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THE PATHOLOGY OF BRONCHIAL ASTHMA*

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INTRODUCTION

In a clinical study of a certain type of food asthma, published nearly ten years ago,[1] one of us expressed the conception that bronchial asthma is a manifestation of allergy in the human, in the following concluding sentences: "In most cases of bronchial asthma the causative factor lies in the allergic reactibility of the individual," and, "The multiplicity of asthmatogenous substances is explained by the multiplicity of proteins which may act as anaphylactogens."

The later clinical and immunologic studies of Walker, Cooke, Rackeman, and Mackenzie, undertaken from the same point of view, have greatly elaborated the evidence for this conception and have brought forward more detailed proofs for its correctness and general validity for the majority of all cases of asthma. Since allergy in the end means changed tissue reaction, it is obvious that the investigation of any allergic condition in the human must necessarily take up the question whether demonstrable morphologic changes are associated with the physicochemical changes which are the first reactions of the organism toward the protein acting as an allergen.

The histologic examination of the animal body postmortem has furnished, in one particular form of allergy, anaphylaxis, very important information which is of the greatest value in the diagnosis and characterization of the anaphylactic death and for our understanding of the pathologic physiology of this immunologic phenomenon. It suggests at the same time that different organ-systems and structures are primarily involved in different species of animals, and opens the still unanswered question whether all tissues of the same species are allergic to the same extent.

Up to the time of the allergic conception of bronchial asthma, the students of this disease, neglecting too much the true underlying

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1. Koessler, K. K.: Bronchial Asthma Due to Hypersusceptibility to Hen's Eggs, Illinois M. J. **23**:66, 1913.

condition, had focused their chief attention on the respiratory crisis, the paroxysmal attacks of dyspnea. This symptom fascinated the physician on account of its explosive and dramatic character and, because of the intense discomfort of the patient, demanded immediate relief, often taxing the resources of medical aid to the utmost. While the respiratory crisis of asthma comprises in itself no more of the pathologic physiology and true nature of the disease than do the convulsive attacks in eclampsia or epilepsy, it has developed in this way that most discussions of this condition have dwelt chiefly on the origin and mechanism of the dyspnea.

The theories that have been formulated to explain the attacks of paroxysmal dyspnea are agreed today that the difficulty of respiration is due to a stenosis of the bronchi, but whether this narrowing is due chiefly or exclusively to a spasm of the bronchial smooth muscle system, to swelling and exudation of the bronchial mucosa, to a true obturation stenosis by the secretion from the bronchial glands, or to a combination of two or more of these conditions seems still to be an unsettled question. The recognition that certain forms of bronchial asthma are manifestations of allergy in man, a conception which has introduced a new era in the study and treatment of this disease, has strengthened the contention that bronchiolar spasm is the important factor in the production of the bronchostenosis. It must be admitted, however, that this view, aside from the indirect proof obtained from the pharmacologic action of atropin and epinephrin, has mainly been deduced from the mental comparison and identification of the emphysema and bronchospasm observed in the classical experiment of anaphylaxis in the guinea-pig and not from a detailed study of the lung structures of the human asthmatic after death.[2]

The diffuse and loose application of the term "anaphylaxis" to every kind of diurnal or nocturnal dyspnea will not advance our knowledge of bronchial asthma. Anaphylaxis is a well defined immunologic phenomenon, and the application of this term should be restricted to those forms of asthma which fulfil at least some of the following conditions:

1. Positive skin sensitization tests for one or more specific proteins. It is possible, however, to be sensitized in the allergic sense and to show no skin sensitization.[3]

2. Blood, sputum and tissue eosinophilia, showing an altered reaction of the human organism to a foreign soluble protein.

2. Meltzer, S. J.: Bronchial Asthma as a Phenomenon of Anaphylaxis, J. A. M. A. **55**:1021 (May 9) 1910.

3. Fleischner, E. C.; Meyer, K. F., and Shaw, E. B.: A Résumé of Some Experimental Studies on Cutaneous Hypersensitiveness, Am. J. Dis. Child. **18**:577 (Dec.) 1919.

3. Relief from the bronchial spasm by the use of atropin or epinephrin.

4. Desensitization of the patient by repeated injections of the exciting protein, e. g., horse dander, pollen or by ingestion of gradually increasing quantities of the exciting protein, e. g., egg-white.

5. Freedom from symptoms on removal of the exciting protein.

6. Passive sensitization of a laboratory animal with the blood of the asthmatic.

7. Postmortem examination in fatal cases to determine if there are any changes which account for the sudden death and which simulate the acute emphysema found post mortem in the guinea-pig and to exclude the dyspnea due to capillary thrombosis or embolism (anaphylactoid reaction of Karsner and Hanzlik); for it is chiefly the pathologic-anatomic examination of the animals postmortem that has characterized the anaphylactic symptom complex peculiar for each species.

On the other hand, we believe it to be a grave mistake to consider all cases of bronchial asthma as a manifestation of allergy. The fallacy becomes especially apparent in a study of the bacterial type of asthma, the so-called asthmatic bronchitis.[4] Bacterial infection may lead in a variety of ways to bronchial stenosis. The infection of the mucosa and the glandular structures may produce an abundant exudate leading to partial or total obstruction of certain bronchi, or the infection may lead to profound injuries of the protecting layer of the mucosa, causing minor losses of substance, thus facilitating absorption of toxic materials which stimulate muscular spasms similar in mechanism to the bronchiolar spasm produced through inhalation of excoriating gases. It is also not improbable that various poisons of the type of peptones or amines are formed by the action of bacteria on tissue proteins. These poisons, when carried by the blood or lymph stream from the intestinal tract, or from distant foci of infection to the peripheral nerve endings in the bronchial musculature, may stimulate it to spastic contraction. Only in very rare instances might bacterial proteins, as such, sensitize a person and act as anaphylactogens. Then the bacterial type of asthma, too, might become allergic in character. Even in the instances of allergic asthma a chronic bronchial infection is often superimposed as a second pathogenetic factor, which only too often obscures, especially in older persons, the primary allergic susceptibility of the patient.

4. Koessler, K. K., and Moody, A. M.: Etiology of Chronic Bronchitis, with Special Consideration of Those Forms Associated with Bronchial Asthma, J. A. M. A. **64**:1104 (March 27) 1915.

These considerations suggest that detailed histological examinations of patients who have died from asthma should furnish information of value for settling certain phases of the problem briefly discussed in the preceding paragraphs.

HISTORICAL REVIEW

Since our work is mainly concerned with the microscopic analysis of the finer lung structure in bronchial asthma, we shall review here only those cases in literature in which a microscopic examination has been made. While the medical literature of the seventeenth, eighteenth and nineteenth centuries contains some excellent post-mortem reports on the macroscopic examination of persons who have died of asthma, the survey of these reports does not, at this time, warrant their inclusion here for the sake of completeness. The number of recorded microscopic studies of the lung structure of persons who, during life, have suffered from true bronchial asthma, is exceedingly small if one considers the frequency of the disorder. So far as we know, only fifteen cases are reported in which a more or less detailed microscopic study of the lungs has been made and of this number only about one-half seem, on close analysis of the data, to be cases of true bronchial asthma.

SUMMARY OF CASES IN LITERATURE

CASE 1. 1886. E. v. Leyden.[5]—*History.*—Female, aged 40, had had asthma

NECROPSY REPORT: *Macroscopic Examination.*—Both lungs show marked vesicular emphysema and their borders are greatly distended. The bronchi are not dilated and not changed, except for a reddening of the mucosa. The small bronchi contain greenish or whitish mucous masses in which there are no fibrin or crystals.

Microscopic Examination.—Some of the alveoli are distended, while others are not, and most are filled by a granular material containing many large cells. The walls of the smaller bronchi are not essentially changed and the lumen of many is practically occluded by a layer of amorphous material which is adherent to the epithelium. One illustrated section is described.

Comment.—From the history, this case appears to be a typical case of bronchial asthma which was complicated during the last months of life by failing heart and kidneys. The occlusion of many bronchi by mucus is the most significant pathologic change described.

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5. v. Leyden, E.: Ueber Bronchial Asthma, Deutsch. Militärärztl. Ztschr. **15**:51, 1886; Ueber Bronchial Asthma, Berlin, 1886, Mittler and Son. since early childhood and was treated by v. Leyden seven years previously. Her attacks appeared and disappeared suddenly, the frequency, severity and number varying considerably. In attempting to relieve her suffering she became a high grade morphin addict. Later severe hydrops and albuminuria developed. The lungs were emphysematous and sibilant râles were diffuse. During attacks, a tough grayish sputum containing fibrinous threads, small firm masses, crystals and epithelial cells were raised. Death followed an attack of severe dyspnea with cyanosis.

CASE 2. 1889. J. B. Berkart.[6] *History.*—Mrs. C., aged 37; family history of tuberculosis. Childhood diseases: whooping cough, measles and scarlet fever. Since childhood she had been subject to frequent colds, especially in early summer. The first attack of bronchial asthma followed a severe prolonged bronchitis at the age of 23. Following this, she had frequent attacks of bronchitis with asthma which, with a swelling of the legs, caused her to enter the hospital a few months before death. On entrance, the heart's action was disturbed and the urine contained albumin. She left the hospital after a stay of three or four months, being considerably improved, except for a generalized edema and frequent severe attacks of paroxysmal dyspnea. Nine days before death she was seen again because of dyspnea, cough, insomnia, diarrhea and weakness. The face was cyanotic and edematous. The chest showed bilateral high pitched resonance with diffuse sonorous and sibilant ronchi. Pulse 100, small, soft and regular. Heart extended beyond the right sternal border and its sounds were loud and clear. Abdomen distended. Urine negative. Twenty-four hour specimen of sputum about 4 ounces, contained Curshmann's spirals, Charcot-Leyden's crystals and eosinophils. Death followed an acute exacerbation of all her symptoms.

NECROPSY REPORT: *Macroscopic Examination.*—Heart, considerable dilatation and hypertrophy, with valves intact. Lungs not collapsed. Extensive adhesions of the right apex. The right main bronchus and one branch of the left main bronchus are almost occluded by dark brown cylindrical branching masses. The smaller bronchi are dilated and some are partially obstructed by exudate. The rest of the lungs are emphysematous. The abdomen contains a moderate amount of fluid. The liver, spleen and kidneys are large, pale and dry.

Microscopic Examination.—The cylindrical masses are composed chiefly of deformed degenerating cylindrical epithelium with no Charcot-Leyden's crystals. The mucous membrane of the right main bronchus shows firm, fibrous avascular excrescences covered by a single layer of oblong epithelium, almost all the remainder of the mucosa being denuded. One deep ulceration in a main bronchus extends almost to the cartilage. There are a few colonies of staphylococci between the folds of the internal fibrous layer. The mucous glands are remarkably few in number, very small, and looking as if atrophied. The bronchi of medium size are irregularly dilated, most of them partially or completely occluded by masses of detritus containing fragments of Charcot-Leyden's crystals. The walls are thickened and there is considerable hyperplasia of the mucous membrane. The finest bronchi are dilated and denuded of epithelium and some contain fibrinous threads and colonies of streptococci. The alveoli are emphysematous and have no epithelium, while some are almost filled with a fibrinous exudate.

Comment.—The clinical history of the case points to a bronchial asthma developing from a chronic bronchitis and complicated in the last few months by a failing heart. The most significant pathology is the ulceration in one of the chief bronchi, the atrophy of the mucous glands and the hyperplasia of the mucosa of the middle sized bronchi.

CASE 3. 1892. A. Schmidt.[7] *History.*—J. S., waitress, aged 49; previous illness articular rheumatism at 44. Six months before death, dyspnea, emaciation and weakness caused the patient to stop work. Two months before death a troublesome cough, which was relieved by raising a small amount of

6. Berkart, J. B.: Bronchial Asthma, London, 1889.

7. Schmidt, A.: Beiträge zur Kenntniss des Sputums insbesondere des Asthmatischen und zur Pathologie des Asthma bronchiale, Ztschr. f. klin. Med. **20**:476, 1892.

tenacious mucus, developed and she was unsuccessfully treated for bronchitis. About three weeks before death the first typical attack of asthma came on and was relieved an hour later by raising some tenacious mucus. Following this, attacks came on frequently and she entered the hospital. Examination showed an emaciated female with a cystic growth the size of a goose egg in the left side of the neck. The lung borders were lowered and many dry râles were heard on expiration. Severe attacks came two to three times daily and three days after entering the hospital she died in collapse following a severe attack of dyspnea.

NECROPSY REPORT: *Macroscopic Examination.*—Tumor nodules press against and partially encircle the structures in the left side of the neck, occlude the thoracic duct and extend into the mediastinum and into the upper lobes of both lungs. A small tumor mass presses against the left pulmonary vein and partially occludes it. The heart is large and shows a marked fatty degeneration. The right ventricle is dilated. The aorta is markedly sclerotic. The apices of both lungs are adherent to the thoracic wall. The section of both lungs shows numerous tumor nodules in the upper lobes, some of which at the hilum press on the bronchi and cause narrowing of their lumina and degeneration of their walls. Peripheral to the narrowed places, the bronchi are dilated. The bronchi of both upper lobes contain yellowish tenacious mucous masses which can be pressed out or pulled out as long spirals, several centimeters in length. Both lower lobes contain much blood and exude a purulent fluid. Neither contain tumor nodules except at the hilum. The remaining organs show no important change.

Microscopic Examination.—The epithelium of the dilated bronchioles is almost intact, the lumen almost or completely occluded by mucous material which stains more deeply in the central portions and contains numerous cells, among which are alveolar epithelium, a few polymorphonuclear neutrophil leukocytes and some homogeneous round, oval or elongated structures without nuclei. The mucus in the bronchioli respiratorii shows the spiral arrangement but the alveoli contain no spirals. The mucous glands of the bronchi are in a state of active secretion, but the gland ducts contain no spirals. The walls of the bronchi and bronchioles contain dense connective tissue fibers and are infiltrated by round cells. Surrounding a few of the bronchi, which contain polymorphonuclear leukocytes, the alveoli contain numerous leukocytes of the same type. The blood vessels of the upper lobes show a marked periarteritis obliterans. The masses of tumor tissue have the arrangement of a medullary carcinoma.

The author discusses the occurrence of Curshmann's spirals, Charcot-Leyden's crystals, fibrin and eosinophil cells in the sputum and shows that, as these structures are found in so many other disorders, the sputum findings are of no great diagnostic importance in bronchial asthma. He considers the attacks of dyspnea as the all important symptom, but believes that there is no sharp distinction between the dyspneas of asthma and of severe bronchitis. But, he says, the work of Biermer and others has shown that there is a distinct nervous form of asthma in which the inflammatory factor is insignificant and he considers this form as proof that the nervous system plays an important rôle in the spasmodic element in the common exudative form of asthma as well, which fact sets asthma apart as a morbid entity distinct from bronchitis.

Comment.—Two important points must be considered in this case: First, the initial attack of asthma occurred within the last three weeks of life; and second, the presence of tumor masses pressing against the structures of the neck, mediastinum and lung. We question, therefore, whether this is to be considered as a typical case of bronchial asthma or whether it is rather to be classed as a symptomatic asthma due to a medullary carcinoma involving the respiratory tract.

CASE 4. 1898. A. Fraenkel.[8] *History.*—Male, aged 63, carpenter. Previous illnesses: rheumatism and gout for years, bronchial catarrh since 60 and followed two years later by asthmatic attacks. About six weeks before death the patient entered the hospital suffering from gout, emphysema, chronic bronchitis and frequent asthmatic attacks. During attacks the lung borders were lowered and numerous râles were heard all over the chest. The sputum contained a few Charcot-Leyden's crystals but no Curschmann's spirals. The patient improved steadily for a time but died suddenly during a severe attack after a five-day period of freedom from attacks.

NECROPSY REPORT: *Macroscopic Examination.*—Both sides of the heart are dilated. The lungs are distended and almost cover the pericardium. The right lung is slightly adherent to the chest wall. The bronchi on both sides are dilated, their mucosa is reddened and they contain a mucous material which can be pulled out threadlike. The bronchial glands are greatly enlarged and pigmented.

Microscopic Examination.—In the stained sections of the bronchial clots there are no typical spirals, but twisted threads, resembling fibrin, are present. The epithelium of the middle sized bronchi is detached from the basement membrane and forms twisted rows of cells which completely occlude some of the bronchi. Some of these cells are greatly elongated. The denuded wall appears thickened and contains many dilated capillaries and round cells. Some of the alveoli are emphysematous and some are compressed, while some contain a few blood cells. In some places the interstitial connective tissue is increased.

Comment.—To us, the most interesting points in this case are the history of a chronic bronchitis, the advanced age of the patient when the first attack occurred (62), attacks for only one year before death and the necropsy findings of an adhesive pleuritis and a thickening of the bronchial walls. It may be questioned whether this is a typical case of bronchial asthma or is a senile dyspnea due to a combination of a chronic bronchitis, emphysema and a failing myocardium.

CASE 5. 1900. A. Fraenkel.[9] *History.*—Male, aged 48. For about one and a half years preceding death, the patient remained in the hospital suffering from almost daily severe asthmatic attacks, during which he raised a tenacious mucus containing Curshmann's spirals and Charcot-Leyden's crystals. The last severe attack resulted in death thirty-six hours later from collapse.

NECROPSY REPORT: *Macroscopic Examination.*—The middle-sized and smaller bronchi of both lungs are almost or completely occluded by screw-shaped clots

8. Fraenkel, A.: Zur pathologischen Anatomie des Bronchialasthmas, Ztschr. f. klin. Med. **35**:559, 1898.

9. Fraenkel, A.: Zur Pathologie des Bronchialasthma, Deutsch. med. Wchnschr. **17**:269, 1900.

which can be pulled out with difficulty. In the larger tubes these clots are looser and several centimeters in length.

Microscopic Examination.—Stained (Bondi-Heidenhain) specimens of these clots show them to be true mucus, the threadlike central portions staining more intensely than the outer portions, which contain numerous eosinophil cells. In the smaller bronchi, from 0.15 to 0.03 mm. in diameter, isolated epithelial cells are elongated to about 20.4 microns in length, resting on a layer of small round cells; the ciliated borders of some are ruptured and the mucous content of the cell protrudes as a drop in the lumen, often fusing with a neighboring drop. In places these cells appear drawn out to form awl-like figures, in others they are heaped up to form layers two or three cells deep. The alveoli are almost free of secretion, containing only a few epithelial and eosinophil cells, and their walls contain dilated capillaries and collections of mononuclear and polynuclear cells. The walls of the small bronchi contain dilated capillaries and are infiltrated from the epithelium to the outer layer by cells, most of which are mononuclear and polymorphonuclear eosinophil cells. These cells are most numerous in bronchi containing glands and cartilages. Charcot-Leyden's crystals are found in places where the eosinophil cells are grouped.

Comment.—This seems to be a true case of bronchial asthma of several years' duration. The most important finding is the microscopic evidence of an extensive chronic infection of the bronchi. It is of especial interest that most of the cells infiltrating the bronchial walls are eosinophilic.

CASE 6. 1905. Jezierski.[10] *History.*—Male, gardner, aged 63. Father died of asthma. Patient first had cough with dyspnea about five years before death and in the last two years of life the symptoms were so severe on two occasions that hospital care was needed. The symptoms consisted chiefly in attacks of severe expiratory dyspnea, sensation of fear, palpitation with tachycardia, pain in the epigastrium and cyanosis.

Physical examination showed a barrel-shaped chest, wide intercostal spaces, lowered lung borders, difficult expiration, and numerous dry and moist râles. After a six months' stay in the hospital the patient contracted a right lobar pneumonia and died two days later.

NECROPSY REPORT: *Macroscopic Examination.*—The upper and middle lobes of the right lung are large and of liver-like consistency. The left lung is small and light and the mucosa of its dilated bronchi is reddened.

Microscopic Examination.—The bronchial lumina of the left lung, which is free from pneumonia, contain mucous masses in which are embedded cell remnants, well preserved ciliated epithelial cells often in rows, leukocytes, lymphocytes, erythrocytes and eosinophils. No fibrin is found. The well preserved epithelium is infiltrated by numerous round cells which invade all layers of the bronchial wall and in places are collected into groups resembling lymph glands. Beneath the epithelial layer the elastic tissue is markedly increased. There are also an unusual number of thin-walled closely-crowded capillaries around the tunica propria. The diaphragm shows some rarification and fatty infiltration. The neck muscles, the vagi and the cervical nerves show no changes, but the phrenic nerve contains groups of degenerating fibers. The right lung is a typical pneumonic lung.

Comment.—The clinical history of attacks of dyspnea for about five years before death in an old man and the microscopic evidence

10. Jezierski: Zur Pathologie des Asthma bronchiale, Deutsch. Arch. f. klin. Med. **85**:342, 1905.

point to infection in the respiratory tract as a probable etiologic or complicating factor in the production of the asthmatic attacks, but the hereditary factor, the occupation and the presence of eosinophils point to an allergic pathogenesis. The most significant pathologic findings are the mucous masses in the bronchi, the cellular infieltration in the bronchial wall, the presence of eosinophil cells and the increase in elastic tissue.

CASE 7. 1905. Jezierski.[10] *History.*—Female, aged 46, silk weaver. Asthmatic attacks began twelve years previously. Patient entered the hospital a short time before death suffering from dyspnea, cyanosis and tachycardia. The lung borders were lowered and there were many buzzing and whistling râles on expiration. Death followed collapse during a severe attack.

NECROPSY REPORT: *Macroscopic Examination.*—Each pleural cavity contains about 200 c.c. of a bloody serous fluid. The left lung is markedly emphysematous and contains much blood. The bronchial lymph glands are anthracotic. Small wormlike mucous masses can be pressed from the small bronchi. The right lung contains fewer of these masses than the left.

Microscopic Examination.—The mucous masses contain many elongated ciliated epithelial cells, some of which are drawn out as long filaments, cuboidal cells from deeper layers of the epithelium, round cells, numerous eosinophil cells, some erythrocytes and cellular debris. These constituents vary considerably in numbers and distinctness in different sections. The epithelium of the bronchi is intact, except in a few places where it is penetrated by round cells which infiltrate the bronchial wall either diffusely or are collected in groups about vessels. This infiltration is so marked in the smaller bronchi that all structures are obscured. The elastic tissue is not increased and there are no new-formed blood vessels. The lung parenchyma is intact.

Comment.—The most significant pathologic findings are the occlusion of many bronchi by mucous masses and the extensive cellular infiltration of the bronchial walls. Many of these cells are eosinophils. While the microscopic evidence in this case points to infection as a probable etiologic factor in the production of the asthmatic attacks in this case, the clinical and necropsy evidence implicating the heart cannot be overlooked.

