyspnea, which is chiefly expiratory. The etiology of which is anaphylactic or a reflex neurosis.

ANATOMY and PHYSIOLOGY of the LUNGS.....The lungs originate by a budding off process from the fore gut. The lung buds push into the surrounding mesoderm. The entoderm of the foregut gives rise to the respiratory epithelium. The mesoderm gives rise to the blood vessels, cartilage, connective tissue, and smooth muscle of the lungs. The smooth muscle of the lungs has the same embryonic origin as the smooth muscle of the intestines. In the main bronchi, the muscular arrangement is the same as in the trachea, most of the muscle being located between the open ends of the horse-shoe shaped cartilages and being attached to these ends. However, the change in pattern of the cartilages is accompani-
ed by a modification of the muscular pattern. The muscles are no longer attached to the cartilages, but assume a spiral arrangement and an open mesh-work in contrast to the compact circular and longitudinal arrangement of the intestinal musculature. Macklin (26) says to demonstrate this, the lungs must be sectioned in the expanded condition. If the lungs are sectioned in the collapsed condition, the muscles are apt to be shown as circular bands. The muscle extends from the larger tubes to the respiratory bronchioles. It is relatively better developed in the smaller bronchioles.

Some observers have reported smooth muscle in the walls of the alveoli, but the prevalent opinion is that it belongs to the respiratory tubes and is not a component of the alveolar walls.

The smooth muscle is intimately intermixed with elastic fibers. These all run parallel and the relationship is so intimate that the term "myoelastic" has been applied. In the entire respiratory tree, the musculature of the bronchioles is relatively the most strongly developed so that the lumen may be completely obliterated by its contraction. This is shown in Fig. I in which a lobe of the lung was placed in a plethysmograph. Stimulation of the vagus nerve caused all volume changes of the lung to stop, although artificial respiration into the trachea was continued. Fig. I demonstrates obliteration of the lumen of the bronchioles due to a nervous stimulation over the vagus nerve.
Fig. I  The upper line is the air pressure used in artificial respiration. The lower line is the electric signal. The middle line represents the volume changes in the lung due to alternate inflation and deflation. Stimulation of the vagus nerve caused all volume changes in the lung to stop, demonstrating a complete occlusion of the bronchioles so that air could neither get in or out of the lungs.
Fig. IV. demonstrates a similar complete obliteration of the lumen of the bronchioles by an anaphylactic shock. In this latter type of reaction no nervous tissue is involved, the reaction is capable of taking place after all nervous tissue is removed.

In tissue culture work, Lewis (24) observed a rhythmic contraction of the respiratory tubes. This action was more marked after the tissue had grown twenty-four hours in culture than it was immediately after explantation. The arrangement of the muscle was such that contraction produced both a narrowing and shortening of the tube. The contraction wave passed the entire length of the tube, expelling any debris which might happen to be in its lumen. In my work, I have been able repeatedly to demonstrate a rhythmic action of the bronchioles which is interpreted to be a peristaltic action. (Fig. II). It must be remembered that in working with the plethysmograph, the action of an individual bronchiole is not recorded. The record is a composite action of all the bronchioles in the lung.
Fig. II. The bottom line of A, represents the alternate inflation and deflation of the lungs. It will be seen that this record has variations which correspond to the diagram B, representing an actual variation in the volume of air which enters and leaves the lung. This change in the volume of air which enters and leaves the lung is due to peristaltic action of the bronchioles. Any changes in the record corresponding to diagram C would not represent a peristaltic action of the bronchioles.
INNERVATION OF THE LUNGS. . . . The cervical sympathetic trunk ordinarily does not innervate the lungs. However, if it does contain broncho-constrictor fibers, they are derived from the vagus nerve near the superior cervical ganglion (23).