CASE 8. 1908. A. G. Ellis.[11] *History.*—Coachman, aged 27, had been under treatment for tachycardia and bronchial asthma during the preceding year, and the day before death was admitted to the hospital during an asthmatic attack, with severe expiratory dyspnea, cough and cyanosis of face and extremities. The attack persisted and the patient collapsed and died the following day.

NECROPSY REPORT: *Anatomic Diagnosis:* Hypertrophy of the left ventricle; dilatation of the right ventricle; pulmonary emphysema; purulent bronchitis; exudative bronchiolitis.

Macroscopic Examination.—The lungs are distended and entirely cover the pericardium. The right lung is slightly adherent to the thoracic wall and both lungs on sections show shiny, often greenish-colored plugs in the smaller bronchi.

Microscopic Examination.—Sections taken from various parts of both lungs reveal the following changes: The alveoli are distended only in patches and

11. Ellis, A. G.: Pathological Anatomy of Bronchial Asthma, Am. J. M. Sc. **136**:407, 1908.

those bordering the bronchi contain mucus, some leukocytes and a few eosinophil cells. The capillaries are uniformly engorged. The lumina of most of the smaller bronchi, from 0.13 to 0.16 mm. in diameter, are partly or entirely filled with a slightly granular mucus which is often arranged in distinct spiral form, the peripheral portions being less dense and containing a greater number of cells. These cells are chiefly polymorphonuclear leukocytes, among which are degenerated epithelial cells. The epithelium is mostly intact and averages about 7 microns in height. The bronchi, from 0.2 to 0.45 mm. in diameter, contain mucus, sometimes with spiral arrangement. Some of the epithelium is retained, other portions are separated en masse from the basement membrane and in one place an eroded blood vessel is exposed. In bronchi 0.8 mm. in diameter the amount of mucous material and desquamated epithelial cells varies, and some of the cells are much elongated (35 microns). In all these bronchi the mucus is arranged in layers, as is shown by the distinct longitudinal rows of cells. A few polymorphonuclear eosinophil cells are present in the lumina of all the bronchi. The walls of the bronchi and of the adjoining alveoli are infiltrated with leukocytes, the inner layer of the wall near the epithelium containing chiefly polymorphonuclear leukocytes, the outer layer containing chiefly large mononuclear cells with vesicular nuclei. Among these cells, especially in the middle sized bronchi, there are varying numbers of polymorphonuclear eosinophil cells. The capillaries in the walls are dilated and in some places small hemorrhages are found. The tunica propria and the basement membrane appear hyalin in some places. There is no change in the muscle or elastic tissue, and the connective tissue is not appreciably increased. The larger blood vessels of the lung contain more than the usual amount of blood and one contains a small thrombus.

Comment.—The most important findings in this case are pleural adhesions of one lung, occlusion of many of the smaller bronchi by mucous masses and the cellular infiltration of the bronchial walls. The extensive cellular infiltration of the bronchial wall shows that a chronic infection was present at death. Without considering the clinical data, these two facts point to infection as a possible etiological factor in this case of bronchial asthma, but the presence of many eosinophil cells suggests an allergic pathogenesis.

CASE 9. 1909. Mönckeberg.[12] *History.*—Male, aged 29, mason. Previous illnesses, pneumonia in twelfth and again in eighteenth year. Psoriasis in twenty-fourth year. After serving in the army without any sickness from his twentieth to his twenty-second year, he first noticed in his twenty-fifth summer an irritating cough and dyspnea following a rapid march. He tried to be exempted from participation in some military maneuvers later that year because of this trouble, but failed. At this time, while in his quarters at night, he had severe attacks every four to eight days, and was later released from service. Following this, severe attacks came more frequently, often from five to six times daily, and for the rest of his life, about four years, he gradually grew worse, except for transient periods of improvement. A short time before death he entered the hospital because of dyspnea and a generalized edema. At this time he had a constant dyspnea which increased in severity, came in attacks every two or three hours and was relieved by coughing up much tough mucus, containing numerous spirals, eosinophil cells and leukocytes. The lung borders were not movable, and numerous vesicular and ringing râles were heard on expiration. The heart was rapid and irregular and the blood contained an increased number of

12. Mönckeberg, J. G.: Zur Pathologischen Anatomie des Bronchialasthmas, Verhandl. d. deutsch. pathol. Gesellsch. **14**:173, 1909.

eosinophile cells. The urine was not decreased in amount. Death followed a series of severe attacks.

NECROPSY REPORT: *Anatomic Diagnosis:* Desquamative bronchial catarrh with hypersecretion of mucus, spiral formation, eosinophilia and asthmatic crystals; vesicular emphysema; bilateral complete adhesive pleuritis; isolated chronic and fresh tubercles in both lungs and in the hyperemic enlarged lymph glands.

Macroscopic Examination.—Well-developed and well-nourished male with generalized edema. Abdominal cavity contains much clear yellow fluid. Thorax barrel-shaped. Both pleural cavities are completely obliterated by adhesions. The right heart is markedly dilated and its walls thickened. The myocardium is a pale yellowish-brown color. No valvular changes. The mediastinal and bronchial lymph glands are large, soft and red. Both lungs are dilated. The cut surface of the lungs shows all the larger and most of the smaller bronchi to be completely occluded by tenacious, yellowish-white branching masses. The bronchial walls are thickened and show two distinct zones, a thin inner grayish-yellow zone and an outer reddish zone. The chief bronchi contain only some tenacious mucus not adherent to the wall. The remaining organs show the usual findings of a chronic passive hyperemia.

Microscopic Examination.—Most of the emphysematous end branches of the bronchi and the alveoli are empty, a few containing fluid and epithelial cells and having thickened walls, some of which are infiltrated by mononuclear and polymorphonuclear cells, chiefly eosinophils. The elastic fiber tissue is not increased, but the muscular tissue in the alveolar and lobular septa is increased. The pulmonary artery is thickened and sclerotic throughout and some branches contain organized thrombi. There are a few scattered new epitheliod miliary tubercles in the thickened cell-infiltrated connective tissue about the larger bronchi. The walls of the pulmonary veins are diffusely thickened. All capillaries are engorged by blood, and in places there are extravasations of erythrocytes into the tissue. The bronchioles up to the diameter of 0.2 mm. are either empty and with intact epithelium, or they contain bands of desquamated epithelial cells with interwoven cilia, a few "Herzfehlerzellen" and some mucus. There are no inflammatory changes in the thin muscular layer of these dilated bronchioles. The lumen of bronchioles, from 0.2 to 0.4 mm. in diameter, contains somewhat more well-preserved desquamated epithelium, round cells and detritus, and the walls contain a few mononuclear and polymorphonuclear eosinophil cells. The bronchial branches from 0.4 to 0.5 mm. diameter have a stronger muscular layer, which is frequently interrupted by diverticula or cryptlike protrusions of epithelium (Schleimhautausstülpungen). The epithelium is mostly intact, and at the crests of the folds is crowded together and appears elongated. The lumen contains cellular detritus, mucus, epithelial cells and round cells, often arranged in whorllike thickenings. The walls are infiltrated by many round cells. The walls of bronchi, from 0.5 to 1 mm. in diameter, contain small cartilages and mucous glands, the muscular layer is markedly developed and the cryptlike diverticula are more numerous and some are branched. The mucous glands which are in active secretion open into some of these diverticula. The broadened and hyalinized basement membrane continues into the diverticula, but the muscular layer is interrupted at the necklike opening of these structures. The epithelium is thickly crowded, and on the crests of the folds is arranged tuftlike and in places is much elongated, especially in the diverticula where these cells contain much mucus. The lumen of these bronchi is almost filled by mucus in which there are varying numbers of isolated or groups of desquamated ciliated epithelial cells, mononuclear and polymorphonuclear eosinophil cells, Charcot-Leyden's crystals and cellular detritus. These constituents are often arranged in twisted thickened lines and arranged in rows. The whole bronchial wall is thickened and infiltrated by round cells. In the bronchi, from 1 to 3 mm. in diameter, the walls are thickened, hyperemic and

thickly infiltrated by round cells, the lymphoid follicles and mucous glands are enlarged, the muscular layer hypertrophic, the diverticula more numerous, and the epithelium single-layered and greatly elongated. The content of the lumen is the same as that in somewhat smaller bronchi. In the chief bronchi mucus exudes from the gland ducts and spreads over the epithelial surface. The hyperemic bronchial glands contain a few fresh epitheloid tubercles.

Comment.—The most important points in this case are: History of pneumonia at 12 and again at 18; relief from dyspnea after raising masses of mucus, bilateral adhesive pleuritis, complete occlusion of most of middle sized bronchi by mucus, thickening of the bronchial walls, apparent hypertrophy of bronchial musculature, cryptlike structures in the bronchial walls, cellular infiltration, largely eosinophilic, of the bronchial walls, enlargement of the mucous glands and epitheloid tubercles. The history of pneumonia, the bilateral adhesive pleuritis and the cellular infiltration of the bronchial walls all point toward infection as a possible etiology in this case, but an allergic pathogenesis is also indicated by the extensive eosinophilia. The hypertrophy of the musculature is no doubt due to the four years of almost continuous asthmatic attacks of dyspnea. The finding of large mucous glands and of the cryptlike structures in the bronchial walls is significant.

CASE 10. 1911. Hermann Heizer.[13] *History.*—Child, aged 2 years. Family history negative. Eczema since fourth month. First attack of dyspnea at 9 months. Attacks often followed exposure to wind or dust, and were accompanied by cyanosis, chest noises and the production of a large amount of tenacious sputum. Death followed an attack.

NECROPSY REPORT: *Macroscopic Examination.*—Lungs distended. Heart enlarged and right ventricle thickened. Trachea and large bronchi contain a purulent secretion. All lymph glands of the body are greatly enlarged.

Microscopic Examination.—The alveoli vary in size, some of their walls are thinned and some are ruptured. Some bronchi are dilated and occluded by masses of mucus containing leukocytes and epithelial cells. The walls of the large bronchi are thickened by infiltrating cells and distended capillaries. The bronchial mucous glands are markedly enlarged and their ducts filled with mucus.

Comment.—The most significant findings reported are the history of eczema for months and of attacks following exposure to wind and dust, the generalized enlargement of the lymphoid tissues, hypertrophy of right ventricle, thickening of the walls of the bronchi by cellular infiltration and capillary distension and the occlusion of many bronchi by mucus. The clinical history points to both foods and inhaled dust (animal or plant) as probable etiologic factors in the production of the attacks of dyspnea.

CASE 11. 1913. M. M. Tichmeneff.[14] *History.*—Female, aged 29, college student. No hereditary peculiarities. Nasal catarrh since early childhood. Following an attack of croup in the eighth year, asthmatic attacks lasting from

13. Heizer, H.: Dissertation, München, 1911.
14. Tichmeneff: Bronchial Asthma with Death, Prakt. Vratch **12**:562, 1913.

two to three days came on four or five times each year, usually in the spring and fall, and on two occasions in later years required hospital care. During an attack three weeks before death she entered the hospital with a severe very productive cough, and on examination showed the characteristic posture, difficult whistling expiration, limited excursion, some emphysema, numerous whistling, buzzing râles, normal heart and normal digestive, nervous and urinary systems. Pulse, 112; temperature, 37.5 C. Hemoglobin, 87 per cent.; erythrocytes, 5,690,000; leukocytes, 15,200, showing by differential count: lymphocytes, 26 per cent.; transitionals, 4 per cent.; neutrophils, 60 per cent, and eosinophils, 7 per cent. Sputum contained many pus cells, Charcot-Leyden's crystals, Curshmann's spirals and eosinophil cells. Urine contained a trace of albumin. The attack of asthma subsided in three to four days and pneumonic symptoms appeared. Two days before death a severe gastro-intestinal hemorrhage began and continued until death.

Clinical Diagnosis.—Bronchial asthma; left-sided exudative pleuritis and pneumonia; ulcer of the stomach or duodenum.

NECROPSY REPORT: *Macroscopic Examination.*—The left pleural cavity is partially obliterated by fibrous adhesions and contains 300 c.c. of a purulent exudate. The left upper lobe contains a small cavity and a row of small consolidations from which pus exudes on pressure. The right lung is soft and exudes a mucopurulent fluid. The pericardial sac contains a small amount of clear yellowish fluid. Heart: 9 by 9 cm.; myocardium pale; large vessels unchanged. Spleen pale and flabby. Liver yellowish. Kidneys pale. Stomach mucosa normal. Large duodenal ulcer 5 cm. from the pylorus showing eroded blood vessels.

Microscopic Examination.—Slight brown atrophy of the heart. In the lumen of some of the small bronchi there is an exudate which contains many round cells and leukocytes. The tightly crowded columnar epithelial cells are much elongated and are arranged in several rows as if in increased proliferation. All the layers of the bronchial wall are considerably thickened, due to an increase in connective tissue, round cell infiltration, and hypertrophy of the muscular layer. Some of the bronchi are dilated, their walls markedly infiltrated by round cells, and are surrounded by areas of pneumonic infiltration. The cavity is a typical bronchiectatic cavity.

Comment.—The most significant pathologic findings are blood eosinophilia, 7 per cent.; adhesive pleuritis and increase in thickness of the bronchial walls due to accumulation of round cells, hypertrophy of muscle layer and increase in connective tissue. This appears to be a true case of bronchial asthma in which death was due to an intestinal hemorrhage. The etiology of the attacks cannot be determined, for the history and the clinical and necropsy evidence point to infection as a possible causal agent, while the eosinophilia points to an allergic pathogenesis.

CASE 12. 1916. Marchand.[15] *History.*—Female, aged 53. Hereditary peculiarities: Mother died of asthma and capillary bronchitis. History of present illness: Capillary bronchitis since 17 and asthmatic attacks since 30. She first entered the hospital in her forty-third year suffering from bronchial asthma, pulmonary emphysema and chronic laryngitis, and left six weeks later much improved. Ten years later, about two weeks before death, she returned to the hospital, following an attack of six weeks' duration, suffering from dyspnea, severe cough with much expectoration, headache, insomnia and

15. Marchand, F.: Beitrag zur Pathologie und pathologischen Anatomie des Bronchialasthmas, Beitr. z. path. Anat. u. z. allg. Path. **61**:251, 1916.

loss of appetite. The attacks came chiefly at night. The examination showed a marked dermographia; cyanosis of the lips and fingers; barrel-shaped chest; iabored respiration; lung borders on both sides anteriorly at the seventh rib and posteriorly at the twelfth spinous process; boxy percussion note all over the lungs; deep humming inspiration; prolonged loud, shrill, whistling expiration; heart action accelerated but with tones clear. Roentgen-ray examination: Diaphragm contracted and with limited motion; distinct hilum shadows; marked pulsation of the right ventricle.

She raised a large quantity of a tenacious mucous sputum which contained some spirals, numerous eosinophil cells, but no crystals. The blood showed a leukocyte count of 12,600, of which 12 per cent. were eosinophil cells. Temperature, 37 C. The blood serum was very toxic for animals, 0.05 c.c. causing death of a guinea-pig. After standing one and one-half hours, the serum contained many crystals. Following a severe attack of two hours' duration, the patient collapsed and died.

NECROPSY REPORT: *Anatomic Diagnosis.*—Severe mucous bronchitis. Vesicular emphysema. Black circumscribed subpleural indurations in both apices. Recent tuberculosis and hypertrophy of the bronchial lymph glands. Fibrous induration and calcification of bronchial glands. Nodular colloidal goiter. Right ventricular hypertrophy and early fatty degeneration of the myocardium. Hyperemia of brain. Chronic perimetritis. Slight atrophic granular kidney. Hypertrophy and hyperemia of spleen.

Macroscopic Examination.—The body is that of a small well-preserved female, weighing 48 kg. The tips of the fingers are cyanotic. The thorax is not arched. The brain shows no signs of disease. The diaphragm is at the sixth rib on the right side and in the fifth intercostal space on the left side, and is contracted. The lungs do not collapse when the chest is opened, almost completely cover the pericardial sac, and are attached to the chest wall by many stringlike adhesions. A fatty remnant of the thymus is present. The pericardial sac contains a small amount of a clear yellowish fluid. The heart is contracted and the right ventricle appears to be increased in size. The valves are slightly thickened. The foramen ovale is not completely closed. The alveoli in the anterior borders of the lungs are markedly dilated. The cross section of the upper lobes are bluish gray and the outer portions are soft and edematous. The lower lobes are firmer and filled with blood. Most of the smaller bronchi in both upper and lower lobes are completely filled by a tenacious transparent material, which on cross section protrudes and can be drawn out as threads several centimeters long. In some places these threads appear as yellowish, opaque masses. The larger bronchi contain a more fluid yellowish gray material. The lower lobes are fairly dry except for the congested areas. Beneath the pleura of both apices there are a few hard black thickenings 1 cm. in diameter. The mucosa of the trachea, larynx and nasal cavities is not essentially changed.

The thyroid is slightly enlarged and contains a small colloid nodule.

The bronchial glands are large and soft, the gland at the bifurcation of the trachea being as large as a pigeon egg and containing numerous grayish nodules. One gland at the hilum of the right lung contains a calcified nodule.

The spleen is enlarged, firm and congested.

Microscopic Examination.—Blocks of tissue from all parts of the lungs, from bronchial glands, trachea, ethmoid region and the middle turbinate were fixed in liquor formaldehyd, alcohol or Zenker's fluid, and the sections stained with various stains.[16]

The upper lobes show a vesicular emphysema with the formation of some large vesicles. The bronchioli respiratorii are for the most part empty, vary considerably in size up to 0.1 mm. and are lined by a low epithelium, some of

16. The detailed descriptions of the sections and of the special form of crystals are omitted in this paper.

which is ciliated and measures 0.009 mm. Bronchioli, from 0.5 to 1 mm. in diameter, are filled by an homogenous mass containing a few cell elements which is adherent to the epithelium. In some of the smaller bronchioli a transparent, almost homogenous, layer covers the epithelium, the central portion being patent. This layer stains poorly, contains a few mononuclear cells, alveolar epithelium, and shows on high magnification a netlike structure which stains with Weigert's stain like fibrin. The cylindrical epithelium of the smaller, middle-sized bronchioli is mostly intact, and is heaped up and deformed only in the angles between folds. There are no mucous glands present, but the muchematein stain shows numerous goblet cells in bronchioles 1 mm. in diameter. The smaller bronchi contain a longitudinally streaked mucous material, with rows of cells and spirals having distinct central threads. The cellular content of the smaller bronchioles is scanty, while in the larger there are numerous round or elongated polymorphonuclear eosinophil cells which are often arranged in clumps, numerous polymorphonuclear leukocytes, some mononuclear, large, pale, swollen cells (alveolar epithelium), and in the larger bronchioli a few mast cells. In bronchioli, from 0.5 to 0.8 mm. in diameter, the epithelium varies in thickness from 0.025 to 0.04 mm., and in bronchi from 3.5 to 4 mm. in diameter, it varies from 0.05 to 0.06 mm. in thickness. The content of the larger bronchi and the trachea is composed of much well-preserved ciliated epithelium, many large markedly swollen round cells which contain droplets of myelin material, granular cells resembling eosinophil cells, a few Charcot-Leyden's crystals and numerous crystals which are different from the Charcot-Leyden's crystals. The trachea also contains several clumps of bacteria, most of which resemble the influenza bacillus. The epithelium of the larger bronchi and the trachea contains numerous goblet cells and is infiltrated by a few leukocytes, eosinophil cells and mast cells. The nasal mucosa over the free borders of the turbinates is thickened and infiltrated by cells.

The walls of all the bronchioles are more or less infiltrated by round cells of different kinds, the lymphoid elements being most numerous and often grouped to from small nodules under the epithelium and in the outer layer. The other kinds of cells, which frequently separate the muscle bundles, are: (*a*) large mononuclear basophilic cells often grouped around the acini of mucous glands; (*b*) eosinophils; (*c*) mast cells varying greatly in size and lying chiefly close to the epithelium; (*d*) a few polymorphonuclear leukocytes.

The mucous glands of the larger bronchi and the trachea show a more or less active secretion with transformation of the cylindrical cells of the duct into goblet cells. The gland cells are for the greater part markedly swollen and filled with mucus.

The blood smears and rib-marrow preparations contained numerous eosinophil cells, while the spleen contained only a few such cells. The lymph glands at the bifurcation of the trachea are enlarged and contain a small tubercle with some caseation and giant cells.

Comment.—The most important pathologic findings are: complete occlusion of most of the smaller bronchi, cellular infiltration in the bronchial wall, enlargement of the bronchial mucous glands and the numerous eosinophil cells in the bronchial wall. The history of bronchitis since the seventeenth year and of asthma beginning in the thirtieth year, the necropsy finding of marked cellular infiltration of the bronchial walls, point to infection as a probable etiologic factor in this case, but the eosinophilia indicates an allergic pathogenesis.

CASE 13. 1916. Marchand.[15] *History.*—Mrs. T. B., aged 45. Previous history: The patient has had two severe attacks of asthma in the year preceding her entrance into the hospital where she had a third fatal attack.

NECROPSY REPORT: *Anatomic Diagnosis.*—Marked fibrinous bronchitis with obturation of the left bronchus; fibrinomucous tracheitis; purulent bronchiolitis; marked pulmonary emphysema; healed right apical tuberculosis; fibrinous lobular pneumonia; cyanosis of the liver, spleen and kidney; small hemangioma of the liver; accessory spleen in tail of pancreas.

Macroscopic Examination.—Small emaciated woman with scanty fatty and muscular tissues. Diaphragm on right side at fourth rib and on left at fourth interspace. Heart not enlarged. Left ventricle, 8 mm. and the right 3 mm. in thickness.

The lungs do not collapse when the chest is opened. There are a few adhesions to the sternum. Both lungs are large and light. The posterior portion of the right upper lobe contains a few hazelnut-sized areas with caseous centers. On cut section the lung tissue is dry and contains little blood. The left chief bronchus and its branches are almost completely occluded by a tenacious exudate. The middle-sized bronchi contain glassy tenacious mucus and the finer branches contain a more fluid yellowish turbid exudate. The mucosa of the chief and smaller bronchi is swollen and reddish. The trachea contains an adherent mucous mass which extends into the right main bronchus. The peritracheal and peribronchial lymph glands are enlarged and contain no nodules. The liver extends two fingers below the costal margin. The spleen is not enlarged.

Microscopic Examination.—The lungs were fixed in liquor formaldehyd and preserved in alcohol. A large number of blocks of completely infiltrated and air-filled portions of the tissue were taken, but the original positions of these blocks could not be established later. The cross section of the exudate filled bronchi appears as whitish round disks in both the infiltrated and air-containing portions. The parenchyma of the infiltrated portions of lung resembles a catarrhal lobular pneumonia and contains many polymorphonuclear neutrophil cells, but no eosinophil cells. The parenchyma of the air-containing portions shows a moderate degree of emphysema.

The content of the lumen of the small and middle-sized bronchi in both air-containing and infiltrated portions is made up of homogenous, transparent mucus which has in many places a streaked appearance and which contains many closely crowded polymorphonuclear neutrophil cells but no eosinophils. The cylindrical epithelium is fairly well retained and contains a few globlet cells. The walls of the bronchi are thickened and contain, especially in the outer layer and between muscle bundles, many mononuclear lymphoid cells, although the blood-filled vessels contain no cells of this type and show no evidence of their migration. In some of these bronchi there are numerous eosinophil cells, either rowlike, scattered or clumped between connective tissue bundles, and most numerous in the inner layers. The eosinophil cells also intermingle with the lymphoid cells in the outer portion of the lymph nodules. There is no definite relation between accumulations of eosinophil cells and the blood vessels. These cells vary in shape and size, in number, distribution, intensity of staining property and size of granules, and in morphology and size of the nucleus. All transitions of nuclei from the mononuclear to the polymorphonuclear are visible. There are no Charcot-Leyden's crystals among the eosinophil cells or in the bronchial wall.

The lumina of some of the larger bronchi, as shown in pictures, are completely occluded by a transparent exudate which is adherent to the wall and is continuous with the content of the gland ducts. The epithelium is partially desquamated and in places necrotic. The tissue of the walls is markedly infiltrated by cells, chiefly polymorphonuclear neutrophils and eosinophils. The latter predominate in some portions of the wall, and with the neutrophils are seen penetrating the hyalin tunica propria. A few Charcot-Leyden's crystals also are present. The blood vessels are engorged with erythrocytes, among which there are a few mononuclear and polymorphonuclear leukocytes, none being eosinophilic. The cells of numerous large mucous glands in the wall are

distended by mucus, as are also many of the duct cells. In some portions of the wall there are circumscribed or diffuse collections of lymphocytic cells.

The left chief bronchus from 1 to 3 cm. from the bifurcation is almost occluded by an exudate and its epithelium partially desquamated. The mucous gland ducts are filled by mucus and the cells of the ducts and acini are distended. The mucosa is markedly infiltrated by round cells, partly mononuclear and partly polymorphonuclear, and many eosinophil cells. Some Charcot-Leyden's crystals are present in the walls and on the surface of the mucosa. The content of the lumen is composed of mucus and fibrin which show a spiral arrangement. In some places well-formed spirals with central threads are seen.

Many eosinophil cells and Charcot-Leyden's crystals are found in the mucosa of the trachea. In some of the thin paraffin sections small groups of organisms resembling the diphtheria bacillus are seen.

Comment.—The most significant findings in this case are: (1) The complete occlusion of many of the larger, middle sized and smaller bronchi by mucous masses. (2) Marked cellular infiltration of the walls of the bronchi. (3) Presence of eosinophil cells, scattered or grouped, in the walls of the trachea and some of the bronchi. (4) Presence of Charcot-Leyden's crystals in the walls of the trachea and in some of the bronchi. (5) Distension of the cells of the mucous glands and their ducts by mucus.

The etiology of the asthmatic attacks in this case has not been determined. The history of the asthmatic attacks coming on in the last year of life in a person 45 years of age, and the evidence of infection in the walls of the bronchi, point to bacteria as probable factors in the production of the attacks, but the extensive eosinophilic infiltration of the bronchi points again to an allergic pathogenesis.

CASE 14. 1918. Marchand.[17] *History.*—Male, aged 48, worker in chemical factory. Family history: Aunt had asthma. Previous illnesses: None. When about 44 years of age he began work in a chemical factory and frequently inhaled poisonous fumes. Before quitting this work, two years later, he had his first attack of asthma after exposure to fumes. After this he often had marked dyspnea on exertion and his work was interrupted frequently, the dyspnea being always more noticeable in damp weather. After a free period during the following summer the attacks returned, accompanied by cough with the raising of a tenacious mucus, and the patient was often compelled to remain in bed for several days. About ten weeks before death both legs began to swell and he entered the hospital with the following findings: Edema and cyanosis of face, high grade inspiratory dyspnea, prolonged whistling expiration; lung lowered and immovable; heart and abdomen negative; sputum scanty, tenacious and containing crystals and eosinophils; urine negative. The blood was examined several times during the stay in the hospital and showed an eosinophilia averaging about 4 per cent. The blood pressure ranged from 135 systolic and 85 diastolic on entrance to 86 systolic and 60 diastolic two weeks before death. The patient's condition gradually became worse and about nine weeks after entrance, he died.

NECROPSY REPORT: *Anatomic Diagnosis.*—Catarrh of the bronchial mucosa; catarrhal rhinitis with retained mucus in the left maxillary sinus; diffuse

17. Marchand, F.: Ein neuer Fall von Asthma Bronchiale mit anatomischer Untersuchung, Deutsch. Arch. f. klin. Med. **127**:184, 1918.

vesicular pulmonary emphysema; slight hypertrophy of the right ventricle; bronchial asthma.

Macroscopic Examination.—The lower part of the thorax is widened. The lungs are expanded and cover the heart. The bronchi up to the smaller branches are filled by yellowish-white tough masses which can be pulled out like threads. The left antrum of Highmore is completely filled by a tough opaque bluish secretion. The bronchial glands are not enlarged. The right auricle and ventricle are dilated and the walls thickened.

Microscopic Examination. — The mucous membrane of the nasal septum, turbinates and trachea contains many distended capillaries and is infiltrated by round cells, many of which are eosinophilic. The fresh secretions from the trachea and principal bronchi contain many prismatic crystals similar to those described in a previous case. (Case 12. Marchand's first case.) The lumen of the bronchi 5 mm. in diameter contains only a small amount of mucus in which are desquamated cells, leukocytes, round cells and a few eosinophils. The epithelium is mostly desquamated. The mucosa is unevenly thickened, its capillaries engorged and all layers contain numerous eosinophil cells which are often arranged in masses near the hypertrophied muscle layer. The mucous gland cells are swollen and contain no eosinophil cells. Smaller bronchi have a similar structure and are filled with mucous masses which have typical spiral arrangement. The smallest bronchioles and the alveoli are not essentially changed. One lymph gland contains a small tubercle.

Comment.—The most important points in this case are the complete occlusion of many smaller bronchi, enlargement of the mucous glands, hypertrophy of the muscle layer and the large number of eosinophilic cells infiltrating the bronchial walls.

CASE 15. 1921. N. Kamchorn and A. G. Ellis.[18] Male. Siamese, actor and fishmonger, aged 52. Family history of asthma in four generations: Father's mother; father; one uncle, one aunt, and one child. Infrequent asthmatic attacks began in childhood and gradually became more frequent. Three months before admission to the hospital the feet and legs began to swell. On entrance eleven days before death, there was a marked edema, cyanosis and respiratory dyspnea. Coughing produced a tough white sputum. The heart sounds were faint and râles were heard over the bases of both lungs. Treatment gave no relief and death resulted from failure of the heart.

NECROPSY REPORT: *Anatomic Diagnosis.*—Summary: Hypertrophy and dilatation of right ventricle; dilatation of right auricle and left ventricle; bilateral chronic adhesive pleuritis; partial atelectasis of left lung and lower lobe of right lung; vesicular and interstitial emphysema of right upper and middle lobes; acute bronchitis of left lung and right lower lobe; congestion of spleen, kidneys, stomach and liver; anasarca; multiple serous effusions.

Macroscopic Examination.—Body edematous. All serous cavities, except the obliterated left pleural sac contain much fluid. The right ventricular wall is 1 cm. thick. The left lung and the right lower lobe are collapsed and their cut surfaces are dark bluish red in color. The middle sized and smaller bronchi contain a moderate amount of tenacious mucus and the mucosa is intensely red. The right upper and middle lobes are overdistended but on pressure and on incision exude frothy serum. The bronchi in these lobes are empty and the mucosa is pale in color.

Microscopic Examination. — The bronchial exudate contains much mucus, typical Curshmann's spirals, columnar epithelial cells and an occasional eosinophil cell. The epithelium of the bronchioles in the collapsed portion of the lungs is desquamated and its place occupied by polynuclear and mononuclear leuko-

18. Kamchorn, N., and Ellis, A. G.: Am. J. M. Sc. **161**:525, 1921.

cytes. The bronchial walls are infiltrated by mononuclear cells. The epithelium of the middle sized bronchi is partially desquamated. There is no evidence of increased fibrous tissue and of thickening of the bronchial wall and the muscularis mucosa does not appear abnormal. The bronchi in the distended portions of the lung have much less marked changes.

Comment.—The following points are the most important in this case: The history of asthmatic attacks since childhood and the microscopic evidence of an extensive respiratory infection sometime during life, as shown by the extensive round cell infiltration of the subepithelial layer of the bronchial tree. The hypertrophy of the wall of the right ventricle is probably due to the extra load thrown on pulmonic circulation during attacks. The remaining pathology in this case is probably dependent on the failing heart.

MODE OF PROCEDURE EMPLOYED IN THIS STUDY AND A DESCRIPTION OF THE NORMAL BRONCHIAL STRUCTURES

Before discussing in detail the various changes involving some of the different structures which may be implicated in the production of bronchial stenosis, i. e., the smooth muscle fiber system, the mucosa, the glandular system, the blood vessels and lymphatics and the nerves, we deem it proper to give a brief description of the finer anatomy of the normal bronchial structures.[19]

When possible, in all cases studied, the intact lung was fixed either in liquor formaldehyd or in Zenker's fixing fluid, and each lobe was sectioned as described so that the blocks of tissue gave either cross or longitudinal views of the main branching of the bronchial tree from the hilum to the pleural surface (Fig. 1). The cross sections for microscopic study were taken as nearly as possible from the plane at right angles to the central axis, as it is clearly seen that sections through oblique planes must give a distorted picture of the structures. The sections were stained with hemotoxylin and eosin and Van Gieson's and Mallory's connective tissue stains.

We have examined microscopically the lungs of several persons which should have shown, according to the history and the macroscopic examination, practically normal structures, yet we have found in all of them some pathologic changes, i. e., foci of round cell infiltration, tubercles, calcified cartilages, capillary dilatation or other changes

19. Oppel: Lehrbuch der vergleichenden mikroskopischen Anatomie **6-7.** Miller, W. S.: Reference Handbook Medical Sciences; Am. Rev. Tuberc. **2:** (May) 1918; **2:** (Jan.) 1919; Anat. Rec. **5:** (March) 1911; Bull. Robert Koch Soc. for Study of Tuberc. (Feb. 11) 1913; (April 20) 1916; Anat. Anz. **28:** 1906; Contributions to Embryology, No. 38. Larsell, O.: Nerve Terminations in the Lung of the Rabbit, J. Compar. Neurol. **33:**105, 1921. Baltisberger, W.: Ueber die glatte Muskulatur der Menschlichen Lunge, Ztschr. f. Anat. in Entwicklungsgeschichte **61:**249, 1921.

which distorted the normal picture in some particular. These findings, in accordance with similar reports from others, show that few of us escape the marks left by acute or chronic respiratory infections which are capable of altering the normal tissue.

The principal bronchi enter the hilum of the lung and divide and subdivide quickly several times into smaller tubes, which when they are reduced in size to from 0.5 mm. to 1 mm. inside diameter, are termed bronchioles. These bronchioles divide to form the atrium, air sac (infundibulum), and the air cell (alveolus).

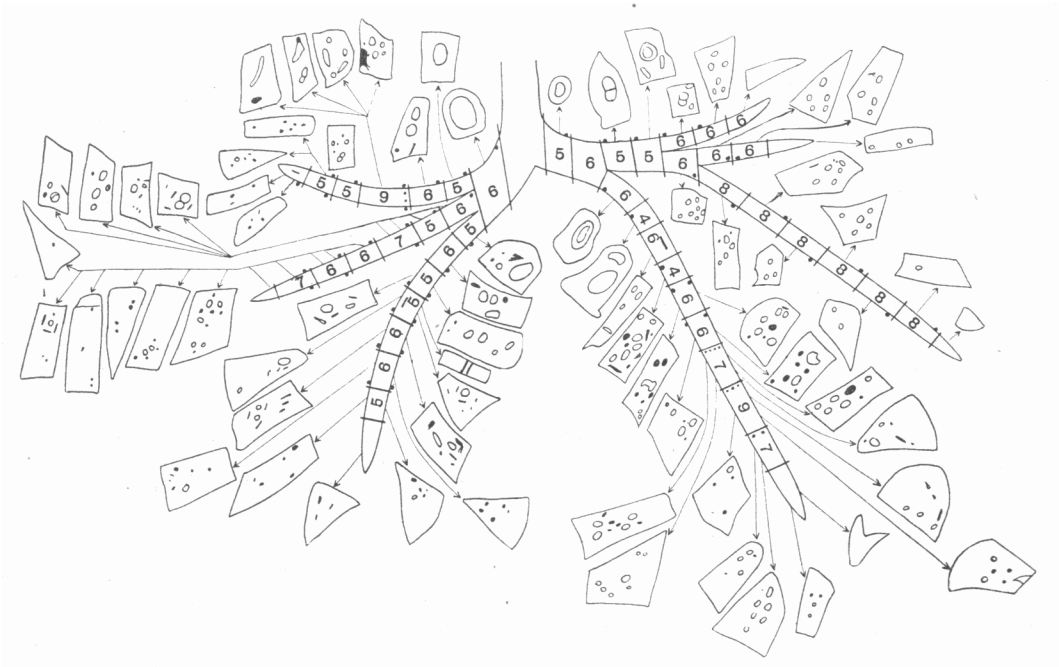

Fig. 1.—Diagram showing the method used for obtaining the blocks of lung tissue which contain the parts of the bronchial tree studied. The figures give the actual thickness in millimeters of the blocks used. The black dots along the bronchial margin indicate the side of the block from which the sections were taken for study. The measurements and sections shown in this diagram correspond to those actually obtained in Case 6.

The structure of all these divisions is, in general, the same, the arrangement, diminution or disappearance of any layer being incidental to the reduction in the size of the tube. We shall discuss briefly the following structures: The epithelium, basement membrane, subepithelial tissue, muscle, mucous glands and the outer fibrocartilaginous layer.

Epithelium.—The epithelium in the trachea and larger bronchi is made up of two or three layers, a deep layer of small, closely approxi-

mated cells, which in places has the appearance of two layers of cells, and a lining layer of ciliated columnar cells from which processes extend and attach to the basement membrane. In this lining layer there are also the goblet cells, which are most numerous in the larger bronchi and gradually disappear as the size of the tube decreases, but may be found even in the bronchioles. The epithelium also gradually changes in character from the layered ciliated type in the large bronchi to the single layer of ciliated or nonciliated cuboidal cells or flat cells in the bronchiole. This epithelium throughout is thrown into shallow longitudinal folds.

Basement Membrane.—The well-marked basement membrane on which the epithelium rests forms a thin compact layer, containing a few spindle shaped cells, and is pierced here and there by gland ducts and by processes passing into the epithelium.

Subepithelial Tissue.—The layer of loose connective tissue which is found just beneath the epithelium in all the divisions of the bronchi down to the bronchiole, has been designated by us the subepithelial connective tissue layer. It contains numerous capillaries, fine elastic fibers, small round cells and connective tissue cells and intermingles in its outer portion with the coarser elastic fiber layer. This latter layer is prominent in all the divisions of the bronchi down to and including the bronchioles, forming distinct longitudinal bundles of fibers which show some irregularities in the direction where gland ducts, vessels, etc., penetrate it. In these places the fibers may appear to form distinct circular bundles.

Muscle.—The description of the nonstriated muscular system of the bronchial tree and the lung parenchyma in histologies, almost without exception, is very meagre and misleading, and few observers, who have made no special study of this system, appreciate its complicated structure, extent and importance. In the trachea and in the main bronchi with similar structure, the muscle tissue is practically limited to the posterior membranous part where it forms bundles that extend between the ends of the incomplete ring cartilages and the interval between them, but, when these cartilages are replaced by irregular plates in the further divisions of the bronchi, the muscle forms a more or less continuous layer, the so-called "ring muscle" layer. The fact is, that, in man at least, this layer is not a true ring muscle, except probably in the finer bronchi, but is made up of short bundles which join each other in such a manner that a netlike sheath encircling the tube is formed, the general direction of the fibers being circular. As the tube diminishes in size, the muscular layer becomes thinner and thinner, and in the respiratory bronchiole and in the lung parenchyma it is represented by only a few delicate fibers. In certain lower animals, e. g., the turtle,

the distribution of smooth muscle fibers in the lung parenchyma is very striking.

The layer which connects the muscularis to the fibrocartilaginous layer consists of areolar tissue and contains mucous glands and mucoserous glands, blood vessels, nerves, and adipose tissue. This layer is best developed in the larger bronchi and, as the size of the tube diminishes, becomes progressively thinner, the glands being rarely found in tubes less than 1 mm. inside diameter.

Glands.—The gland system, like the muscle system, has not received the attention of the histologist that it deserves. The glands are of the tubulo-alveolar variety and are distributed chiefly between the cartilages and the muscle layer about the whole circumference of the bronchus, but in middle sized and smaller bronchi they are best developed in the tissue between the edges of the cartilage plaques and may even appear outside the cartilages. They are chiefly mucous glands but contain also a few crescents of Gianuzzi. The acini are lined by columnar epithelium and the ducts which often form ampullae-like widenings on entering the mucosa are lined by cuboidal ciliated epithelial cells. In certain animals, especially in rodents, gland tissue is absent in all the bronchial divisions within the lung. In others where glands are present the proportion of mucous to serous gland tissue varies greatly, thus in the sheep and the dog the serous glands are in preponderance while in cattle the amounts of serous and of mucous gland tissue are about equal.

Fibrocartilage Layer.—The outer layer of the bronchial tree is composed chiefly of connective tissue which in all except the finer divisions of the bronchi contains cartilages. These cartilages in the trachea and the primary bronchi form incomplete rings extending over the ventral and lateral walls, but in further divisions of the tube are broken up into irregularly shaped plates of various sizes and are disposed over the whole circumference of the tube. These plates gradually diminish in size and number and are rarely present in tubes with an inside diameter of less than 1 mm. The connective tissue, however, continues as a distinct layer into the much smaller divisions. It is interesting to note here that cartilages are absent in that portion of the bronchial tree within the lungs of some small animals, chiefly rodents.

Lymphoid Tissue.—This is found in all the main branchings of the bronchial tree, the amount varying according to the size of the tube. There are a few scattered cells of the lymphoid type in the subepithelial layer but true follicles and nodes are found only outside the muscular layer. Here these structures may lie between the muscle and cartilages, in the tissue between the cartilages, or as is usual for distinct nodes, outside the cartilages. The distinct nodes are usually located at the

point of bifurcation of the tube. Small lymphoid follicles are also found scattered in the wall of small bronchioles and even among the alveoli or beneath the pleura. Distinct glands are found about the trachea and larger division of the bronchi.

Blood Supply.—The blood supply of the bronchial tree is furnished by a special set of vessels, the bronchial arteries, branches of which are found in all the divisions of the bronchus down to the bronchiole. The main branches of this artery are situated in the outer fibrous coat of the bronchus, numerous radicles being given off to form plexuses which supply blood to the glands, muscles and other structures, the capillary network being especially rich in the subepithelial layer.

Nerves.—Nerves and nerve ganglia are found in the walls of all divisions of the bronchial tree down to the bronchiole, usually lying in close apposition to the branches of the bronchial artery.

REPORT OF CASES

CASE 1.—Mrs. B., aged 55, married, American, was first seen by one of us (K.) in April, 1915, suffering from frequent severe attacks of spasmodic dyspnea.

Family History.—Negative.

Previous History.—At 44 she had had a severe tonsillitis and one attack of severe abdominal pain (appendicitis?), but after that time she was well until April, 1913, when she suffered from an acute coryza and severe cough lasting three weeks. During the following summer (1913) she was very nervous and irritable, and in August she went to the White Mountains. Then she first noticed wheezing sounds in the chest at night. During the latter part of August and in September she had frequent head colds accompanied by severe coughing attacks, and in the latter part of September, following a severe prolonged coughing spell, the first distinct attack of spasmodic dyspnea occurred. These attacks of coughing and dyspnea increased rapidly in number and severity, and by October 10 they were coming four and five times daily, but were usually almost instantly relieved by small subcutaneous doses of epinephrin (1:1000). While visiting in the South in November and December she had complete relief from dyspneic attacks but the severe cough persisted, although usually relieved quickly by inhaling the smoke of stramonium leaves. While returning North in January, 1914, she contracted a severe cold and the dyspneic attacks returned with increased severity, forcing her to stop off at Atlanta, Ga., where she remained under a physician's care for about three months, apparently suffering from a bronchopneumonia. In April, in Chicago, the paroxysmal attacks of dyspnea again returned with increased frequency and severity and were incompletely relieved by subcutaneous injections of epinephrin, but the troublesome cough was relieved by small doses of potassium iodid. The attacks of dyspnea and coughing persisted to a greater or lesser degree all summer while traveling in the West. In September, 1914, she entered a Chicago hospital for observation by a local internist. There a tooth infection was cleaned up and a vaccine, made from her sputum cultures, was administered, but these measures seemed to give only a transient relief of symptoms. Following a pneumococcus infection in February, 1915, with a rise in temperature, she had almost complete relief from both the dyspneic attacks and the harassing cough until the latter part of March, when both returned in a severe form. At this time she entered the Presbyterian Hospital in Chicago.

Laboratory Examination.—Temperature, 98.6 F.; pulse, 96; respiration, 24. Blood pressure, 115/75.

Blood: Hemoglobin, 95 per cent.; leukocytes, 14,000; red cells, 5,700,000. Differential count: Small lymphocytes, 10 per cent.; large lymphocytes, 10 per cent.; large mononuclears, 5 per cent.; transitionals, 2 per cent.; neutrophils, 62 per cent.; eosinophils, 11 per cent.

Urine: Acid; specific gravity, 1.020; no albumin, sugar, acetone, or casts; few leukocytes; no blood; indican, a trace.

Sputum: Very abundantly produced, thick, mucoid, stringy with white particles; no Charcot-Leyden crystals, Curshmann's spirals or blood, a few eosinophils, but no polymorphonuclear neutrophil leukocytes.

Feces: Negative for blood and pus.