The vagus nerve supplies broncho-constrictor fibers to the lungs. At first it was thought that the vagus nerve supplied the lung on the homolateral side only. Dixon and Ranson (12) came to the conclusion that the broncho-constrictor fibers in the vagus cross to a variable extent but some crossing is the rule. Stimulation of the intact vagus or stimulation of the peripheral end of the cut vagus will produce constriction of the bronchioles. This is represented in Fig. III by the decrease in excursion of the writing lever. It must be remembered that stimulation of such an important nerve as the vagus will produce other changes in addition to the bronchial constriction. Some of these changes are represented in the record by the rise in base line of the record. The bronchial constriction is represented by the decrease in excursion of the writing lever (18).

Fig. III
Fig. III    The top line represents the air pressure used in artificial respiration. The air current being interrupted fifty times per minute. The middle line represents the alternate inflation and deflation of the lungs. The height of these lines represents the volume of air which enters and leaves the lungs. On stimulation of the vagi, the bronchioles were constricted allowing only a small volume of air to enter and leave the lungs. This is represented by the decrease in excursion of the writing lever.
PATHOLOGY ..... Deaths from asthma are rare. When they do occur, the outstanding finding is an increase in the actual thickness in the wall of the bronchi and bronchioli of more than 0.2mm. outside diameter as compared with similar structures in non-asthmatic persons. All structures in the wall of the bronchi show a hypertrophy, from the epithelium to the outer fibrocartilagenous layer. The increased secretion of the epithelium and the hyperactive glands obstruct in some cases completely, the already narrowed lumen of the middle sized and small bronchi and bronchioli. In this way both systems, the exudative and the bronchomuscular, act simultaneously in the production of the stenosis, in some cases one more than the other, but always both to some extent(21).

Curschmans spirals are most frequently seen in bronchial asthma although they are occasionally seen in other diseases of the lungs, such as chronic bronchitis. They are whitish or yellow waxy threads coiled about a colorless central line. Sometimes, the spirals are imperfectly formed, consisting merely of twisted strands of mucus.

Charcot-Leyden crystals are quite characteristic of sputum from asthma patients. They may be absent when the sputum is first expectorated, but appear after the sputum has stood for some time. In some way, these crystals are associated with the eosinophilic cells. They are occasionally found in the feces in cases of animal parasites.

Eosinophilic leukocytes are quite commonly found in large numbers in the sputum near the time of the paroxysm.
They are also found in increased numbers in the blood of asthma patients.

ASTHMA

CLASSIFICATION.....As nearly as possible, an etiological classification of asthma will be given. Only the disease which produces a constriction of the bronchial tubes will be considered. Dyspnea due to other causes such as "cardiac asthma" or "renal asthma" will not be considered.

I. REFLEX ASTHMA
   (a) Somatic reflexes
   (b) Psychic reflexes

II. ALLERGIC ASTHMA
   (a) Inhalants...pollens, animal eminations, vegetable powders, dust and drugs.
   (b) Foods

III. INFECTIOUS ASTHMA
   (a) Reflex
   (b) Allergic
   (c) Toxic....lymph, blood, direct continuation.

To classify all cases of asthma would be a difficult task. However, an accurate classification is not always necessary for the proper treatment of the case. For example, the asthma may be due to nasal infections. From a therapeutic standpoint perhaps it makes little or nor difference whether the bronchioles are being constricted due to: (I) Reflexes from the nose, (2) Absorption of protein substances (3) Absorption of products of bacterial growth. Perhaps in many cases two or more factors may play a part. From the therapeutic standpoint, the nasal infection should be
treated regardless of the mechanism by which the bronchial constriction is being produced.

MECHANISM .... The presence of a reflex group of asthmas is based upon both laboratory and clinical evidence. Dixon and Brodie(II) demonstrated the constriction of bronchioles due to stimulation of the nasal mucous membrane. Later Ranson(34) showed that pouring water over the nozzle of a tracheotomized animal produced a contraction of the bronchial musculature. These experiments were done on animals and the methods are not applicable to man. However, Francis(I4) in his clinical work believed that asthma was due to a reflex contraction of the bronchial muscles, the stimulus of which arose in the nose. The exact reflex arc has never been determined but evidently the efferent impulses pass over the vagi because after cutting these nerves, a reflex bronchial constriction by stimulation of the nasal mucous membrane can't be produced in the experimental animal.