Physical Examination.—Skin, pale and dry, with cyanotic hue of the lips, nose, fingers and nails. No palpable glands. Throat, nose and sinuses negative (Dr. Shambaugh). Teeth negative (Dr. Moorehead). Chest: Increased in anteroposterior diameter. Intercostal spaces widened. Posture (sitting in bed) stooped. Lower lung borders anteriorly in midclavicular line at the seventh intercostal space; posteriorly, at the level of the twelfth spinous process. Excursion on deepest inspiration scarcely one-half inch. Vocal fremitus not increased. Percussion note hyperresonant over both lungs. Both inspiratory and expiratory phases markedly prolonged. Sonorous and sibilant râles over whole chest. Heart: Apex beat not visible or palpable. Epigastric pulsation present. Heart borders not determinable. All heart sounds soft and feeble but clear. No murmurs. Liver: Easily palpable and extends about 2 cm. below costal arch. Spleen: Palpable. No masses in the abdomen. Sputum: Bacteriologic examination done at several periods of her stay in the hospital showed aerobic: *Streptococcus viridans; Micrococcus catarrhalis* and *pneumococcus.* Anaerobic: *Bacillus annuliformis; Streptococcus parvus; Bacillus fusiformis.*

Treatment and Course.—Epinephrin, atropin, potassium iodid and strong coffee gave symptomatic relief of short duration. The administration of autogenous vaccines was followed by short periods of improvement. This, however, was not permanent and the recurrence of several paroxysms of dyspnea depressed the patient to such a degree of despondency that she sought and found a voluntary death through drowning. The body was in the water about three hours and was examined five hours after death.

Macroscopic Examination.—Not obtainable. (Coroner's case.)

Microscopic Examination.—The pleurae of both lungs vary in thickness and contain but a few foci of round cells. Most of the alveoli are of normal size, contain only an occasional endothelial cell, and have thin walls which also contain a few small foci of round cells. In the outer borders of both lungs the alveoli are dilated and some have ruptured walls. One small group of alveoli in the right lower lobe contains a fine granular precipitate in which there are numerous polymorphonuclear neutrophilic leukocytes. The ductuli respiratorii are patent, slightly dilated and their walls without appreciable change. The bronchioles, even to the smallest, are somewhat dilated and most of them are occluded by homogenous mucous masses which contain a few epithelial cells, round cells and many polymorphonuclear cells, many of which are eosinophilic. The walls are thin because of the dilatation, contain only a few round cells and have thin strands of smooth muscle fibers and of elastic tissue. The epithelium is only partially retained and in all except the smallest bronchioles it rests on a very prominent hyalinized basement membrane. Many bronchioli are dilated to such a degree that they can be differentiated from small bronchi only by their structure.

The small and middle sized bronchi are dilated so that longitudinal folds are obliterated, and almost all are occluded by mucous masses which vary somewhat in structure and constituents. In some, the mass is homogenous

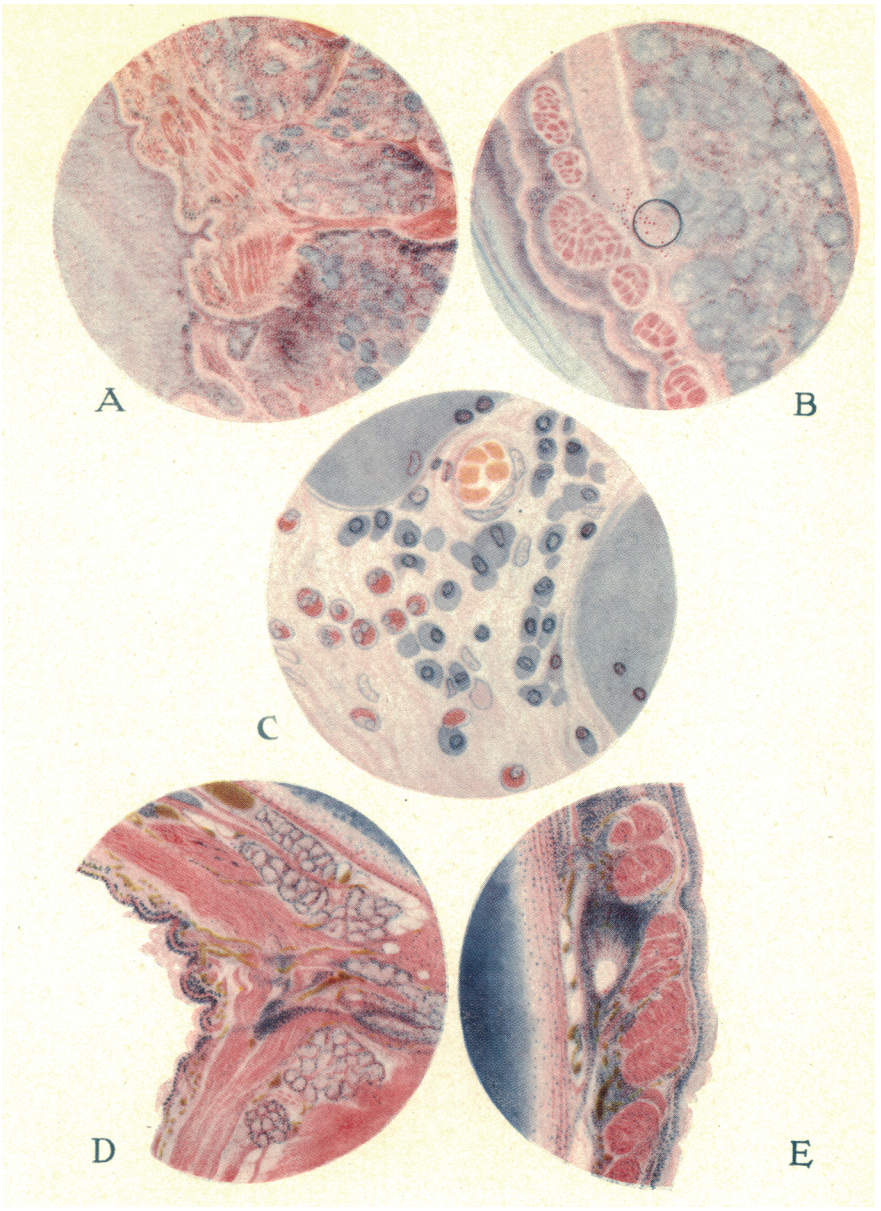

PLATE 1

Plate 1.—Bacterial type of asthma. Case 1. A. Cross section of a large bronchus. Note the muscle bundles, basement membrane, marked hypertrophy of mucous glands, and cellular infiltration.

B. Longitudinal section of a large bronchus. Note the muscle bundles, cellular infiltration, mucous glands, and eosinophil cells. High magnification of the area marked by the circle is shown in C.

C. High magnification of the area marked by the circle in B.

D. Bacterial type of asthma. Case 2. Cross section of a large bronchus. Note the muscle bundles, mucous glands, and distended capillaries.

E. Longitudinal section of a large bronchus. Note the muscle bundles, distended capillaries and cellular infiltration.

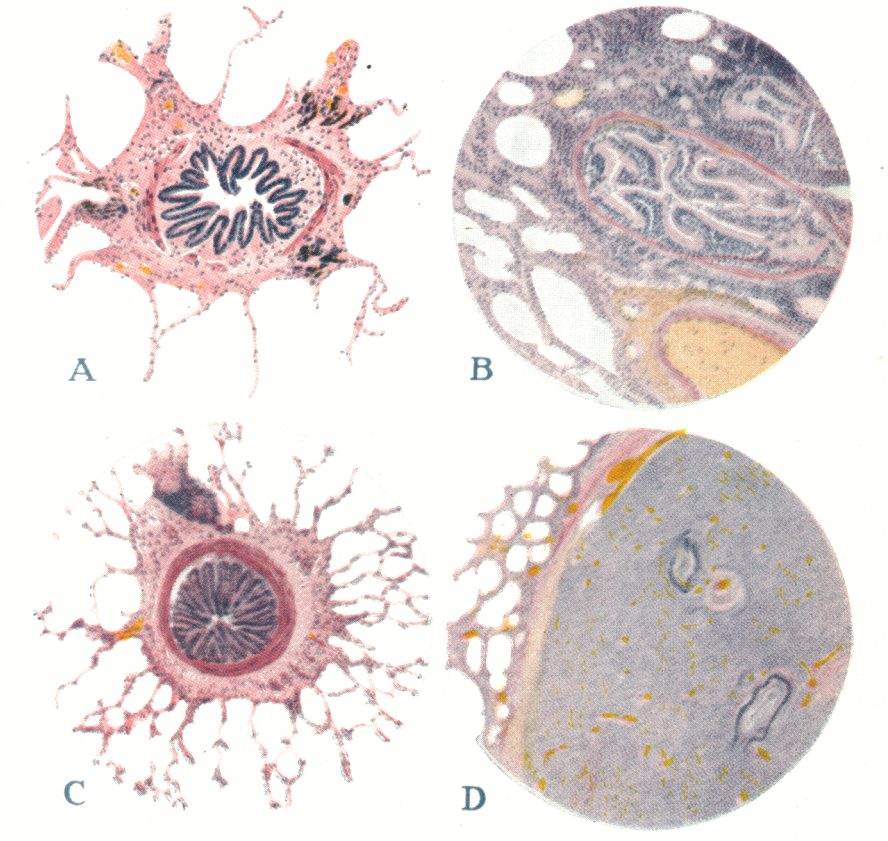

PLATE 2

Plate 2.—Bacterial type of asthma. Case 2. A. Bronchiole almost occluded by a folding of the epithelium.

B. Case 3. Bronchiole occluded by folds of epithelium.

C. Bronchiole of a guinea-pig. Fatal horse serum anaphylaxis.

D. Food asthma. Case 6. Area of absorption atelectasis with an adjoining area of normal lung tissue.

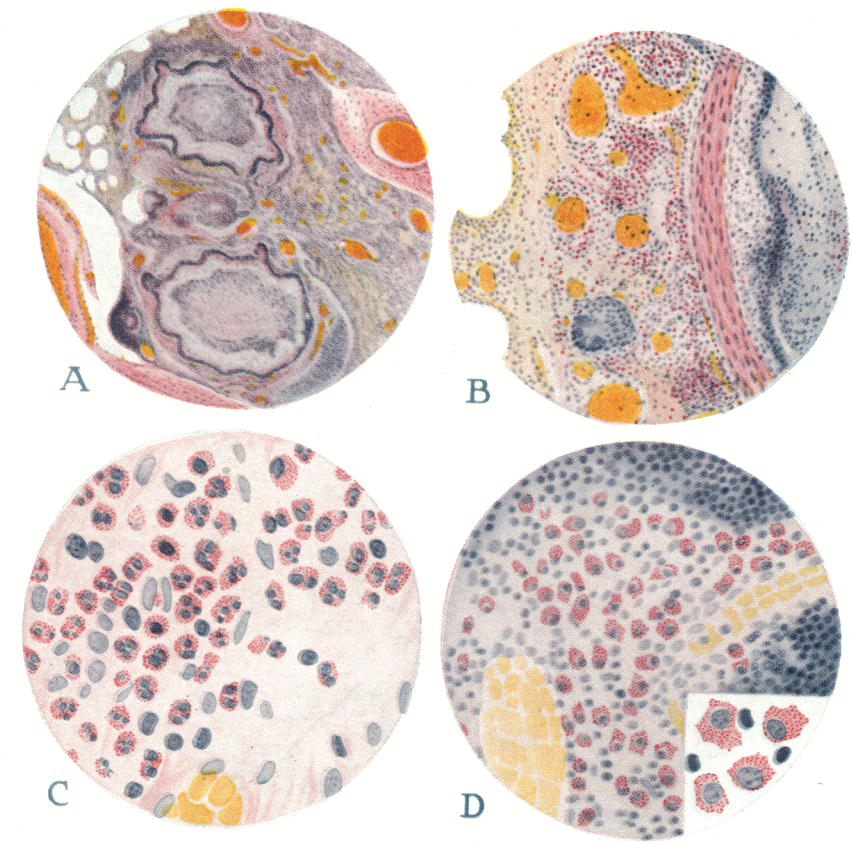

PLATE 3

Plate 3.—Food asthma. Case 6. A. Occlusion of bronchi by mucous exudate.

B. Cross section of a large bronchus. Note the muscle bundles, distended capillaries and extensive infiltration by eosinophil cells.

C. High magnification of an area of eosinophilic infiltration in the bronchial wall.

D. Mononuclear eosinophil cells in the thymus. Insert: a high magnification of these cells.

and contains diffusely scattered and polymorphonuclear cells which are mostly eosinophilic, some round cells and near the outer zone desquamated epithelial cells. In others, the mass appears much twisted, having whorllike thickened lines and rows of cells intermingled with layers of homogeneous cell free mucus. In many bronchi the mucous masses appear to be flowing stream-like into the bronchi from the gland ducts. No fibrin and only a few erythrocytes are found. The epithelium is for the most part desquamated, only the lower layer of small cells remaining attached to the thickened prominent basement membrane. The basement membrane is conspicuous and extends as a prominent band up into the gland ducts, at times even up to the gland itself. The subepithelial layer contains many cells chiefly small round cells, a few eosinophil cells, mostly polymorphonuclear, and a few mast cells. The elastic tissue is prominent in some bronchi and in all, the capillaries are numerous but small. The muscle tissue varies greatly in thickness, being prominent in all bronchi but in some forming large bundles which are best seen in the longitudinal sections (Fig. 2). There is no evidence of hyaline degeneration or fatty infiltration of the muscle. The mucous glands are very large and many are densely infiltrated by cells (Fig. 3). In most the acini are large, filled by mucus and are often separated widely by infiltrating cells which obscure large portions of the gland structure. These cells are mostly small round cells, but in some glands the predominating cells are polymorphonuclear eosinophil cells. Some glands are almost completely destroyed by this infiltration. The gland ducts leading from these glands are large and in many places distinct ampullae are formed which contain mucus or mucus inclosing many cells. Many of the ducts are surrounded by a zone of round cells (Plate 1, A, B, C). Some of the cartilaginous plaques in both lungs show small areas of calcification. The walls of some of the bronchial arteries are thickened. No nerves or nerve ganglia are invaded by round cells.

The structure of the larger bronchi is similar to that of the smaller bronchi except that the mucus does not completely occlude any of them. No Charcot-Leyden's crystals or Curshmann's spirals are found, and although the epithelium is missing throughout, no evidence of true ulceration can be demonstrated.

The bronchial lymph glands of both lungs are large and anthracotic; their sinuses contain a few polymorphonuclear eosinophils and they contain no evidence of tuberculosis.

Summary.—The most significant pulmonary pathologic findings in this case are: (1) Complete occlusion of the majority of the middle sized and small bronchi and of the bronchioles by a mucous cellular exudate. (2) Numerous large mucus-filled gland-duct ampullae (Schleimhautausstülpungen of Mönckeberg). (3) Large active mucous glands. (4) Marked cellular infiltration of the subepithelial layer and of the mucous glands. (5) Prominence of the basement membrane and of the muscular layer. (6) Tissue eosinophilia.

Comment.—The history of previous attacks of bronchitis and of pneumonia, of asthmatic attacks beginning after the fiftieth year, and the microscopic evidence of infection in the bronchial walls point to bacteria as the causal agent in this case of asthma.

CASE 2.—Mr. G., aged 55, married, American, entered the Presbyterian Hospital, July, 1917, under the care of one of us (K.).

History.—Except for having had the usual diseases of childhood, he was exceptionally well until his forty-ninth summer (1911), when a severe bronchitis developed and persisted for six months, being accompanied near the end by wheezing sounds and one definite attack of spasmodic dyspnea. The following spring he had a second attack of bronchitis accompanied by wheezing sounds and one attack of spasmodic dyspnea. Following this the attacks

came more frequently each year so that, at the time of entrance into the hospital, six years after the first attack, they occurred as frequently as from three to five times daily with only short periods of freedom. During this time (six years) the weight gradually fell from 155 to 90 pounds. Tobacco and alcohol never used. Gonorrhea and syphilis denied.

During the three years prior to July, 1917, the following surgical and medical procedures were instituted without giving relief. 1914: Nasal polypi removed. 1915: Twenty injections of a stock vaccine. Potassium iodid up to 50 minims, three times daily. Teeth were roentgenographed and two were removed. Polypi and turbinates removed. 1916: Tonsils removed. Eleven injections of arsphenamin (negative blood Wassermann!). 1917: Use of mixed

Fig. 2. Case 1. Bacterial asthma. Large bronchus. Longitudinal section. Epithelium intact. Basement membrane thick and hyalinized. Subepithelial layer infiltrated by round cells. Muscle bundles very large. Glands have distended acini and contain foci of round cells. l = lumen; e = epithelium; $b\,m$ = basement membrane; $e\,t$ = elastic tissue; $r\,c$ = round cells; m = muscle; $g\,d$ = gland duct; g = gland. Magnification, 65 diameters.

vaccine. Removal of colon was advised by family physician as roentgen-ray examination showed a viceroptosis, especially marked of the transverse colon. The patient had noted that frequent catharsis and use of enemas seemed to alleviate the attacks.

Family History.—Mother, two sisters, one brother, and one child have had asthma.

Physical Examination.—At the time of entrance into the hospital in the summer of 1917, the following observations were made: Small, much emaciated

man. Head and neck, negative. Chest: thin walled, expansion fair, numerous squeaky and whistling râles on both sides. Heart: Left border 10 cm. from midsternal line. Rate, tone and rhythm appear normal. Abdomen: Wall muscular. Small umbilical hernia. Liver: Palpable 2 cm. below costal margin in midclavicular line. Spleen: Not palpable. Inguinal glands: Easily palpable. Extremities: Negative.

Blood: Hemoglobin, 75 per cent.; leukocytes, 7,900; red cells, 3,670,000. Differential count: Small lymphocytes, 23 per cent.; large lymphocytes, 8 per cent.; polymorphonuclear neutrophils, 59 per cent.; polymorphonuclear eosinophils, 10 per cent.

Urine: Specific gravity, 1.032; no albumin, casts, sugar or pus.

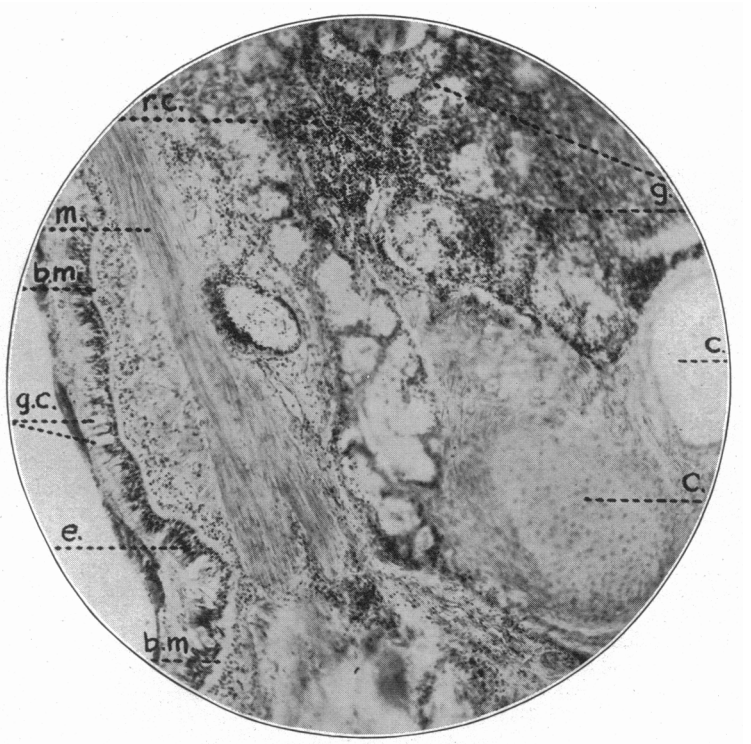

Fig. 3. Case 1. Bacterial asthma. Large bronchus. Cross section. Epithelium intact and containing goblet cells. Basement membrane thick and hyalinized. Subepithelial layer infiltrated by round cells. Muscle bundles large. Mucous glands large and infiltrated by round cells. e = epithelium; $g\,c$ = goblet cells; $b\,m$ = basement membrane; m = muscle; $r\,c$ = round cells; g = gland; c = cartilage. Magnification, 70 diameters.

Gastric content: Ewald test meal: Free acid, 8 per cent.; combined acid, 37 per cent.; total acidity, 45 per cent.

Electrocardiogram: Slight hyperbalance of right heart.

Blood pressure: 122/75.

Medication.—Potassium iodid, epinephrin and autogenous vaccine. At the time of entrance to the hospital the patient suffered from two to four attacks of dyspnea daily, coughed a great deal, raised a small amount of sticky mucus and complained of pain in chest and of abdominal distention and distress.

Ten minims of epinephrin usually gave prompt relief. However, after enjoying a period of quiescence for ten days, the patient died in an attack which had lasted three days. The necropsy was performed the next day.

NECROPSY REPORT: *Anatomic Diagnosis.*—Chronic fibrous myocarditis; marked emphysema of the lungs; barrel-shaped chest; hyperemia of the pericardial sac; passive hyperemia of the liver and spleen; slight chronic interstitial nephritis and hyperemia of the kidneys; fibrous episplenitis; calvities and canities.

Macroscopic Examination.[20]—The body is that of a white man about 55 years of age, weighing approximately 100 pounds. Rigor mortis is marked and posterior lividity is present. Muscular development is fair and the bones are of medium size. The chest wall is bulging, and the abdomen flat. The subcutaneous fat in the midline of the trunk in front has a maximum thickness of 5 mm. The inguinal rings are closed. The liver extends two finger breadths below the costal margin. The diaphragm on the right side extends upward to the middle of the fourth rib, on the left to the fifth interspace. Thorax: The pericardial sac is blue, caused by the engorgement of the vessels which supply it. There is only the normal amount of fluid present. The apex of the heart is made up of the right ventricle. The pulmonary artery and the right heart contain only fluid blood. The wall of the left ventricle at its thickest portion measures 2 cm.; the right, 7 mm. It weighs 320 gm. The heart muscle is pale red and slightly fibrous. The lungs are huge and are free from adhesions. They are red and black in color and bulge out when the sternum is removed in the usual manner. The cut sections are spongy and some blood flows from their surfaces. Liver: The liver is reddish brown and weighs 1,450 gm. Its capsule is smooth, except in places where it has been adherent to the diaphragm. There is a yellow scar on the right lobe 8 mm. in its largest diameter, which when cut does not extend into the liver substance. The cut surfaces are red and exude much blood. Kidneys: The kidneys together weigh 230 gm. Their capsules are smooth, but strip with difficulty, leaving a rough irregular surface. The cut surfaces are red and the cortical markings are fairly distinct. Spleen: The spleen is rough and slaty blue, except the rough surface made up of yellowish nodules averaging 2 mm. in diameter. The cut surfaces are very red and pulpy, much blood flowing from these surfaces. It weighs 150 gm.

Microscopic Examination.—The pleura varies in thickness from 0.06 to 0.09 mm., and shows no abnormalities except a few widely distended blood vessels. The alveoli are not abnormally distended, except in patches in the periphery of the upper lobes of both lungs and they are empty, except in the left lower lobe where a few small areas are obliterated by accumulations of a fine granular precipitate which contains only a few erythrocytes. The alveolar walls throughout both lungs are thickened by distention of capillaries and an occasional accumulation of small mononuclear cells. The epithelium of the ductuli respiratorii is intact and shows no abnormalities. The walls of these passages contain short muscle bundles from 0.010 to 0.015 mm. in thickness and only a few small mononuclear cells.

The bronchioles in all parts of the lungs are similar in structure. In a few of the smaller bronchioles the lumina are narrowed by a deep folding of the epithelium (Plate 2 A). In a few others the lumina are occluded by a fine granular precipitate containing only a few large pigmented mononuclear cells, while in the majority the lumina are patent and contain only a few of the pigmented cells. The epithelium is well perserved, is thrown into longitudinal folds varying in height from 0.010 to 0.085 mm. and having a thickness in the smaller bronchioles of from 0.0075 to 0.020 mm. and in the larger bronchioles from 0.050 to 0.095 mm. No goblet cells are visible. The basement membrane is not conspicuous. The subepithelial layer is thin and contains only a very few

20. Only those parts of the complete necropsy reports which seemed to have a possible relationship to the problem of our study are given here.

mononuclear cells. The muscle layer, varying in thickness from thin strands to definite bundles 0.060 mm. thick, does not form a continuous layer and varies greatly in size in different parts of the circumference of the bronchiole. The elastic tissue is scanty and the fibrous tissue is found only in moderate amounts.

The structure of the bronchi in all parts of the lungs is essentially the same. The lumina of all contain only a small amount of granular precipitate in which there are fragments of desquamated epithelium. The epithelium is thrown into longitudinal folds from 0.06 to 0.24 mm. high and contains only a few goblet cells. There is no evidence of new or old ulcer formation in the epithelium. The basement membrane is visible only in parts of the circumference. The subepithelial layer is thin and contains distended capillaries, scattered small mononuclear cells, a few polymorphonuclear eosinophil cells, plasma cells and small bundles of elastic tissue. The muscle layer, which in many bronchi lies unusually near the epithelium, is very well developed, the bundles in some of the larger bronchi being 0.23 mm. in thickness (Fig. 4). These bundles, as seen best in the longitudinal sections, are separated from each other by only a thin connective tissue layer containing distended capillaries (Plate 1 D, and E). The mucous glands are of moderate size and their acini are small. Most of the glands contain dense foci of small mononuclear cells, and in many of them only small fragments of gland tissue remain. The outer portions of many of the glands contain many fat cells. Many of the gland ducts in the subepithelial layer are surrounded by a wide zone of closely placed small mononuclear cells, and in many ducts the lumina form conspicuous ampullae-like enlargements between the cartilage and muscle layer. These ampullae-like structures contain a small amount of mucus in which there is much desquamated epithelium. The cartilages are unchanged. The distended capillaries in all layers of the bronchi are very conspicuous and show well their distribution in these structures. The walls of many of the bronchial arteries in the larger bronchi are very thick. The ganglia, nerves and nerve sheaths are not infiltrated or surrounded by cells.

Comment.—The most significant pathologic changes in this case are: (1) The numerous large gland duct ampullae. (2) The extensive cellular infiltration in the bronchial mucous glands. (3) Small size of bronchial mucous glands and abundant periglandular collections of fat cells. (4) Prominence of the bronchial muscular system. (5) Thickening of the walls of the bronchial arteries. The history of a severe bronchitis preceding and accompanying the attacks of dyspnea, of asthmatic attacks beginning about the fiftieth year and the microscopic evidence of infection of the bronchial mucous glands point to bacteria as the causal agents in this case of asthma.

CASE 3.—Miss L., aged 17, entered the Cook County Hospital suffering from an acute infection.

History.—Since early childhood she had had frequent severe attacks of spasmodic dyspnea which were always worse in summer and were accompanied by severe coughing and raising of a thick sticky sputum. The attacks, while less frequent in the past year, had become more severe in character.

Family History.—Negative.

Examination.—Pulse, 116; respiration, 28; temperature 99.4 F.; blood pressure, 110/72. Blood: Hemoglobin, 75 per cent.; leukocytes, 17,200; red blood cells, 4,420,000. Differential count: small lymphocytes, 8 per cent.; large lymphocytes, 2 per cent.; neutrophils, 84 per cent.; eosinophils, 5 per cent.;

transitionals, 1 per cent. Marked pyorrhea alveolaris; bilateral cervical adenopathy.

Urine: Positive for albumen and casts. Thorax: increased anteroposterior diameter; normal lung borders; diminished excursion on both sides; percussion note hyperresonant over whole chest; numerous wheezing and squeaking râles on both sides; one small area of crackling râles over the medium dependent portion of the left lower lobe. Heart: Heart tones indistinctly heard; no murmurs. Abdomen: Negative. Adenopathy of axillary and inguinal glands. Reflexes, normal.

Diagnosis.—Bronchial asthma; localized patch of bronchitis; emphysema; nephritis and pyorrhea alveolaris.

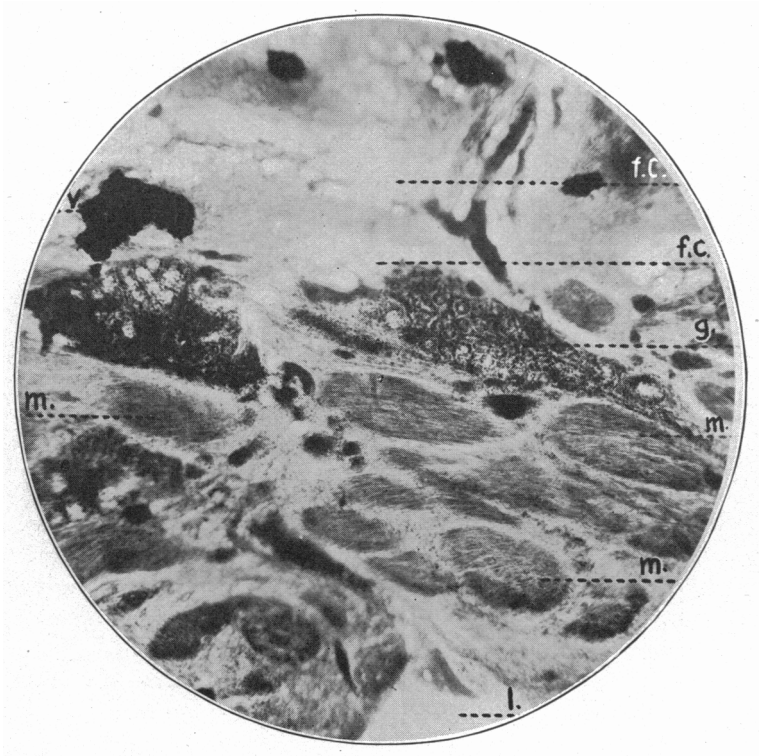

Fig. 4.—Case 2. Bacterial asthma. Large bronchus. Cross section. Epithelium desquamated. Basement membrane not visible. Subepithelial layer contains few cells. Muscle bundles large. Glands small and contain foci of round cells. All vessels distended. l = lumen; m = muscle; g = gland; $f\,c$ = fat cells; v = vein. Magnification, 45 diameters.

Course.—There was a steady improvement in condition for sixteen days, then a sore throat developed, with abdominal pain, vomiting and other symptoms of acute intoxication. The patient died three days later.

Necropsy Report (Dr. Stangl): *Anatomic Diagnosis.*—Acute hemolytic streptococcus pericarditis and peritonitis; cloudy swelling of myocardium, liver and kidneys; acute emaciation; fibrous obliteration of the right pleural cavity; hyperplasia of the spleen. Bacterial cultures of pericardial fluid and heart blood showed hemolytic streptococci.

Macroscopic Examination.—The body is that of a small, poorly nourished white girl about 12 years of age. Height, 146 cm. The lips and fingers are cynotic. The thyroid is slightly enlarged. The skeletal muscles are well developed. The axillary lymph glands are somewhat enlarged. Abdomen: The abdominal cavity contains a large quantity of a brownish fluid in which are flocculi of fibrin. The omentum hangs low and is covered with fibrin. The peritoneal surface of the intestines is reddened and coated with fibrin. The lower border of the liver is at the costal margin. There are fibrous adhesions between the fundus of the gallbladder and the stomach and duodenum. The diaphragm reaches to the fifth rib on the right side and to the fourth rib on the left. Pleural cavity: The right pleural cavity is entirely obliterated by fibrous adhesions. The left cavity is free of adhesions. There

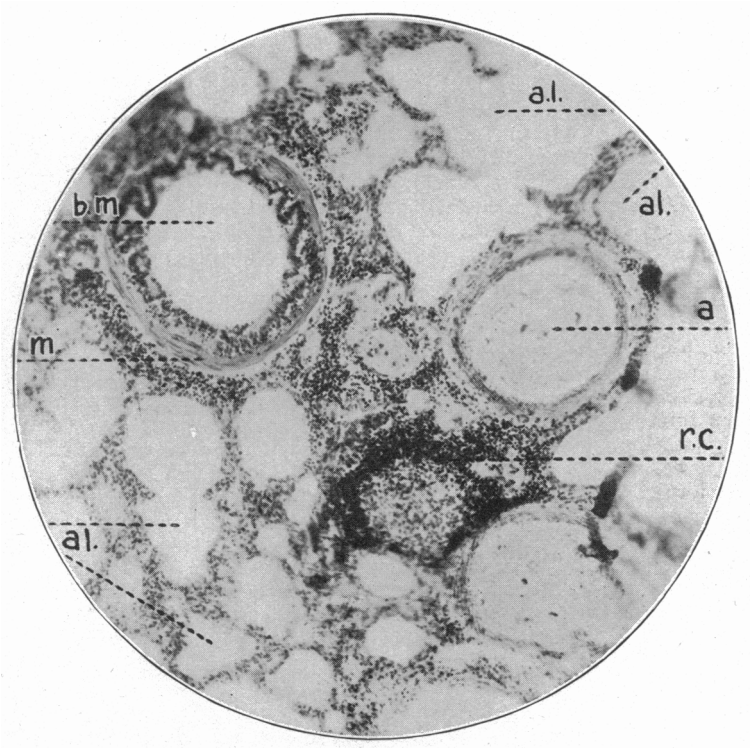

Fig. 5.—Case 3. Food (?) asthma. Bronchiole. Cross section. Muscle layer prominent. Area of round cells. *b r* = bronchiole; *m* = muscle; *a* = artery; *al* = alveoli; *r c* = round cells. Magnification, 85 diameters.

is a moderate amount of granulation tissue at the site of the thymus. Pericardial cavity: The pericardial cavity contains a small amount of turbid fluid in which there is fibrin. There are many petechial hemorrhages beneath the epicardium. Heart: The venae cavae are engorged with dark clotted blood. The tricuspid and aortic valves are normal. There is a healed vegetative growth on one cusp of the mitral valve. The myocardium is pale red and grossly without change. The heart weighs 400 gm. Lungs: The surface of the right lung is covered by extensive fibrous adhesions, but it crepitates everywhere and is free from coal dust pigmentation. It weighs 320 gm. The surface of the left lung is smooth and it crepitates everywhere. The trachea and

bronchi exude a thick mucopus and the mucosa is hyperemic. The tracheobronchial lymph glands are brown in color. Liver: The liver is mottled reddish brown and yellow and its capsule is smooth and dull. Spleen: Large and firm and weighs 320 gm. The solitary lymph follicles of the large intestine are prominent (2 mm.), and some are surrounded by small hemorrhages. There is one small cyst in each ovary. Kidneys: Weight, 400 gm.; mottled in color; fetal lobulations. The capsule is smooth and strips readily, leaving a smooth surface. The cortical striations are plainly visible. The lining of the pelvis is smooth and unchanged. Head: The brain and meninges show no gross changes.

Microscopic Examination.—Left lung examined. The pleura is slightly thickened throughout and contains numerous small foci of small round cells. Most of the alveoli are small, containing only a few pigmented endothelial cells, and their walls are considerably thickened by dilated capillaries, and numerous small accumulations of small round cells. The remaining alveoli are moderately dilated, contain no exudate and have thinner walls.

The bronchioles in the whole lung vary markedly in size and structure, some being dilated and with thin walls, others being markedly contracted. In some the folds of epithelium have sloughed off and completely occluded the lumen (Plate 2 B). The lumina of the former vary in size from 0.25 to 0.5 mm. and the latter from 0.07 to 0.15 mm. The other measurements are given in Table 1. The single layered low cuboidal epithelium is intact and the subepithelial layer contains a few small round cells, a small amount of elastic tissue and an occasional polynuclear eosinophil cell. The muscular layer in some bronchioles form a distinct complete circular ring but in most it is interrupted (Fig. 5).

The lumina of the smaller and medium sized bronchi contain only a small amount of exudate which adheres to the epithelium and consists chiefly of mucus containing epithelial cells either isolated or in clumps. Among these cells there are a few polymorphonuclear neutrophils and eosinophils and a few round cells. The epithelium is intact except in the deeper cryptlike pockets between folds where only the lower layer of cells remains. The outer layer of the epithelium contains numerous goblet cells and in some bronchi there are a few small round cells and polynuclear eosinophil cells between the epithelial cells. There is no appreciable lengthening of the epithelial cells in any portions of the bronchi. The basement membrane is distinct and appears hyalin even in the bronchioles.

The subepithelial layer varies considerably in thickness even in the same bronchus, as is well shown by the longitudinal sections. This layer, especially that portion lying nearest the basement membrane, is infiltrated by numerous small round cells, plasma cells and a few polymorphonuclear eosinophil cells. The longitudinal and circular bundles of elastic tissue are not increased in size and the capillaries are not distended.

The muscular layer in all bronchi is well developed and shows especially in the longitudinal sections the distinct bundle arrangement (Fig. 6). The connective tissue separating and extending into these bundles contains a few polymorphonuclear eosinophil cells and a few small round cells.

The mucous glands which are found in all bronchi having an outside diameter greater than 2 mm. are large and most are infiltrated extensively by small round cells. The acini of the glands are not in active secretion and in many glands they are distorted and widely separated by the infiltrating round cells, while in some glands only a few small acini remain. The walls of the mucous-gland ducts contain many round cells and the tissue around many ducts is extensively infiltrated. Many of these gland ducts are widely dilated and form distinct ampullae containing mucus, desquamated epithelium and round cells. No eosinophil cells are found in any of the glands.

Cartilages are found in smaller divisions of the bronchi than the glands and many contain small calcified areas. One cartilage in a small bronchus with an outside diameter of 2.8 mm. contains a small ossified portion with a true marrow center (Fig. 7).

The walls of the bronchial arteries are moderately thickened and the nerves and ganglia are surrounded by connective tissue containing only a few round cells.

The content and walls of the larger bronchi are similar to that in the smaller bronchi, except that the goblet cells are somewhat more numerous in the former. There is no essential difference in findings in the bronchi of the upper and the lower lobes. Measurements of the bronchi will be found in Table 2.

Comment.—The most significant pulmonary pathologic findings in this case are: (1) Right sided adhesive pleuritis. (2) Extensive

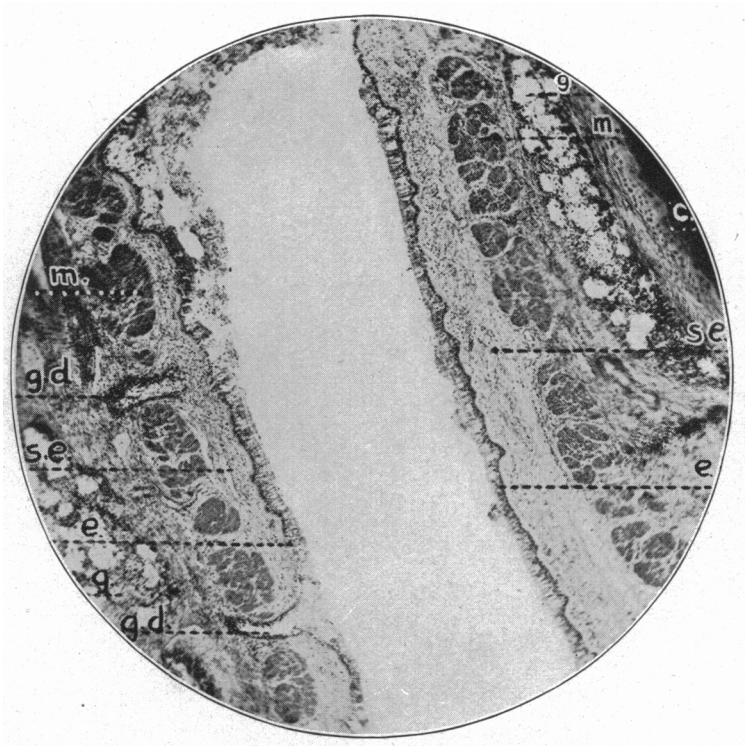

Fig. 6.—Case 3. Food (?) asthma. Small bronchus. Longitudinal section. Epithelium shows goblet cells. Basement membrane prominent. Subepithelial layer infiltrated by round cells. Muscle bundles prominent. Glands contain round cells. e = epithelium; $g\,c$ = goblet cells; $s\,e$ = subepithelial layer; m = muscle; $g\,d$ = gland duct; g = gland; c = cartilage. Magnification, 45 diameters.

cellular infiltration of the subepithelial layer, the mucous glands, and the walls of mucous-gland ducts. (3) Numerous ampullae-like gland ducts. (4) Prominence of muscle layer. (5) Calcification and ossification of cartilages. (6) Eosinophilic infiltration of bronchial wall.

The history of asthma since childhood suggests the probability of sensitization to plant or animal proteins. This point cannot be determined definitely, as no skin sensitization tests were made and a complete clinical

history was not obtainable. The evidence of an old infection, the adhesive pleuritis, and the evidence of present infection in the mucous glands and the subepithelial layer of the bronchi point to bacteria as secondary agents in this case of asthma.

CASE 4.—Mr. E. L., aged 29.

History.—The complete history is not available. Patient had had frequent head colds and asthmatic attacks since the age of 10 and was unable to do any work until his twenty-seventh year when, following medication and use of an autogenous vaccine there was a period of improvement.

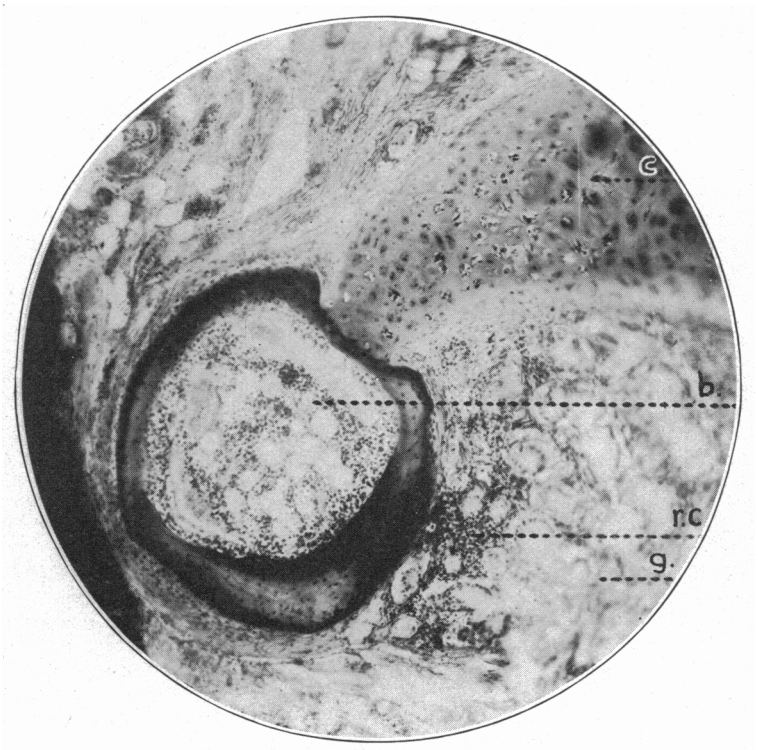

Fig. 7.—Case 3. Food (?) asthma. Bronchial cartilage with ossification. $b =$ bone with typical bone marrow; $r\,c =$ round cells; $g =$ gland; $c =$ cartilage. Magnification, 70 diameters.

Family History.—Mother had asthma after thirty-fifth year.

Course.—While in the army he discovered that proximity to horses or mules precipitated attacks of asthma and he therefore wished to be desensitized. This was attempted by his physician and death occurred within ten minutes after an intravenous injection of 1 minim of horse serum. Here we need give only a few points of particular interest, as the complete report of the necropsy findings is given by Boughton.[21] He says in part:

21. Boughton, T. H.: Anaphylactic Death in Asthmatics, J. A. M. A. **73:** 1912 (Dec. 29) 1919.

Both lungs were enormously distended and emphysematous. The left lung showed a small area of hemorrhage on the lateral portion of the lower lobe, about 4 cm. in diameter, with a gelatinous organizing exudate at this point. On section the lungs are dry. The right pleural cavity was largely obliterated by firm fibrous adhesions. No fluid was present in either cavity. The heart was firm and of normal size and appearance except for a few subpericardial petechial hemorrhages on the posterior surface.

Microscopic Examination.—Lungs: There was a moderate passive hyperemia, but no edema. There were a few small interstitial hemorrhages. A little mucus and a few desquamated epithelial cells were seen in some of the bronchioles. The peribronchiolar muscle was well developed. A few arteries showed greatly thickened walls, and many showed a moderate thickening of the walls. Eosinophils were very numerous in the spleen.

Microscopic Examination.—Drs. Boughton and Raulston, the pathologists, kindly furnished us with the blocks of tissue from this case so that we could make a more detailed study of the lungs. Our findings are as follows: The structure of the pleura varies from a thin layer 0.09 mm. thick with no appreciable changes to a layer 1.35 mm. thick. This increased thickness is due chiefly to fibrous tissue, the outer layer of which is less compact and contains numerous small extravasations of erythrocytes. The pleura, especially in the thickened portion, contains numerous small capillaries, scattered small round cells, a few small foci of round cells, but no eosinophil cells. In some obliterated interlobar spaces and in portions of thickened pleura, where adhesions are evident, small thick-walled arteries are very conspicuous. The alveoli have no uniformity in size due to the unusual variation in structure of the interstitial tissue. Some are widely dilated and have thin intact or ruptured walls while those adjoining may be small and have walls thickened by fibrous tissue and cellular infiltration. The lumina of most of the alveoli contain only an occasional large pigmented mononuclear cell, but in a few small areas they are completely filled by a finely granular precipitate containing an occasional erythrocyte. The patchy thickening of the interstitial tissue is very striking and in many parts of the lungs patches of alveoli are almost completely obliterated by a dense tissue which consists of a network of fibrous tissue surrounding various sized groups of cells. These cells are chiefly small round cells, often grouped, with densely stained nuclei and scanty cytoplasm, large cells with small nuclei and abundant homogeneous cytoplasm, plasma cells, pigmented endothelial cells, a few polymorphonuclear neutrophil cells and an occasional polymorphonuclear eosinophil cell. Throughout this tissue there are numerous fragments of hyperplastic epithelium, some small isolated bronchioles with walls that are densely infiltrated by small round cells, and which are surrounded by a thick zone of fibrous tissue, thin strands of nonstriated muscle fibers, and numerous small thick walled arteries surrounded by a thick zone of dense fibrous tissue.