In anaphylactic reactions no reflex arc is involved. After an animal has been sensitized to a protein, the smooth muscle in that animal's body can be made to contract after it has been removed from the influence of all nervous tissue. (I & 29).

The fact that a reflex asthma depends upon the function of the parasympathetic nervous system and allergic asthma is due to direct action upon smooth muscle, gives one a test by which it is theoretically possible to separate the two types when only one of the mechanisms is involved.
Gillespie(17) says: ". . . . a full dose of atropine might be injected at the onset of the attack. In those cases where contraction of the bronchial muscles is due to direct chemical stimulation of the muscle, atropine would be expected to have no effect, whereas in the truly nervous type the attack would be aborted". Others(?) in speaking of the smoking of stramonium leaves, which contain atropine, say: "In some patients the relief is prompt and satisfactory; in others apparently similar clinically, no relief is obtained". If one recalls the pathology of asthma, in that two systems, (a) the bronchomuscular and (b) the exudative are involved, there is a logical explanation for this. In reflex asthma, atropine should relieve both the bronchial constriction and the hypersecretion by paralysis of the vagus nerve endings, giving a marked degree of relief. In allergic asthma, atropine might be expected to give some relief by drying up secretions, but it could not be expected to relieve the spasm of smooth muscle, because the contraction of smooth muscle in allergy is not due to impulses coming over the vagus nerve. By use of this atropine test it should be possible to separate the reflex asthma from the other types, if the reflex is the only mechanism involved.

REFLEX ASTHMA.....Dixon and Brodie(11), in experimental work, found that reflex bronchial constriction could best be obtained by stimulation of the nasal mucous membrane, the upper and posterior part of the nasal septum being the best area from which to produce the reflex(13). That the efferent impulses are over the vagus nerves is supported by
The top line represents the air pressure used in inflation of the lungs. The middle line represents the volume changes of the lungs due to their alternate inflation and deflation. The lower line represents the electric signal indicating the time the stimulus was applied.

On stimulation of the nares, a bronchial constriction was produced as shown by the decrease in excursion of the writing lever, indicating a decrease in the volume of air which was entering and leaving the lungs.

Since the spinal cord was severed at the base of the skull, it was necessary for the stimulus, which was applied to the nose, to produce the bronchial constriction by having the efferent impulses travel over the vagus nerves.
the work of Dixon and Ranson(I2) when they say: "In no case have we observed any sign of broncho-constriction after section of the vagus nerves". Shanks(36) believes that the afferent paths are over the fifth nerve from the bulbar nuclei connections are made with the vagus nerves.

In doing clinical work, Francis(I4) believed that the irritation producing the asthma might originate in the nose. The gross lesions in the nose were not necessarily the cause of the asthma, but both the gross lesions and the asthma had the same etiology. He relieved these cases of reflex asthma by applying cocaine to the nasal septum. More recently(I6, 36 & 32) the paranasal sinuses have been drawing more attention in the treatment of asthma than the nose proper. The ethmoid and maxillary sinuses being the more important. No account of experimental work on reflexes from the paranasal sinuses to the bronchi was found.

The nose contains the only tissue in the body from which we have good evidence of giving rise to reflex asthma as the result of stimulation. Dixon and Brodie(I1) found that little or no bronchial constriction could be obtained by stimulation of the sciatic, central vagus, superior laryngeal nerves, or the cornea. Binger, Gaarde, and Markowitz(5), in work on quarternized guinea pigs, claims to have produced reflex bronchial constriction by stimulation of the vagina and skin. They obtained these results even after cutting the vagus nerves. From these data, they drew the conclusions that broncho-constrictor fibers existed in the sympathetic nerves from the thoraco-lumbar region.
They also claimed to be able to demonstrate psychic reflex bronchial constriction by producing sudden noises or flashing a bright light. While studying the physiology of the lungs, I(I8) tried to verify their work, but came to the conclusion that they had misinterpreted their records. Having placed the wrong interpretation on their records, the conclusions could hardly be correct. I have seen no experimental evidence to support the view that there is a psychic reflex bronchial constriction or a reflex bronchial constriction from any other part of the body except the nose.