The epithelium of the ductuli respiratorii is intact and the supporting layer of tissue contains numerous small round cells, a few polymorphonuclear eosinophil cells, and in many places short bundles of smooth muscle from 0.01 to 0.02 mm. thick.

The smallest bronchioles contain only an occasional pigmented mononuclear cell and their lumina are narrowed by longitudinal folds of epithelium from 0.03 to 0.04 mm. high. The epithelium is intact and contains no goblet-like cells. The basement membrane appears hyalin and is distinctly visible for only parts of the circumference. The subepithelial layer contains numerous small mononuclear cells, a few polymorphonuclear eosinophil cells, a few plasma cells, and a few constricted capillaries (epinephrin effect?). The muscular layer varies greatly in thickness in different bronchioles and does not form a continuous band. The outer layer of tissue is composed of loose fibrous tissue in which are many cells similar to those in the subepithelial layer.

The larger bronchioles are almost filled by a granular precipitate which contains only a few cells, chiefly pigmented mononuclear cells, a few neutrophil polymorphonuclears, and a few erythrocytes. The epithelium is from 0.027 to 0.05 mm. high and forms longitudinal folds from 0.12 to 0.18 mm. high. The portion of the epithelium nearest the lumen is made up of long ciliated

cells among which are numerous goblet-like cells. The deeper portions of the epithelium contain numerous small round cells. The other layers of the wall are similar to those of the smaller bronchioles except that the muscle layer forms larger bundles and the cellular infiltration is more marked. In the outer portion of the walls of many of these bronchioles there are masses of fibrous tissue from 0.21 to 0.50 mm. in thickness surrounding arteries with irregularly thickened walls. These vessels suggest the nodal arrangement of the bronchial arteries of guinea-pigs that have succumbed to anaphylactic shock[22] (Figs. 8, 9 and 10).

The lumina of the small bronchi contain only a small amount of a granular precipitate similar to that in the larger bronchioles. The epithelium, which is similar in structure to that in the larger bronchioles, is from 0.09 to

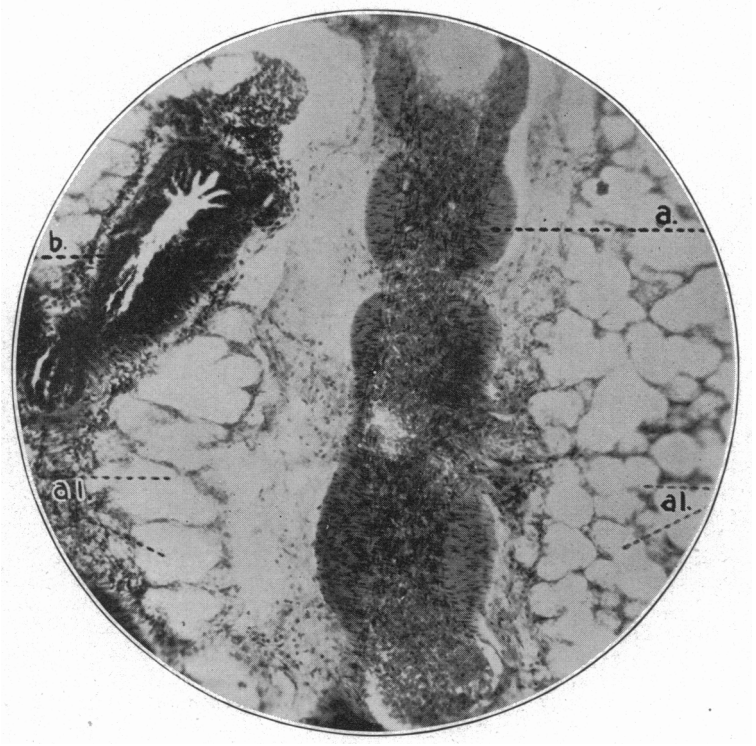

Fig. 8.—Guinea-pig. Fatal horse serum anaphylaxis. Artery. Nodular thickening of muscle. *a* = artery; *al* = alveoli; *b* = bronchiole. Magnification, 90 diameters.

0.12 mm. high and is thrown into folds from 0.20 to 0.27 mm. high. The basement membrane is thick and hyalin in appearance. The subepithelial and muscular layers are similar to those in the bronchioles but are markedly thicker. The mucous glands are almost completely obliterated by infiltration of small mononuclear cells, only a few atrophic acini remaining in most of the glands. The gland ducts are small and their walls are infiltrated by many

22. Schultz, W. H., and Jordan, H. E.: A Microscopic Study of the Anaphylactic Lung of the Guinea-Pig and Mouse, J. Pharmacol. & Exper. Therap. **2**:375, 1911.

small mononuclear cells. Throughout the tissues studied there is no evidence of new ulcer formation in the epithelium and no evidence of healed ulcers except possibly localized collections of small round cells in the subepithelial layers (Fig. 11).

The pulmonary and bronchial arteries and veins in many parts of the lungs are surrounded by varying amounts of dense fibrous tissue containing a few round cells and ranging in thickness from 0.15 to 0.5 mm. The media of many bronchial arteries is irregularly thickened and measures 0.18 mm. in some cases with a diameter of 0.45 mm. The walls of many smaller arteries contain areas of calcification. The spleen contains a large number of polymorphonuclear eosinophil cells.

The cartilages show some areas of calcification and one cartilage contains a small calcified area surrounding typical bone marrow.

Fig. 9.—Case 4. Horse asthma. Fatal horse serum anaphylaxis. Artery and bronchiole surrounded by fibrous tissue. a = artery; br = bronchiole; m = muscle; $f\,t$ = fibrous tissue. Magnification, 60 diameters.

Comment.—The most significant pathologic findings in this case are: (1) Right sided adhesive pleuritis. (2) Completely consolidated areas of pulmonary tissue. (3) marked cellular infiltration of the walls of the bronchi and bronchioles. (4) Moderate thickening of muscle tissue in the bronchi. (5) Atrophy of bronchial mucous glands. (6) Thickening of the walls of many pulmonary and bronchial arteries. (7) Wide zone of fibrous tissue surrounding many pulmonary and bronchial

arteries. (8) Eosinophilic infiltration in bronchial wall and in the spleen. (9) Calcification and ossification of bronchial cartilages.

The history of head colds and asthma since the tenth year with the subsequent discovery of the sensitiveness to horse dander leads one to believe that this case was from the beginning one of horse asthma. The adhesive pleuritis, the areas of consolidated lung tissue, and the evidence of extensive bronchial infection cannot be overlooked and the question naturally arises whether these factors are the result of the asthmatic attacks or are implicated in the production of the attacks.

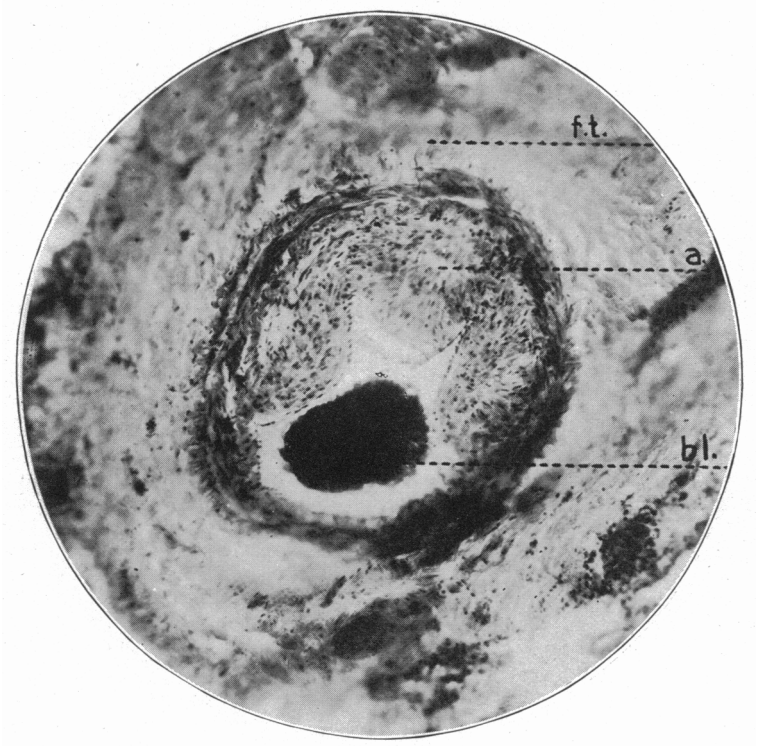

Fig. 10.—Case 4. Horse asthma. Fatal horse serum anaphylaxis. Artery surrounded by fibrous tissue and having irregularly thickened walls. *a* = artery; *bl* = blood; *f t* = fibrous tissue. Magnification, 100 diameters.

CASE 5.—Mr. L., aged 32, single, American, car repairer.

History.—Previous illnesses: Measles, whooping cough and malaria. From childhood until going to California in his twenty-fourth year he suffered from frequent paroxysmal attacks of dyspnea. After a free period of seven years in California he returned to Chicago six months before death and suffered from a recurrence of the attacks. One week before death, April 4, 1912, he entered the Cook County Hospital suffering from bronchopneumonia.

Physical Examination.—Slightly built, white male. Head and eyes negative. Chest: Supraclavicular fossae deep; epigastric angle wide; accessory respira-

tory muscles used during respiration, coarse sibilant râles heard posteriorly. Heart and abdomen negative. Urine contains erythrocytes. Sputum, no tubercle bacilli. Blood differential count: Neutrophils, 84 per cent.; large mononuclears, 8 per cent.; small mononuclears, 8 per cent. Temperature, 102 F. The condition of the patient gradually became worse and death occurred seven days after entrance. Postmortem examination by Dr. H. G. Wells.

NECROPSY REPORT: *Anatomic Diagnosis.*—Acute, left, serofibrinous pleuritis; abscess in the lower lobe of the left lung; pulmonary emphysema; fibrinous pneumonia of the posterior portion of the left upper lobe; bronchopneumonia in right lung, chronic bronchitis; acute mediastinal lymphadenitis; slight hypertrophy of the right ventricle.

Macroscopic Examination.—External appearance: The body is that of a poorly nourished man; height 160 cm. The chest is very prominent anteroposteriorly; the costal cartilages bulge forward, particularly on the right side, and the intercostal spaces are considerably increased in width. The diaphragm reaches to the fifth interspace on the right side; to the sixth rib on the left side. Thorax: The right pleural cavity contains no fluid. The left cavity, however, contains considerable fluid which is turbid, blood stained, and full of fibrin. The serous membrane of the pericardium is smooth and shining, and shows no evidences of inflammation. Mouth: The pharynx is normal except for a slight edema about the arytenoids. Heart: Contracted and extremely rigid. Its size and proportions are apparently normal except for a slight hypertrophy of the right ventricle. Its weight is about 300 gm. The walls of the right ventricle are very muscular, averaging 4 mm. in thickness. The aortic, pulmonic, mitral and tricuspid valves all appear normal. Neither the aortic ring nor the thoracic aorta show any sclerosis. Lungs: The right lung is adherent anteriorly to the chest wall by weak fibrous adhesions, while its base is attached by firmer adhesions to the diaphragm. The lung itself shows no tendency to collapse and on being placed in water floats high. The substance of the lung itself is soft, pale, spongy and inelastic. Palpation reveals slight nodular and irregular hardenings. The pleura shows evidences of hemorrhage. The cut surface appears slightly raised, and mottled with the irregular hardened areas of bronchial pneumonia. Posteriorly this lung is full of fluid. The left lung, externally, appears light in color much as if it had been boiled. Like the right lung it does not collapse. The lower lobe is small, due to the compression of the fluid found in the left pleural cavity, and its lower portion contains much fluid. Its cut surface reveals prominent, thickened bronchi, and in one place a small abscess, 5 x 8 mm., which lies just beneath the pleura. Over this abscess the fibrin is much thicker and whiter than elsewhere. The upper lobe presents in its posterior portion a diffuse consolidation such as is seen in very wet, early pneumonia, such as is secondary to edema. The walls of the bronchi in this lobe are also thickened. There are no evidences of tuberculosis.

Peribronchial lymph glands: Are enlarged and reddened due to their proximity to the adjacent pleuritis. None caseous or calcified. Liver: Weight, 1,400 gm. The cut surface shows the lobules to be well marked and slightly darker at their periphery. Spleen: The spleen is of normal size, pinkish gray and soft. Gastro intestinal tract: In the lower portion of the ileum Peyer's patches show some slight pigmentation such as frequently follows typhoid.

Microscopic Examination.—Spleen: The malphigian corpuscles are small; increase in number of trabeculae; hyaline changes around the arteries. Liver: Shows slight passive hyperemia. Heart muscle: Slight increase in connective tissue. Lungs: There is an increase in the connective tissue around the arteries and bronchi. The alveolae are filled with desquamated cells and fibrin and some polymorphonuclears. Some of the alveolae show edema. Some areas show beginning abscesses. The mucous glands show hyperplasia. Kid-

ney: There is fibrosis of some of the glomeruli with round cell infiltration under the capsule. There are some albuminous casts in the tubules. Lymph glands: The glands show a great deal of anthracosis, some hyperplasia and some eosinophils.

Detailed Histologic Examination.—A systematic study of the lungs of this case was not possible as only portions of the lungs were preserved. Our findings are as follows: The pleura, with a fairly uniform thickness of from 0.075 to 0.15 mm. contains numerous distended capillaries, scattered small round cells, and a few small foci of round cells. The lung structure are obliterated in patches by pneumonic foci which are surrounded by alveoli containing a granular precipitate and in some areas extravasations of erythro-

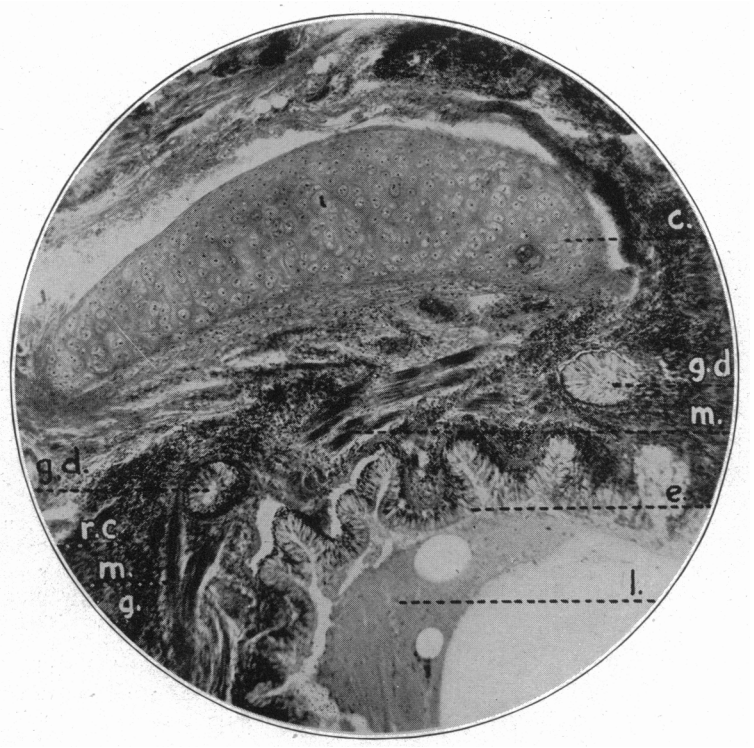

Fig. 11.—Case 4. Fatal horse serum anaphylaxis. Small bronchus. Cross section. Epithelium swollen. Subepithelial layer infiltrated by round cells. Glands small and infiltrated by round cells. l = lumen; e = epithelium; m = muscle; g = gland; $g\,d$ = gland duct; c = cartilage. Magnification, 45 diameters.

cytes. The alveolar walls in the areas not involved in the pneumonic process are not appreciably changed.

The lumina of the smaller bronchioles are partially occluded by fragments of desquamated epithelium, polymorphonuclear neutrophil cells, and a few erythrocytes. The single layered epithelium is partially desquamated and the basement membrane is indistinct. The subepithelial layer contains numerous small mononuclear cells, a few plasma cells, a few polymorphonuclear neutrophil cells and some distended capillaries. The muscle bundles are small and do not form a continuous layer. The larger bronchioles are similar to the

smaller, except that all layers are proportionately better developed. The elastic and fibrous tissues are very scanty in all the bronchioles.

The lumina of the small middle-sized bronchi contain the same character of material as that found in the bronchioles. The stratified epithelium is almost completely desquamated and the basement membrane is inconspicuous. The subepithelial layer is markedly thickened and contains many small mononuclear cells, a few polymorphonuclear neutrophil cells, occasional polymorphonuclear eosinophil cells, numerous distended capillaries and small bundles of elastic tissue. The smooth muscle layer is not prominent and its short bundles are separated and more or less obscured by fibrous tissue and invading small mononuclear cells. The cartilages show only a few small calcified areas.

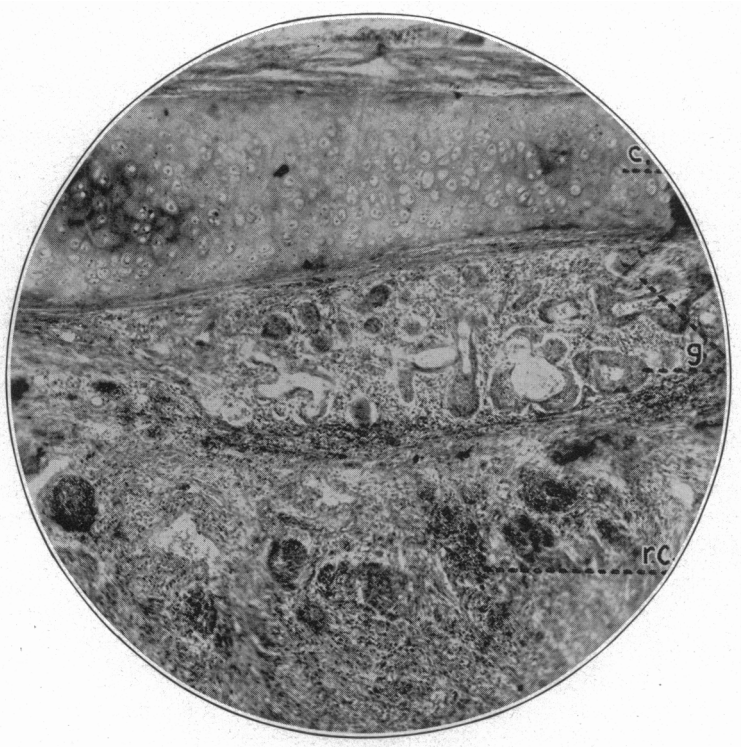

Fig. 12.—Case 5. Asthma. Bronchus. Cross section. Subepithelial layer markedly infiltrated by round cells. Mucous gland infiltrated and containing hyperplastic acinar cells. *r c* = round cells; *g* = gland; *c* = cartilage. Magnification, 60 diameters.

Most of the mucous glands are small their acini are few in number, markedly distorted and separated by a cell rich tissue containing plasma cells, small mononuclear cells, a few polymorphonuclear neutrophil cells, a few mononuclear eosinophil cells, and a type of cell with a large pale nucleus and an abundant homogenous cytoplasm. These acini may form small compact circular or tubular masses of cells, or they may form larger leaf shaped masses surrounding varying amounts of mucus. The acinar cells in these masses are larger than normal and contain large pale nuclei. In all the wall layers between the gland and the lumen there are many compact collections of a similar type

of cell, the shape and distribution of which indicate that these masses are remnants of gland ducts (Fig. 12).

The bronchial arteries have thickened walls involving chiefly the media and are not surrounded by increased fibrous tissue.

The nerves are not appreciably changed and are not surrounded by small round cells.

Comment.—The most significant pathologic findings are: (1) Partial occlusion of the lumina of bronchi and bronchioles by exudate. (2) Infiltration of the subepithelial layer of bronchi and bronchioles by small round cells and eosinophil cells. (3) Infiltration of mucous glands by small round cells. (4) Hyperplastic changes in acinar cells of bronchial mucous glands. (5) Slight hypertrophy of the right heart.

The etiology of the asthmatic attacks in this case is not clear. The history of attacks since early childhood with a free period following a change of climate and then a recurrence, could be interpreted either as sensitiveness to food or animal proteins or to infection in the respiratory tract.

CASE 6.—*History.*—Infant M., female, aged 15 months. Normal delivery. Birth weight 8½ pounds. Family history is negative. Breast fed for three months with a gain in weight to 15 pounds, but because of a facial eczema she was put on artificial feedings by the family physician. At the eighth month she was admitted to the Children's Memorial Hospital Dispensary with eczema and weighing 11 pounds. Under dispensary management the skin condition improved and the weight increased. At the age of 12 months she was brought into the Children's Memorial Hospital suffering from a pharyngitis, accompanied by dyspnea and cyanosis of the face.

First Examination.—Well nourished. Temperature 101.6 F.; pulse, 160. Head: negative except for reddening of both ear drums, cyanosis of the lips and facial eczema. Neck, marked cervical adenopathy. Thorax: barrel shaped, markedly emphysematous and hyperresonant; marked expiratory stridor; squeaky râles all over the chest. Abdomen: distended and slightly tympanitic. Genitalia and extremities negative. Small doses of epinephrin and atropin gave only slight relief. The dyspnea and stridor gradually subsided, but the eczema persisted. Pus was obtained from both ears after paracentesis. Urticarial lesions appeared on the abdomen, back, groin and face one-half hour after a feeding of farina, and subsequent cutaneous protein sensitization tests revealed a marked degree of sensitiveness to wheat proteins and to whole wheat and a slight degree of sensitiveness to cow's milk and to lactalbumin. The reactions to orange, egg yolk, egg albumin, beef, mutton, navy bean, spinach, carrot, cocoa, coffee, rye, oats and barley were negative. Wheat protein and whole wheat, both of which gave definite reactions, were eliminated from the diet and oatmeal substituted as the cereal.