The following case report might suggest the diagnosis of psychic asthma, except with a careful history and physical examination, the presence of a paroxysmal tachycardia and cardiac decompensation is discovered. The patient got relief from digitalis.

CASE NO. 1......H. J., white male age 60, entered the Douglas County Hospital on Feb. 10, 1937. The patient has been in ill health for most of his life. About thirty years ago, he first developed difficult breathing. This was preceded, by several years, with attacks of hay fever. The difficult breathing was made worse by mental excitement. He also noticed that his heart would pound and beat very rapidly during these spells. He noticed swelling of the ankles at about the same time the dyspnea developed. At that time, he was standing most of the day working as a street car motor man. The swelling of the ankles would disappear during the night.

The spells of dyspnea were intermittent and were made
worse by exertion, damp weather, summer months, and previous to weather changes. He did not notice that his symptoms were made worse by the presence of animals or by special articles of diet. A change of climate did not give him relief. Digitalis gave him relief from his symptoms. Subcutaneous injections of epinephrine and ephedrine sulphate capsules by mouth also gave him relief.

The family history is negative with the exception of one brother that died of asthma at 63 years.

The patient has had numerous operations for hernia, appendicitis, cholecystitis, vesical stones and tonsilitis.

Physical examination showed an emphysematous chest, resonant throughout. Wheezing breath sounds were heard in all parts of the chest. There was difficult expiration. The apex beat of the heart was 3 cm. to the left of the mid clavicular line, 5 cm. below the zyphoid process. The point of maximum intensity being in the epigastric region at the lower end of the sternum. There were no cardiac murmurs. The rate was regular at 80 per minute with strong forceful beats. Blood pressure 110/98. The liver border extended 6 cm. below the costal margin. It was smooth and tender. The ankles showed pitting edema, a brick red discoloration and scaling.

The urine analysis was negative. Blood count: Hemoglobin 78%. Erythrocytes 4,100,000. Leukocytes 7,800. Granulocytes 69% Lymphocytes 23% Monocytes 3%. Eosinophiles 5%.

The above case is interesting because of the psychic
element producing a tachycardia which in turn would make his asthma symptoms worse. This together with the signs of cardiac decompensation indicates a strong cardiac element in the cause of the symptoms.

The following case report illustrates a reflex asthma produced by somatic reflexes from the upper respiratory tract.

CASE II (38).....January 22, 1929. Girl age 16.

Complaint and history.....Asthmatic attacks and nasal obstruction since 6 years of age, first attack followed a severe "cold". Has slept propped up on pillows for years. Tonsils and adenoids operated when 7 years old.

Examination showed nostrils filled with polyp, antra dark on transillumination. X-ray showed rudimentary frontals, cloudy antra and ethmoids.

January 26.....Right and left radical antra operation; antra were filled with polypi. Removal of polypi from middle fossae and part of left middle turbinate removed.

For three months she was free from asthma and was able to sleep flat in bed. She also gained 20 pounds in weight during that time, when attacks, but of less severity, again occurred. Polyps were found in each nostril, antra clear.

April 26.....Right middle turbinate, right polyp and ethmoids were removed and on May 1st. same operation on left side.

No asthma since then although a few small polyps have been removed on two subsequent occasions.
Fig. IV  The top line represents the air pressure used in artificial respiration. The middle line is the blood pressure. The lower line represents the inflation and deflation of the lungs.

This rabbit had previously been sensitized to egg-white. An anaphylactic shock was produced by injecting more egg-white into the jugular vein. Immediately the bronchioles began to constrict, as represented by the decrease in excursion of the writing lever, until their lumen were completely occluded as represented by the stopping of all volume changes in the lungs.

Epinephrine was then given. After about a minute the bronchioles began to relax as represented by the resumption of volume changes in the lung.