Course.—At the end of one week, the patient was discharged from the hospital with very little bronchitis, no râles in the chest, and much less of the facial skin involvement. Six days later she was again admitted to the hospital suffering from an asthmatic attack which may have been brought on by the ingestion of wheat containing food. Four days later the patient was again discharged from the hospital with very little bronchitis, no râles in the chest and no eczema. For two months her condition improved, wheat containing foods having been gradually added to the diet, then she was again admitted to the hospital suffering from a cold in the head and an attack of asthma.

Second Examination.—Leukocytes, 7,950. Hemoglobin (Sahli), 96 per cent. Respiration, 64. A fairly well-developed and nourished female child with

respiratory difficulty and markedly cyanotic. She has a marked respiratory wheeze and the accessory respiratory muscles are used. The head is inclined to be square shaped and is held in a retracted position. The anterior fontanel is open and bulging and quite tense. Craniotabes is present. Skin of the cheeks is rough. Chest is inclined to be barrel shaped, and on percussion there is a hyperresonant note over the entire chest. The heart tones are hard to hear on account of the wheezing noises in the chest. The liver is two fingers' breadth below the costal margin in the mammary line. The spleen is not palpable. There are no tumor masses in the abdomen. The knee reflexes are active. The use of epinephrin, atropin and benzyl benzoate afforded only transient relief and the patient died about thirty-two hours after entering the hospital. The postmortem examination was made a few hours later by Dr. W. G. Hibbs.

NECROPSY REPORT: (Only the most important findings are given.)

Anatomic Diagnosis.—Huge hypertrophic emphysema of the lungs. "Barrel-shaped" chest. Downward displaced diaphragm and liver. Hypertrophy of the right ventricle of the heart. Slight passive hyperemia of the liver, kidneys and skin. Hypertrophy of the thymus, cervical and mesenteric lymph nodes, the spleen, the lymphoid tissue of the base of the tongue and the lymph nodes of the ileum. Narrowed aorta (congenital). Fatty changes of the liver. Needle puncture wounds of the upper arms. Suppurative vaginitis (gonococcus). Hyperemia of the uterus and adnexa. Eczema (?) of the skin of the face.

Macroscopic Examination.—This is the body of a white, female child about 15 months old. Only the front teeth, both lower and upper, are present. Body nourishment is fair. The chest is noticeably "barrel-shaped." The lower one third of the sternum is raised about 1 cm. above the general level of the corpus sterni as the body lies on the table. The abdominal wall in front is slightly distended and rigid. The external genitalia and anus are unchanged. The skin of the face is hard, crusted and in places scaled (eczema?). The content of cranium is not examined (permission refused). Abdomen: The uterus and its appendages are markedly hyperemic. The diaphragm on the right side is pushed down to opposite the level of the fifth rib, the fifth interspace on the left. The lower level of the liver is 1 cm. below the costal arch. The gallbladder is normally free. The urinary bladder is unchanged. The peritoneum is everywhere smooth and shiny. Thorax: The costal cartilages are soft. The lungs completely fill the pleural cavities. The lungs are free of adhesion. The pleura is everywhere smooth and shiny. There is no free fluid in the pleural sacs. The lungs and intact trachea from below the thyroid cartilage are removed en masse (weight 1677.5 gm.), and put into 10 per cent. liquor formaldehyd for later detailed study. Heart: the pericardial sac contains about 3 c.c. of clear fluid. The apex of the heart consists of right and left ventricles and in front the right ventricle is as broad as the left. The pulmonary artery contains only fluid blood. The pulmonary cusps are unchanged, as are the tricuspid leaflets. The right ventricle between base and apex is 1.5 cm. thick. There is no change of the linings of the carotid arteries, the inferior vena cava and the aorta. The aorta is about two thirds the usual size and measures 12 mm. in greatest diameter. Lymphoid tissue: The deep cervical lymph nodes are from 5 to 18 mm. in diameter. They are firm, pale yellow and generally hyperplastic. The tonsils and the lymph nodules of the base of the tongue are about twice the normal size. Kidneys: The kidneys together weigh 62 gm. The cortical striations are well defined and the cortices are uniformly from 3 to 5 mm. thick. They are grossly unchanged. Weights of organs: Suprarenals together, 5 gm.; thyroid, 2.5 gm.; thymus, 15 gm.; spleen, 20.2 gm.; pancreas, 7.5 gm.; liver, 293.5 gm.; heart, 57.5 gm.

Gross Description.—The lobes of both lungs are distended by air (Fig. 13), float high in water, and are soft and feathery to touch. The pleural surfaces

everywhere are smooth and shining and are grayish in color, except for a few scattered brownish slightly depressed, sharply defined, nodule-like areas measuring about 0.5 cm. in diameter. There are some large emphysematous bullae in the apices and in the anterior margins of both lungs. The trachea and the main bronchi contain a small amount of mucopurlent tenacious exudate and their epithelial lining is reddened. The peritracheal and peribronchial lymph glands are conspicuous and their cut surfaces are reddish gray in color. The cut surfaces of all lobes of both lungs are dry, grayish red in color and are air filled except for the above described nodule-like areas which are distributed from the hilum to the pleural surface. The connective tissue septae throughout the lungs are conspicuous. A few of the medium sized and smaller bronchi are patent but most are almost or completely occluded by a grayish tenacious exudate and their walls appear thickened. The larger blood vessels especially in the lower lobes of both lungs are distended by blood.

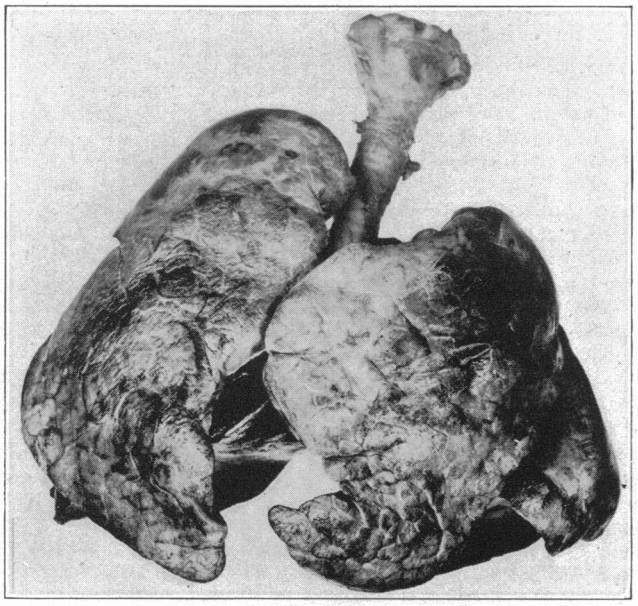

Fig. 13.—Case 6. Food asthma. Infant. Lungs showing acute emphysema.

Microscopic Description.—The structure of the different lobes of both lungs varies so little that a separate description of each is not necessary. The pleura throughout appears normal in structure and variations in thickness depend on the amount of air in the underlying tissue. Numerous connective tissue septa extending into the lung from the pleura are very conspicuous grossly and microscopically and sharply mark off definite units of lung tissue. These septa are composed of fibrous tissue which contains a few distended blood vessels and a few scattered lymphoid cells. There are also a few small collections of lymphoid cells beneath the pleura. The apices and anterior margins of both lungs are markedly emphysematous, the alveoli being widely distended and their walls thin and in places ruptured. The alveoli in the greater part of both lungs are air filled, moderately distended, and their walls of normal structure and thickness. The bronchioles and their finer divisions in these portions of the lungs are dilated and contain a more or less mucinous exudate in which there are varying numbers of polymorphonuclear neutrophil cells and

a few polymorphonuclear eosinophil cells. The epithelium is intact and is folded in only the contracted bronchioles. The basement membrane is not conspicuous. The subepithelial layer is relatively thin and contains only a few lymphoid cells and an occasional polymorphonuclear eosinophil cell. The muscle layer is scanty and irregular in distribution. The other connective tissue layer is thin and contains throughout numerous small definite lymphoid nodules with distinct germ centers.

The remainder of the lung tissue falls into two distinct groups which differ markedly from each other and from that already described. One of these is composed of definite areas from 0.5 to 1.5 cm. in diameter which are sharply marked off by septa and are scattered irregularly throughout both lungs. The alveoli are small and almost completely filled by a fine granular precipitate containing a few polymorphonuclear neutrophil cells and a few red blood cells. The walls of these alveoli are thickened by distended capillaries. The bronchioles and their divisions are occluded by a mucous exudate containing many polymorphonuclear neutrophil cells, a few polymorphonuclear eosinophil cells and a few epithelial cells. The epithelium of the bronchioles is slightly thickened and the ciliated border is fused with the mucus in the lumen. The subepithelial layer is thin and contains a few round cells. The muscle layer is scanty and irregular in distribution. The outer connective tissue layer is increased in amount and in many bronchioles is infiltrated by lymphoid cells and polynuclear eosinophil cells which in some are grouped about blood vessels. Distinct lymph nodules are prominent in the walls of some of the bronchioles.

The other group of well defined areas are more scattered, air free, somewhat smaller in size and retain, as the only evidence of lung tissue, small contracted bronchioles whose lumina are completely occluded by a mucous exudate containing a few polynuclear neutrophile cells absorption atelectasis (Plate 2, D). The major portion of these areas consist of closely crowded small mononuclear cells, among which are a few small capillaries, fibroblasts, large mononuclear cells (endothelial cells) and polymorphonuclear neutrophil and eosinophil cells. The blood vessels are small and are surrounded by an abnormal amount of fibrous tissue.

The small and medium sized bronchi in all parts of the lungs vary greatly in appearance, and these variations seem to bear no definite relation to the abnormal lung tissue. Approximately two thirds of these bronchi are almost, or completely occluded by a mucous exudate (Plate 3, A) which contains varying numbers of polymorphonuclear neutrophil and eosinophil cells, a few desquamated epithelial cells, but no fibrin and showing in longitudinal sections distinct layer formation. The epithelium is intact, thrown into shallow folds and contains a few polymorphonuclear eosinophil cells. The outer ciliated border seems to fuse with the content of the lumina. The basement membrane is not prominent. The subepithelial layer is thin and contains only a few lymphoid cells and a few polymorphonuclear eosinophil cells. The muscle layer is thin and irregularly distributed. The mucous glands are very prominent, their acini large and separated from each other by a loose connective tissue containing only a few lymphoid cells and a few polymorphonuclear eosinophil cells. Outside the muscle layer the collections of polymorphonuclear eosinophil cells (Plate 3, B and C) usually surrounding moderately distended blood vessels, make a striking picture. The cartilages are of normal appearance. The outer fibrous tissue layer is prominent. The blood vessels are distended only in both lower lobes. The peribronchial nerves and nerve sheaths are not infiltrated by cells and are unchanged. The lymph nodes along all bronchi are very numerous and prominent and contain large germ centers with scattered cells, and their sinuses contain a few polymorphonuclear eosinophil cells. The remainder of the small and medium sized bronchi are widely dilated and contain small amounts of mucous exudate similar to that described above. The walls are similar in structure, except that they are thinner. In many sections, occluded and distended bronchi lie

side by side. The main and large bronchi contain varying amounts of mucus. Their walls except for the normal structural differences, are similar to the walls of the medium sized bronchi. The collection of polymorphonuclear eosinophil cells about small blood vessels between the muscle layer and the cartilages is very striking throughout the whole bronchial tree. The peribronchial lymph glands are numerous and very large. Their sinuses are distended and the germ centers prominent and all glands contain many eosinophil cells. A slight anthracosis is present. The thyroid, parathyroid, liver, pancreas, suprarenals and kidneys are normal in structure. The sinuses of the spleen are filled with blood and the splenic pulp contains large numbers of polynuclear eosinophil cells. The cervical and mesenteric lymph glands are large, the germ centers are prominent and have loosely arranged cells but no evidence of necrosis, and some contain many distended blood vessels. All lymph glands examined, except the mesenteric, contain many polymorphonuclear eosinophil cells. The thymus is well developed and the cortical portions contain many diffusely scattered, irregularly shaped, deeply stained cellular masses, Hassall's corpuscles. The cortical and medullary portions contain many groups of mononuclear eosinophil cells (Plate 3, D).

Comment.—The chief pathologic findings in this infant may be summarized as follows: (1) complete occlusion of the majority of the middle sized and smaller bronchi by mucus. (2) Two distinct stages in the formation of areas which are interpreted as evidences of past asthmatic attacks (absorption atelectasis). (3) Extreme eosinophilia of the following structures: Bronchial wall, mucous content of bronchial lumen, mucous glands, spleen, lymphoid tissues and thymus. (4) Thickening of the walls of the bronchi and blood vessels. (5) Cell inclusions in the thymus. (6) Hypertrophy of entire lymphoid apparatus. (7) Narrowing of aortic arch. (8) Enlargement of the thymus.

The last three statements point to the possibility of this case being one of status lymphaticus, although the characteristic areas of necrosis in the lymph glands, which have been emphasized,[23] are absent. The clinical picture also is not characteristic.

The history of head colds and bronchitis preceding severe attacks is a point of interest. The history of eczema, of positive cutaneous tests for wheat proteins, of improvement in condition following the use of a wheat free diet and the lack of microscopic evidence of former infections in the subepithelial layer and in the mucous glands place this case in the category of the food asthmas.

MEASUREMENTS OF BRONCHI AND BRONCHIOLI

Since the abnormal inflation of the lungs and the impairment of respiration in asthma are undoubtedly associated with a narrowing of the lumina of the bronchial tubes, it is in order to ask what factors are involved in the production of this stenosis. Naturally, the attention is directed toward the smooth muscle fiber system, which acts by

23. Symmers, D.: Status Lymphaticus, Am. J. M. Sc. **156**:40, 1919.

diminishing the size of the tube, and toward the exudative system (i. e., *a,* mucous epithelium; *b,* glands, and *c,* blood vessels and capillaries) which adds to the stenosis by its increase in size and in secretory activity. Both these systems, of course, are regulated in function by the nervous system.

If the bronchial muscle contracts, certain temporary changes in the structure of the walls must immediately occur, i. e., there must be an increase in the thickness of the muscle bundles and in the height of the epithelial folds. The question arises then whether repeated spasmodic attacks over a long period of time might not ultimately cause a true hypertrophy of the smooth muscle system as well as changes in other portions of the tubes. Previous workers noted that their cases seemed to show an increase in the thickness of the bronchial wall

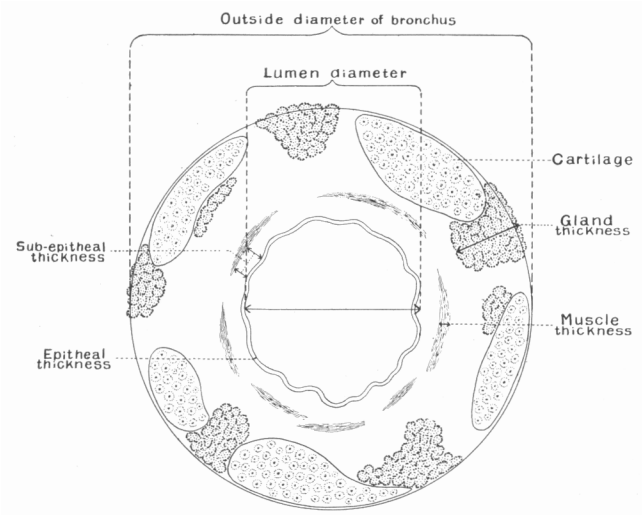

Fig. 14.—Diagrammatic view of the cross section of a bronchus to show the method used in making the measurements of the different structures.

but to our knowledge no actual proof has yet been given for the existence of such a change. In order to obtain definite evidence on this important point, we have made a comparison of the measurements of the bronchial structures of asthmatic and nonasthmatic individuals.

The typical transverse sections of the bronchi and bronchioli on which histologic studies were made were measured microscopically with the micrometer, in the following manner: a = mean distance between outer borders, b = mean diameter of lumen, c = epithelial layer thickness, d = basement membrance thickness, e = subepithelial layer thickness, f = muscle bundle thickness, and g = mucous gland diameter (Fig. 14). The classification of bronchi as to size is based on the measurement between outer borders and not on the diameter of the

lumen, as is usually done. This method gives, we believe, especially in all cartilage-bearing tubes, a better basis for comparison than the usual method. The measurement of the lumen takes into account the slight irregularities due to the shallow longitudinal epithelial folds. The epithelial thickness is measured from the attachment of the cilia to the point of contact with the basement membrane. The basement membrane thickness is measured only in those sections in which its borders are

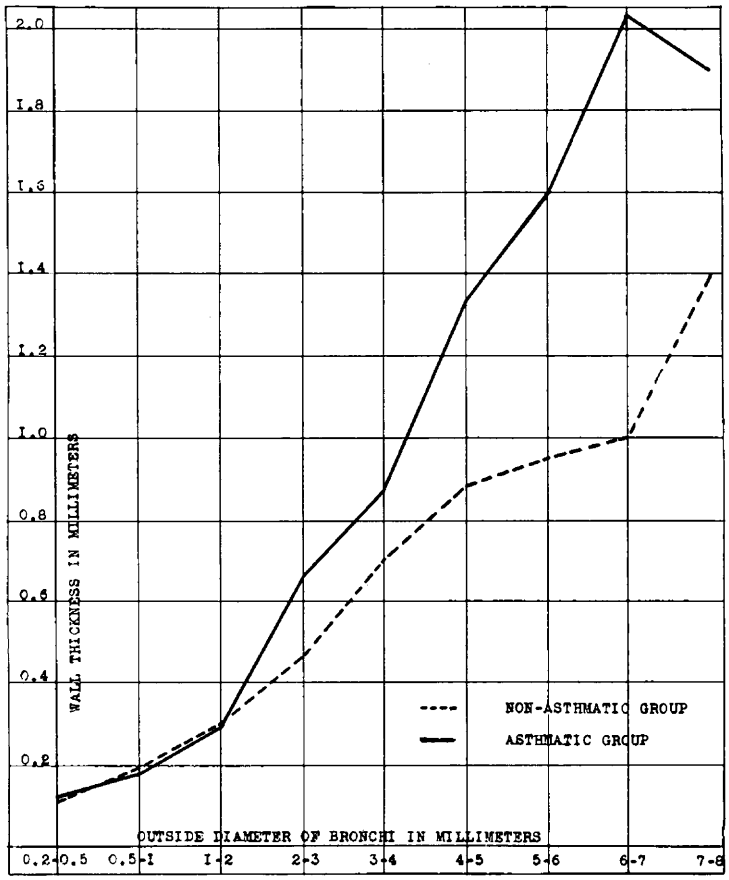

Fig. 15.—Graphs showing comparison of wall thickness.

distinct. The measurement of the subepithelial layer, which includes all tissues between the basement membrane and the muscle layer, also takes into account the longitudinal epithelial folds. The diameters of the muscle bundles and of the mucous glands are measured at right angles to the tube lumen. All measurements are made, as far as possible, in the tube segment with most uniform structures, otherwise the mean of several measurements is taken.

Thirteen individuals, six asthmatic and seven nonasthmatic constitute our material on which the measurements of the bronchial structures were made. Some important data concerning them are given in Table 1.

TABLE 1.—DATA REGARDING INDIVIDUALS WHOSE BRONCHI WERE MEASURED

	Sex	Age	Death Due to	Chief Complaint
1. B.	F	55 yrs.	Suicide—drowning	Asthma
2. G.	M	55 yrs.	Asthma	Asthma
3. Le.	M	29 yrs.	Abscess of lung	Asthma
4. E. L.	M	29 (?) yrs.	Acute fatal anaphylaxis	Asthma—horse
5. L.	F	17 yrs.	Acute streptococcus infection	Asthma
6. Baby A.	F	15 mos.	Asthma	Asthma
7. Gr.	M	70 yrs.	Cardiac decompensation	Chronic bronchitis
8. Br.	F	62 yrs.	Carcinoma of stomach	Carcinoma
9. A.	M	50 yrs.	Pneumonia of l. lower lobe	Chronic bronchitis
10. N. L.	M	27 yrs.	Suicide, jugulars severed	Psychosis
11. R.	M	26 yrs.	Suicide, shot through heart	Psychosis
12. B.	M	25 yrs.	Brain abscess	Brain abscess
13. Baby N.	F	15 mos.	Enteritis	Enteritis

Numbers 7 and 9 are omitted from all graphs because of the questioned diagnosis of early asthma. Numbers 6 and 13 are also omitted from all graphs because of the youth of these patients, however, separate graphs, not reproduced here, show similar increased thickness in the tubes of the asthmatic child.

The measurements obtained from these subjects are given in Tables 2 and 3.

There are certain unavoidable apparent sources of error in the figures given in Tables 2 and 3 and in order to offset these the largest number of measurements possible are taken. Groupings by tube size is open to the objection that more measurements may be made near one extreme in one group than in the other, but our figures show that such occurrences influence the graphs about equally. Because of the marked variations in the size of the bronchi at the same distance from the bifurcation of the trachea in different persons, the criticism that the increase in wall-thickness in our asthmatic subjects may be due to a uniform contraction of all tubes cannot be answered definitely. The size and thickness of the bronchial cartilaginous plaques vary greatly, depending somewhat on nearness to a bifurcation, so that measurement of these plaques is of little value in determining location. However, the longitudinal folding of the epithelial layer, which may be one evidence of contraction, shows no consistent variation in the two groups of cases. It will be noted that tubes of the same size in the same individual show marked variations in structures but these are as striking in one group as in the other. Differences in numbers of measurements obtainable from different persons are unavoidable—the greatest numbers being obtained in those whose lungs furnished the greatest number of typical sections. The number of typical sections obtainable from each individual is limited by the amount of lung tissue originally obtained and the amount of tissue uninfluenced by other pathologic conditions such as pneumonia, etc.

TABLE 2.—MEASUREMENTS IN MILLIMETERS OF BRONCHI AND BRONCHIOLI. ADULTS

These tables are arranged so that the outside diameter of the bronchial tubes is taken as the fixed standard of comparison. The differences in the size of structures of the asthmatic and non-asthmatic individuals as obtained from these measurements are demonstrated graphically in Figures 15, 16 and 17.