The bronchioles were as completely relaxed at the end of the experiment as they were at the beginning.
ALLERGIC ASTHMA.....Allergy is defined as a hypersensitivity of body cells to one or more specific proteins. The body cells become hypersensitive as the result of entrance of a foreign protein parenterally. The patients body produces an antibody which becomes attached to the globulins of the cell(37). With a subsequent entrance of more of the specific foreign protein parenterally, it comes in contact with the sensitized body cell, producing morbid conditions and symptom complexes depending upon the type and location of the sensitized body cells(6). In this paper only asthma will be considered. The allergic reaction, in the lungs, produces a contraction of smooth muscle of the bronchioles, edema, and hypersecretion of the glands. There is an eosinophilia in the blood and in the secretions from the respiratory tract.

In asthma due to inhalants, the offending protein may be pollens, animal eminations, vegetable powders, dust and drugs. These substances enter the body with the inspired air, where in the lungs they produce the lesions of edema, hypersecretion, and spasm. This pathology produces the clinical symptoms of asthma. The diagnosis of asthma, due to inhalants, can often be made on the history. Many of these are caused by pollens which enter the air at a definite time each year and continues for a definite length of time, usually until the first frost. The annual attacks of asthma will correspond to these dates. Asthma due to the other inhalants, are more difficult to diagnose from the history, but a clue can sometimes be obtained by the
fact that the patient notices an attack after being around animals, in dusty places and other suggestive evidence. Appropriate skin tests must then be used.

Asthma, which is produced by foods, may be caused by a wide variety of substances. The proteins apparently enter the circulation through the gastro-intestinal mucosa. Whether a diseased mucosa is necessary, before this absorption can take place, is uncertain. It has been shown that fibrinogen is rapidly absorbed from the intestines and can be demonstrated in the circulating blood by its effects on the clotting time(27). The history of a dislike for a particular kind of food, in an allergic patient, should be studied very carefully as the dislike for that food may arise from an allergic manifestation of the intestinal wall characterized by edema of the mucosa and spasm of the intestinal musculature(6). Such foods should be studied by skin tests and elimination from the diet.

The following case report is one of allergic asthma. It is one reported by Rudolph and Cohen(35).

CASE III.....The patient is R. W. eight years of age, came to us on Dec. 28, 1929, with the following complaints: He had had attacks of bronchitis and wheezing and asthma recurring regularly since he was two years of age, eczema since he was three years of age, and hay fever to the full summer variety. His attacks of asthma were so severe that he would have gastric distress and would vomit. There was a definite history of allergy on his mother's side. With the exception of a canary bird there was nothing of any
significance in his environment.

Upon examination we observed an asthmatic boy about eight years of age. He had a slight eczema of both armpits. His nose appeared typically allergic. His chest was somewhat barrel-shaped and was hyperresonant to percussion but clear on auscultation. Both scratch and intradermal tests showed a mild hypersensitivity to beets, carrots, cabbage, lettuce, califlower, cucumber, lima bean and condiments. He also gave very strong reactions to the grasses (timothy, June grass, red top) and to ragweed (short and giant).

Pollen therapy was started and the reactive foods were eliminated from his diet. The eczema cleared up completely and the June and August symptoms did not recur.

However, following the ragweed season of 1930, symptoms began in October and continued in severe form. His parents attributed this attack to changing weather and were very much upset by the result. We felt, however, that some other factor was responsible, and on very diligent questioning and searching we discovered that whenever this boy would play in his yard where a great many leaves were scattered, he would come down with a sneezing and wheezing spell. We asked the parents to collect some of these leaves for us and upon identification we had oak, elm, maple and birch leaves.

These leaves were extracted in Coca's fluid for twenty-four hours, and the extracts were then used on the boy by the scratch method. Maple leaves gave a very definite reaction.
This was checked by the intradermal method.

This year the boy has been treated with maple extract in addition to his regular pollen therapy, and for the first time since the onset of his trouble he has complete relief from symptoms.

INFECTIOUS ASTHMA.....By this term is meant an asthma which is produced by an infectious process within the body. These infections seem to be located almost entirely in the nose, paranasal sinuses and bronchi. Writers, on this subject, do not mention an infectious process in another part of the body, such as pleuritis, peritonitis or abscess cavity as being an etiological factor. It would seem that if the bacterial proteins or the products of bacterial growth alone were responsible for the asthma, one would have to assume that the tissue localization of bacteria was such that the bacteria which produce asthma by growing in the nose, paranasal sinuses, and bronchi, would not grow and produce their products of metabolism in any other tissue of the body. The infectious processes, on the respiratory epithelium, will be the only ones considered as playing a part in the etiology of asthma.

Bacteria growing upon the respiratory epithelium, may produce enough mechanical irritation of the sensory nerve endings as to set up a reflex, the efferent impulses passing down the vagus nerves to produce a constriction of the bronchial muscles. This involves the same mechanism as has been discussed under reflex asthma.
The bacteria, which grow upon the respiratory epithelium, are a foreign protein to the body of the host. It is conceivable that this protein can produce a sensitization of the body cells and at subsequent times provide the antigen which precipitates the allergic reaction. That bacteria do play an important role in allergy is recognized by Benson(4) who says: "Bacterial anaphylaxis has been thoroughly established as a scientific fact. Active and passive sensitization may be induced with bacterial antigens as determined by the occurrence of anaphylactic shock or by Dales technic with the isolated uterus. The reactions are specific and desensitization can be demonstrated". He goes on to say that sensitization to bacterial antigens cannot be produced with the same ease and certainty as when horse serum and egg-white is used. A single dose often fails to produce any demonstrable sensitization. The most successful results are obtained by repeated small injections of antigen followed by an interval of three weeks or longer. Gelfand(15) says that sensitization to bacteria by skin tests is difficult to prove. In his work, Benson(4) found that the intradermal tests sometimes gave a greater reaction with the bacterial bodies than with the filtrate. At other times the filtrate gave a greater reaction than the bacterial bodies. Sometimes the two would react equally. If the clinician feels that bacterial sensitization is the important factor in infectious asthma, he attempts to desensitize the patient by means of autogenous vaccines(20). Benson(4) made a vaccine with heat killed bacteria and unheated bacterial
filtrate. This was based upon the assumption that the filtrate and bacterial capsule probably contained a predominating amount of a specific substance, while the bacterial bodies retained the bulk of the less specific but antigenic nucleoprotein fraction. He believes that the specific substance in the filtrate and capsule is a carbohydrate which in itself is not antigenic but when combined with the protein molecule lends specificity to the allergic reactions. In his work with pneumococci, Avery(2) has shown that the capsule contains a carbohydrate which exhibits immunologically the same specificity as do the bacteria of which they originally formed a part. This carbohydrate is excreted in the urine of patients with pneumonia. The carbohydrate from pneumococci types II and III do not contain nitrogen. To demonstrate that the carbohydrate is the substance which gives specificity to the reaction, he united the carbohydrate from type III pneumococci to the globulin of horse serum. This compound was capable of stimulating antibody formation which agglutinated type III pneumococci. He went on to show that, after sensitizing an animal to a specific protein, a fatal anaphylactic shock could later be produced by injecting a minute amount of the homologous polysaccharide. His conclusions are: "There is now ample evidence to support the view that protein free, even nitrogen free, carbohydrates may induce acute anaphylaxis in specifically sensitized animals". This work on the role of carbohydrates in allergy has been done in connection with bacteria and their products. No account of the study of carbohydrates in other allergic
conditions which are due to food or pollen sensitization has been found. It is well known that a carbohydrate molecule is usually associated with a protein molecule. The work of Avery indicates that, the specific protein molecule is not as important in allergic manifestations as is the carbohydrate molecule which is attached to that protein molecule. No accounts were found of studies having been made to determine the presence of a foreign polysaccharide in the urine of patients who suffer from allergic reactions, in the same way that Avery found a polysaccharide in the urine of patients suffering from pneumonia.

It is well known that an attack of asthma is often ushered in with an acute upper respiratory infection. Rackeman(33) says: "Acute colds and sinus infections can cause asthma in short attacks, which last for the duration of the infection". With such a history, it is probable that the asthma is due to the infection, although the exact mechanism by which the bronchioles are caused to constrict is in doubt. The organisms which are isolated and grown in culture from respiratory epithelium of asthmatics, produce in the culture medium a histamine like substance which when injected into an animal acts as a powerful constrictor of the bronchial muscles(39). Some investigators believe that these organisms when growing on the respiratory epithelium will produce the same histamine like substance as they did in the culture medium. This assumption may or may not be true. If it is true, such a chemical would leave the situa-
of its formation very rapidly and would therefore be very difficult to demonstrate. Such a substance would reach the bronchial muscles through one of three avenues: (1) Absorption into the blood stream, (2) Absorption into the lymphatics, (3) Direct extension along the respiratory epithelium to the muscles of the bronchioles. Knott and Thornton(22) in a study of 333 cases isolated Gram-negative bacilli from bronchiolar infections which in cultures produced this histamine like substance, capable of constricting the isolated bronchi and isolated uterus of the guinea pig. The action being strictly comparable to histamine. They say: "Juvenile asthmatics are much less liable than adult asthmatics to show bronchiolar infection, this being apparent in all types of infection". It seems that such a statement would tend to indicate that, the infection in the bronchioles is secondary to the onset of the asthma and would therefore not be the cause of the asthma.

CASE IV.....F. C., University Hospital No. 43437, single, male, colored, American laborer, age 22, entered the hospital May I, 1933, complaining of difficult breathing. He had always been well, with no previous history asthma, until two months ago. At that time he was working in a garage washing cars. He caught a cold which became worse and changed into asthma. There was a sensation of fullness and congestion in the nose and dull pain in the internal canthus of the eye preceding the asthma attack. There was a productive cough with blood in the sputum and pain in the right lower quadrant of the chest only when coughing. He has never
had hay fever, asthma or urticaria. No palpitation of the heart either before or during the attacks. No food idiosyncrasies. No edema.

A urine analysis was negative. A blood count: Hemoglobin 85%. Erythrocytes 5,000,000. Leukocytes 11,000. Granulocytes 60%. Lymphocytes 21%. Eosinophiles 11%. Monocytes 8%.

X-ray showed slight increase in the density of the frontal sinuses with poor visualization of the ethmoids.

The above case demonstrates an asthma due to an upper respiratory infection. This was his first attack of asthma. It is difficult to say whether the attack was due to: (a) A reflex constriction of the bronchioles, (b) Constriction of the bronchioles due to toxins which are the products of bacterial growth, (c) Constriction due to sensitization to bacterial proteins.

The following case report was taken from an article by Potts(31). It was selected because it illustrates the importance of treating the nose and paranasal sinuses in cases of asthma.

CASE V.....R. O. C., October 11, 1926. Has had asthma for the past three months. Unable to work, poorly nourished, breathing labored, thoracic type. Nose....right nares no gross pathology; left nares some purulent secretion, large polypus in front of middle turbinate. Radiograph....right accessory sinuses fairly clear, left maxillary and ethmoid sinuses shaded. Operation....removal of polypi and anterior ethmoid. Window drainage of left maxillary sinus. Follow-
ing this the asthma was much less. Had a little trouble at night. He continued much like this for two years and then became worse, and returned for assistance. He now showed definite evidence of infection of both ethmoids, the right frontal sinus, and had some polypi in the left middle fossa. I now did a bilateral middle turbinectomy and ethmoidectomy, and made a free intranasal opening into the right frontal sinus. Following this he was fairly comfortable but was never able to work. One year later, he returned again with his breathing labored, emaciated and his asthma very bad. His nose looked clean except for pus coming from the right frontal sinus. There were two polypi. The nasofrontal duct was freely open. A radiograph showed all sinuses clear except the right frontal. A radical right frontal sinus was done. It was found full of a very thick sticky secretion and the mucosa was thick and tough like leather. His asthma cleared almost at once and has not returned.

URINARY PROTEOSE....In 1923, Mills et al(27) studied the absorption of protein from the intestines and its excretion in the urine. They fed tissue fibrinogen to man. Within 2½ minutes it appeared in the finger tips, as determined by changes in the clotting time of blood. Such a rapid action indicates its passage through the intestinal wall without digestion by enzyme action. This fibrinogen is also absorbed through the intestines, from the subcutaneous tissues and peritoneal cavity of animals. However, the
absorption from the subcutaneous tissues and peritoneal cavity is much slower than from the intestines. In the animal experiments, this fibrinogen was excreted in the urine. It failed to appear in the urine of man. Bayliss, Kerridge and Russell(3) have shown that proteins are excreted by the kidneys of anesthetized cats and rabbits and by the isolated perfused kidneys of dogs. By these experimental methods, gelatin, Bence-Jones protein, and egg albumin were excreted and concentrated. Serum albumin and globulin of their own and other species was not excreted. Hemoglobin was excreted only when its plasma concentration reached a certain level and was not concentrated. They found that the proteins which were excreted all have a molecular weight of less than 70,000. Hemoglobin is near the border line with a molecular weight of 68,000. Proteins with a molecular weight greater than 70,000 are not excreted. Histological examination of these kidneys showed no evidence of damage. Protein was seen in the capsular spaces of two kidneys in which egg albumin was excreted in high concentration.

Although serious objections can be raised to the above laboratory experiments, they support the view that proteins are capable of being absorbed unchanged through animal membranes. The kidneys are capable of excreting certain of these proteins. In 1930, Oriel and Barber(28) showed that the urine of normal persons contains a proteose which is in too small amounts to be detected by ordinary clinical methods. In normal individuals this varies from 8 to 33 mg. per day. In sensitive patients it varies from 34 to 290 mg. per day.
They also showed that this protease is capable of producing a positive skin reaction in the allergic patient from whom it was isolated. Darley and Whitehead (8, 9 & 10) found that a normal individual failed to react to his own urinary protease. They say: "Whatever the theoretical significance of this protease, it is evident that it is specific for a given primary antigen. ....... Protease obtained from a case of serum sickness will give a positive intradermal reaction when tested in another patient known to be sensitive to horse serum. A similar specificity has been observed in other allergic conditions". They report improvement in 6 out of 9 asthma cases. Others (25) work agrees quite well with this. The skin reactions of patients to their own urinary protease has caused considerable controversy. Pearson (30) in studying this found that in a control series of fifty healthy men, two per cent gave significant reactions to their own urinary protease. In his asthma patients who were known to be sensitive to one or more proteins, fifty per cent gave significant skin tests to their own urinary protease. He says that the immediate skin reaction should be used to judge sensitivity, as the delayed reaction is obtained in both allergic and non-allergic people. Glathar (19) used the urinary protease to desensitize the patient even though the skin reaction was negative. He reports good results and does not think that the skin reaction is necessarily a criterion for the therapeutic value of the protease.

The following case report is taken from Darley and
Whitehead(IO). It was chosen to illustrate the therapeutic use of urinary proteases.

CASE VI....Female, age 8. Onset in early summer Complicated by asthma the previous season. Skin tests for pollen sensitivity not done. The intradermal protease test was violent in that erythema persisted for over 12 hours. Following protease administration the symptoms cleared completely and there was no recurrence of her asthma.

If the kidneys of the allergic patient are capable of excreting the protein to which he is sensitive, this method should provide a means of desensitizing the patient without searching through an innumerable number of proteins to find the ones to which he is sensitive. If he is sensitive to a number of proteins, they may or may not all be represented in the urine. While these workers are centering their attention on the protease in the urine, it might be well to recall the work of Avery(2) and Benson(4) who have shown that it is the carbohydrate molecule which gives specificity to the allergic phenomena. The work of Avery in particular would tend to indicate that, the type of protein molecule is unimportant but it is the attached carbohydrate which gives specificity to the reaction. He also showed that a polysaccharide from the capsule of the pneumococci is excreted in the urine of patients. In the work of those who studied the urinary proteases, no mention was made of the presence of a carbohydrate in combination with these substances.
This phase of the subject should be investigated, as it is possible that the presence of such a substance would remove many misunderstandings on the subject.
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