Name	Diagnosis	Outside Diameter	Inside Diameter	Wall Thickness	Epithelial Thickness	Basement Membrane Thickness	Sub-Epithelial Thickness	Muscle Thickness	Gland Diameter
Normal L.	Normal	0.22	0.12	0.05	0.013	.....	0.016	0.010	....
Normal B.	Brain abscess.	0.28	0.18	0.05	0.016	.....	0.013	0.010	....
Mr. E. L.	Asthma	0.28	0.18	0.05	0.025	.....	0.010	0.016	....
Miss L.	Asthma	0.30	....	....	0.019	.....	0.016	0.013	....
Mr. G.	Asthma	0.32	0.14	0.09	0.016	.....	0.036	0.026	....
Mr. G.	Asthma	0.33	0.17	0.08	0.016	.....	0.016	0.023	....
Miss L.	Asthma	0.35	....	....	0.022	.....	0.016	0.012	....
Normal L.	Normal	0.36	0.14	0.11	0.010	.....	0.007	0.010	....
Normal L.	Normal	0.36	0.12	0.12	0.016	.....	0.033	0.020	....
Mr. E. L.	Asthma	0.36	0.12	0.12	0.039	.....	0.028	0.028	....
Mr. E. L.	Asthma	0.38	0.14	0.12	0.023	.....	0.028	0.021	....
Normal B.	Brain abscess.	0.40	0.15	0.125	0.016	.....	0.016	0.026	....
Normal B.	Brain abscess.	0.42	0.10	0.16	0.016	.....	0.016	0.010	....
Mr. R.	.....	0.44	0.28	0.08	0.013	.....	0.013	0.013	....
Mr. G.	Asthma	0.48	0.15	0.165	0.020	.....	0.033	0.050	....
Normal B.	Carcinoma	0.50	0.21	0.145	0.013	.....	0.019	0.013	....
Normal B.	Brain abscess.	0.50	0.14	0.18	0.013	.....	0.010	0.033	....
Mr. E. L.	Asthma	0.50	0.14	0.18	0.036	.....	0.023	0.050	....
Mr. E. L.	Asthma	0.50	0.26	0.12	0.033	.....	0.023	0.019	....
Mr. Gr.	Bronchitis	0.50	0.22	0.14	0.013	.....	0.020	0.033	....
Normal B.	Carcinoma	0.58	0.25	0.165	0.016	.....	0.026	0.033	....
Normal L.	Normal	0.59	0.30	0.145	0.029	.....	0.033	0.018	....
Mr. R.	.....	0.61	0.24	0.185	0.013	.....	0.026	0.023	....
Miss L.	Asthma	0.64	0.10	0.27	0.033	.....	0.023	0.019	....
Mr. R.	.....	0.64	0.22	0.21	.....	.....	0.023	0.019	....
Mr. R.	.....	0.67	0.24	0.215	0.033	.....	0.026	0.026	....
Normal L.	Normal	0.68	0.30	0.19	0.025	.....	0.042	0.025	....
Mr. R.	.....	0.70	0.24	0.23	0.033	.....	0.033	0.037	....
Mr. Le.	Asthma	0.70	0.20	0.25	.....	.....	0.042	0.016	....
Mr. R.	.....	0.71	0.30	0.205	0.021	.....	0.023	0.026	....
Mr. R.	.....	0.71	0.26	0.225	0.033	.....	0.050	0.049	....
Mr. R.	.....	0.71	0.31	0.20	0.013	.....	0.033	0.033	....
Mrs. B.	Asthma	0.71	0.40	0.155	.....	0.0066	0.028	0.014	....
Normal B.	Brain abscess.	0.80	0.52	0.14	0.018	.....	0.021	0.021	....
Normal L.	Normal	0.80	0.60	0.10	0.019	.....	0.016	0.019	....
Mrs. B.	Asthma	0.86	0.60	0.13	.....	0.0066	0.014	0.014	....
Normal L.	Normal	0.87	0.70	0.085	.....	.....	0.016	0.016	....
Normal L.	Normal	0.87	0.48	0.195	0.016	.....	0.026	0.019	....
Mr. R.	.....	0.87	0.32	0.275	0.019	.....	0.050	0.039	....
Mr. Gr.	Bronchitis	0.88	0.66	0.11	.....	.....	0.056	0.042	....
Normal L.	Normal	0.91	0.40	0.255	0.052	.....	0.042	0.042	....
Mr. G.	Asthma	1.00	0.62	0.19	0.040	.....	0.026	0.023	....
Mrs. B.	Asthma	1.00	0.70	0.15	.....	0.010	0.070	0.100	....
Mrs. B.	Asthma	1.00	0.70	0.15	.....	0.0066	0.028	0.014	....
Mr. R.	.....	1.00	0.53	0.235	0.013	.....	0.066	0.039	....
Mr. R.	.....	1.10	0.50	0.30	0.033	.....	0.033	0.040	....
Normal B.	Brain abscess.	1.10	0.64	0.23	.....	.....	0.026	0.016	....
Mr. G.	Asthma	1.12	0.62	0.25	0.026	.....	0.033	0.026	....
Normal B.	Brain abscess.	1.20	0.80	0.20	0.013	.....	0.084	0.028	....
Normal B.	Brain abscess.	1.20	0.80	0.20	.....	.....	0.070	0.028	....
Mr. R.	.....	1.28	0.63	0.325	0.023	.....	0.083	0.050	....
Normal L.	Normal	1.40	0.86	0.270	0.025	.....	0.070	0.019	....
Mr. G.	Asthma	1.43	0.60	0.415	0.033	0.0066	0.040	0.037	0.17
Mr. G.	Asthma	1.60	1.16	0.22	0.045	.....	0.056	0.033	0.18
Normal Br.	Carcinoma	1.68	1.00	0.34	0.023	.....	0.039	0.050	....
Miss L.	Asthma	1.80	1.10	0.35	0.050	.....	0.050	0.033	....
Normal Br.	Carcinoma	1.80	1.16	0.32	.....	.....	0.033	0.033	....
Mr. A.	Bronchitis	1.80	0.92	0.44	.....	.....	0.056	0.140	0.50
Normal Br.	Carcinoma	1.84	1.16	0.34	.....	.....	0.033	0.033	....
Mrs. B.	Asthma	1.90	1.50	0.20	.....	0.010	0.015	0.043	....
Normal L.	Normal	1.95	1.25	0.35	.....	.....	0.056	0.040	0.46
Normal Br.	Carcinoma	1.96	1.27	0.345	.....	.....	0.033	0.033	....
Mrs. B.	Asthma	2.10	0.62	0.74	.....	0.010	0.090	0.110	0.31
Mr. E. L.	Asthma	2.10	0.92	0.59	0.060	.....	0.058	0.150	....
Mrs. B.	Asthma	2.20	1.30	0.45	0.033	0.012	0.042	0.042	0.30
Mr. R.	.....	2.20	1.60	0.30	.....	.....	0.053	0.026	....
Normal Br.	Carcinoma	2.20	1.00	0.60	0.045	0.0066	0.070	0.070	0.24
Mr. G.	Asthma	2.28	1.16	0.56	.....	.....	0.070	0.084	....
Mr. A.	Bronchitis	2.30	1.10	0.60	.....	0.0099	0.100	0.140	0.50
Mr. A.	Bronchitis	2.40	1.00	0.70	.....	.....	0.120	0.180	0.28
Mrs. B.	Asthma	2.40	1.00	0.70	.....	.....	0.100	0.100	0.58
Mr. G.	Asthma	2.40	1.00	0.70	0.065	.....	0.056	0.056	0.50

TABLE 2.—MEASUREMENTS IN MILLIMETERS OF BRONCHI BRONCHIOLI. ADULTS—(*Continued*)

Name	Diagnosis	Outside Diameter	Inside Diameter	Wall Thickness	Epithelial Thickness	Basement Membrane Thickness	Subepithelial Thickness	Muscle Thickness	Gland Diameter
Mr. F. L.	Asthma	2.40	1.10	0.65	0.066	0.0072	0.056	0.056	0.26
Miss L.	Asthma	2.50	1.40	0.55	0.084	0.0066	0.026	0.050	0.29
Mrs. B.	Asthma	2.60	2.20	0.20	.....	0.010	0.043	0.043	....
Normal L.	Normal	2.70	1.70	0.50	0.033	.....	0.052	0.026	....
Miss L.	Asthma	2.70	1.60	0.55	0.084	0.0066	0.026	0.056	0.36
Mr. Le.	Asthma	2.80	1.20	0.80	.....	.....	0.140	0.126	....
Mrs. B.	Asthma	2.90	1.80	0.55	.....	0.012	0.140	0.086	0.32
Mrs. B.	Asthma	3.00	1.50	0.75	.....	.....	0.070	0.070	0.88
Mr. A.	Bronchitis	3.00	1.46	0.77	.....	0.0099	0.070	0.140	0.72
Mr. Le.	Asthma	3.00	0.70	1.15	.....	.....	0.140	0.180	0.50
Mr. Le.	Asthma	3.00	0.70	1.15	.....	.....	0.180	0.200	0.36
Mr. E. L.	Asthma	3.00	1.70	0.65	0.083	0.0072	0.100	0.110	0.37
Mrs. B.	Asthma	3.12	1.72	0.70	.....	.....	0.100	0.180	0.80
Mrs. B.	Asthma	3.20	1.40	0.90	.....	0.010	0.070	0.086	0.48
Miss L.	Asthma	3.20	1.84	0.68	0.058	0.0072	0.054	0.066	0.28
Mr. Gr.	Bronchitis	3.33	1.68	0.825	.....	.....	0.070	0.084	0.34
Mr. Gr.	Bronchitis	3.33	1.74	0.795	.....	.....	0.045	0.039	0.29
Mr. G.	Asthma	3.40	1.80	0.80	.....	.....	0.056	0.070	....
Mr. L.	Asthma	3.40	1.30	1.05	0.078	.....	0.083	0.110	0.40
Mrs. B.	Asthma	3.42	1.56	0.93	.....	.....	0.110	0.160	0.86
Mr. A.	Bronchitis	3.50	1.40	1.05	0.056	.....	0.085	0.220	0.14
Normal Br.	Carcinoma	3.50	1.75	0.875	0.050	0.0066	0.040	0.070	0.38
Mr. G.	Asthma	3.50	1.94	0.78	0.056	.....	0.070	0.140	0.34
Mrs. B.	Asthma	3.60	1.80	0.90	.....	0.010	0.100	0.100	0.90
Normal L.	Normal	3.80	1.75	1.025	0.045	.....	0.100	0.095	0.30
Mr. R.	.....	3.80	2.60	0.60	0.050	.....	0.084	0.120	0.20
Mrs. B.	Asthma	4.00	1.90	1.05	.....	0.010	0.100	0.180	0.70
Normal L.	Normal	4.00	3.00	0.50	0.033	.....	0.100	0.042	0.30
Normal L.	Normal	4.00	3.00	0.50	0.039	.....	0.033	0.060	0.32
Normal L.	Normal	4.20	2.28	0.96	.....	.....	0.110	0.084	0.44
Mrs. B.	Asthma	4.20	1.80	1.20	.....	0.010	0.170	0.200	0.70
Mr. Gr.	Bronchitis	4.50	....	....	0.056	.....	0.120	0.120	0.80
Mr. Gr.	Bronchitis	4.50	2.40	1.05	0.050	0.0066	0.090	0.180	0.60
Mrs. B.	Asthma	4.64	2.80	0.92	.....	.....	0.100	0.140	0.86
Mrs. B.	Asthma	4.80	2.24	1.28	.....	.....	0.100	0.130	0.58
Mrs. B.	Asthma	4.80	0.86	1.97	.....	.....	0.220	0.200	1.10
Normal B.	Brain abscess	5.00	3.50	0.75	.....	.....	0.096	0.090	0.30
Normal Br.	Carcinoma	5.04	3.14	0.95	0.042	.....	0.066	0.072	0.70
Miss L.	Asthma	5.06	2.50	1.28	0.063	0.0066	0.100	0.140	0.72
Normal L.	Normal	5.10	3.20	0.95	0.056	.....	0.115	0.084	0.32
Mrs. B.	Asthma	5.44	1.92	1.96	.....	.....	0.260	0.260	1.00
Mr. Gr.	Bronchitis	5.60	2.54	1.53	.....	.....	0.200	0.200	0.71
Mrs. B.	Asthma	5.76	2.40	1.68	.....	.....	0.220	0.180	1.00
Mr. Gr.	Bronchitis	6.00	3.50	1.25	.....	0.0066	0.120	0.190	1.00
Mr. G.	Asthma	6.08	4.08	1.00	0.071	0.0099	0.120	0.230	0.72
Mr. Gr.	Bronchitis	6.40	3.30	1.55	0.062	.....	0.056	0.110	0.62
Normal L.	Normal	6.50	5.00	0.75	0.050	.....	0.100	0.140	0.38
Normal L.	Normal	6.50	4.00	1.25	0.036	.....	0.115	0.056	0.18
Mrs. B.	Asthma	6.50	2.70	1.95	0.052	0.013	0.110	0.110	1.10
Mrs. B.	Asthma	7.00	2.52	2.24	.....	0.010	0.210	0.180	1.10
Miss L.	Asthma	7.15	3.95	1.60	0.056	0.0066	0.130	0.220	0.33
Mr. G.	Asthma	7.30	4.92	1.19	0.050	.....	0.157	0.140	0.60
Miss L.	Asthma	7.50	3.00	2.25	0.056	0.0066	0.140	0.240	1.00
Mr. Gr.	Bronchitis	7.50	4.20	1.65	0.056	0.0066	0.070	0.180	0.71
Normal B.	Brain abscess	8.00	5.50	1.25	.....	.....	0.112	0.126	0.58
Normal Br.	Carcinoma	8.00	5.00	1.50	0.050	0.0066	0.110	0.090	0.30
Mr. R.	.....	8.40	5.20	1.60	0.056	0.0066	0.042	0.120	0.50
Mr. R.	.....	8.40	5.72	1.34	0.056	.....	0.070	0.120	0.58
Normal B.	Brain abscess	8.50	5.50	1.50	0.056	0.0060	0.070	0.084	0.74
Mrs. B.	Asthma	8.50	5.00	1.75	0.033	0.010	0.200	0.200	1.20
Mr. G.	Asthma	8.50	5.00	1.75	0.050	0.011	0.10	0.160	0.33
Mr. Gr.	Bronchitis	9.20	5.20	2.50	.....	0.0066	0.12	0.140	0.88
Mr. G.	Asthma	9.00	4.50	2.25	0.071	0.0099	0.120	0.090	0.72
Normal B.	Brain abscess	9.50	5.50	2.00	.....	0.0066	0.084	0.070	0.58
Mr. A.	Bronchitis	10.00	6.50	1.75	.....	.....	0.200	0.190	0.88
Mr. G.	Asthma	10.00	6.00	2.00	0.060	0.0099	0.120	9.240	0.31
Normal L.	Normal	11.00	6.50	2.25	0.056	0.0066	0.120	0.256	0.80
Mr. Gr.	Bronchitis	11.00	6.50	2.25	0.056	0.0080	0.070	0.180	0.71
Mr. Gr.	Bronchitis	12.00	6.00	3.00	.....	.....	0.200	0.250	0.88
Mr. A.	Bronchitis	12.00	7.00	2.50	.....	0.0066	0.200	0.350	0.88
Mr. Gr.	Bronchitis	12.00	6.50	2.75	0.064	0.0099	.....	0.140	1.20
Miss L.	Asthma	12.00	8.50	1.75	0.071	0.0066	0.022	0.240	0.72

TABLE 3.—Measurements in Millimeters of Bronchi and Bronchioli. Infants

Name	Diagnosis	Outside Diameter	Inside Diameter	Wall Thickness	Epithelial Thickness	Basement Membrane Thickness	Sub-Epithelial Thickness	Muscle Thickness	Gland Diameter
Infant A.....	Asthma.....	0.38	0.18	0.10	0.016	.....	.....	0.007	....
Infant N.....	Enteritis.....	0.38	0.20	0.09	0.013	.....	0.007	0.010	....
Infant N.....	Enteritis.....	0.50	0.38	0.06	0.016	.....	0.013	0.010	....
Infant A.....	Asthma.....	0.66	0.36	0.15	0.033	.....	0.070	0.056	....
Infant N.....	Enteritis.....	0.72	0.46	0.13	0.026	.....	0.016	0.013	....
Infant A.....	Asthma.....	0.92	0.62	0.15	.....	.....	0.019	0.010	....
Infant N.....	Enteritis.....	0.94	0.50	0.22	0.040	.....	0.020	0.017	....
Infant A.....	Asthma.....	1.00	0.46	0.27	.....	.....	0.016	0.016	....
Infant N.....	Enteritis.....	1.18	0.86	0.18	0.050	.....	0.033	0.017	....
Infant A.....	Asthma.....	1.40	1.00	0.20	.....	.....	0.028	0.042	....
Infant A.....	Asthma.....	1.40	0.50	0.45	0.036	.....	0.033	0.016	....
Infant N.....	Enteritis.....	1.54	0.86	0.34	0.050	.....	0.033	0.017	....
Infant A.....	Asthma.....	1.60	0.88	0.36	.....	.....	0.033	0.020	0.20
Infant N.....	Enteritis.....	1.80	1.00	0.40	0.050	.....	0.025	0.025	....
Infant N.....	Enetritis.....	1.80	1.00	0.40	0.050	.....	0.027	0.020	....
Infant A.....	Asthma.....	2.20	1.20	0.50	.....	.....	0.066	0.033	0.20
Infant A.....	Asthma.....	2.20	1.00	0.60	0.040	.....	0.070	0.024	0.36
Infant A.....	Asthma.....	2.20	1.40	0.40	.....	.....	0.070	0.042	....
Infant A.....	Asthma.....	2.40	1.10	0.65	.....	.....	0.084	0.042	0.22
Infant A.....	Asthma.....	2.40	1.60	0.40	0.039	.....	0.10	0.023	0.20
Infant N.....	Enteritis.....	2.40	1.56	0.42	0.042	.....	0.042	0.023	0.14
Infant N.....	Enteritis.....	2.56	1.56	0.50	0.042	.....	0.056	0.042	0.28
Infant A.....	Asthma.....	2.60	1.3	0.65	0.033	.....	0.084	0.042	0.42
Infant A.....	Asthma.....	2.64	1.36	0.64	0.033	.....	0.084	0.019	0.36
Infant N.....	Enteritis.....	2.68	1.54	0.57	0.040	.....	0.013	0.013	0.28
Infant A.....	Asthma.....	3.00	1.8	0.60	.....	.....	0.046	0.026	0.42
Infant A.....	Asthma.....	3.40	1.4	1.00	0.029	0.066	0.157	0.042	0.30
Infant A.....	Asthma.....	4.50	2.4	1.05	0.026	.....	0.140	0.10	0.70
Infant N.....	Enteritis.....	5.50	3.5	1.00	0.013	0.0066	0.084	0.146	0.30
Infant A.....	Asthma.....	5.60	2.40	1.60	0.033	0.0066	0.142	0.10	0.72
Infant A.....	Asthma.....	6.50	2.50	2.00	0.046	0.0066	0.10	0.056	0.42
Infant A.....	Asthma.....	7.50	3.50	2.00	0.042	.....	0.070	0.084	0.58
Infant N.....	Enteritis.....	7.50	4.50	1.50	0.036	.....	0.070	0.120	0.58

Figure 15 shows graphically the differences in wall thickness in the asthmatic and nonasthmatic subjects. Figures 16 and 17 show graphically the differences in the subepithelial layer and the muscle bundle thickness in the same groups of subjects. The increase in the wall thickness in asthmatics is accounted for only in part by the increased size of the subepithelial layer and of the muscle bundles. Measurements show, however, that the mucous glands in most of our asthmatic subjects are considerably enlarged, and as this gland system is present inside, outside and between the edges of the cartilaginous plaques, no adequate system of measurement could be devised to determine the actual increase due to gland changes. We recognize also the change produced by hyperemia in the tissues between the cartilages and muscle bundles, but this change is difficult to determine by measurements because of the influence of glandular changes. The tubes with an outside diameter of less than 2 mm. show in the graphs only a slight variation in thickness; the asthmatic group showing somewhat smaller measurements probably due to the influence of emphysema. The thickness of epithelium, subepithelial layer and muscle bundles in

divisions of the tubes below the bronchioli are practically the same in the two groups.

A great deal of caution must be observed in the interpretation of epithelial fold formation as evidence of abnormal bronchial contraction, as deep folds are frequently found postmortem in apparently normal bronchi and bronchioli much like the folding of the intima in arteries.

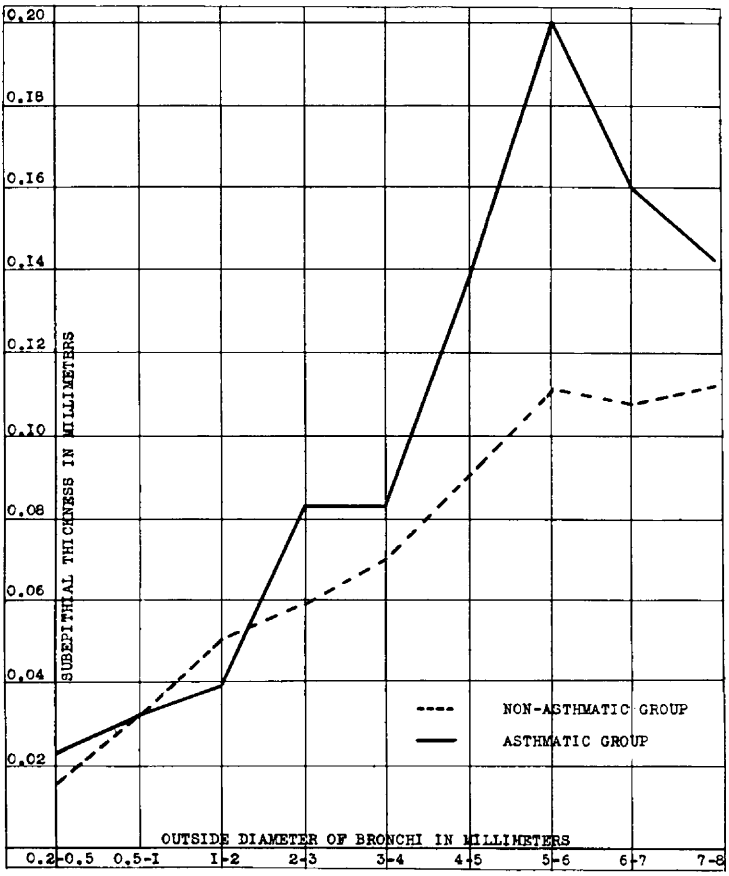

Fig. 16.—Graphs showing comparison of subepithelial thickness.

We have examined the bronchi and bronchioli of many persons who died of various disorders and have gained the impression that the epithelial folding, when present in asthmatics, is of a greater degree than that found in nonasthmatic (Cases 2 and 4). The amount of variation is of about the same degree as that found in the normal and in the anaphylactic guinea-pig lung. Pictures like those shown in Figures 18 and 19 are not usually seen in the lungs of normal guinea-pigs when the animal is killed by a stroke on the head. It is just such

pictures, in addition to the theraputic (inhibitive) effect of epinephrin and atropin, which form the chief evidence for the bronchospastic origin of the acute emphysema of the anaphylactic shock in the guinea-pig. While asthma is a chronic condition and is frequently accompanied by varying degrees of emphysema, the acute paroxysmal attack is the

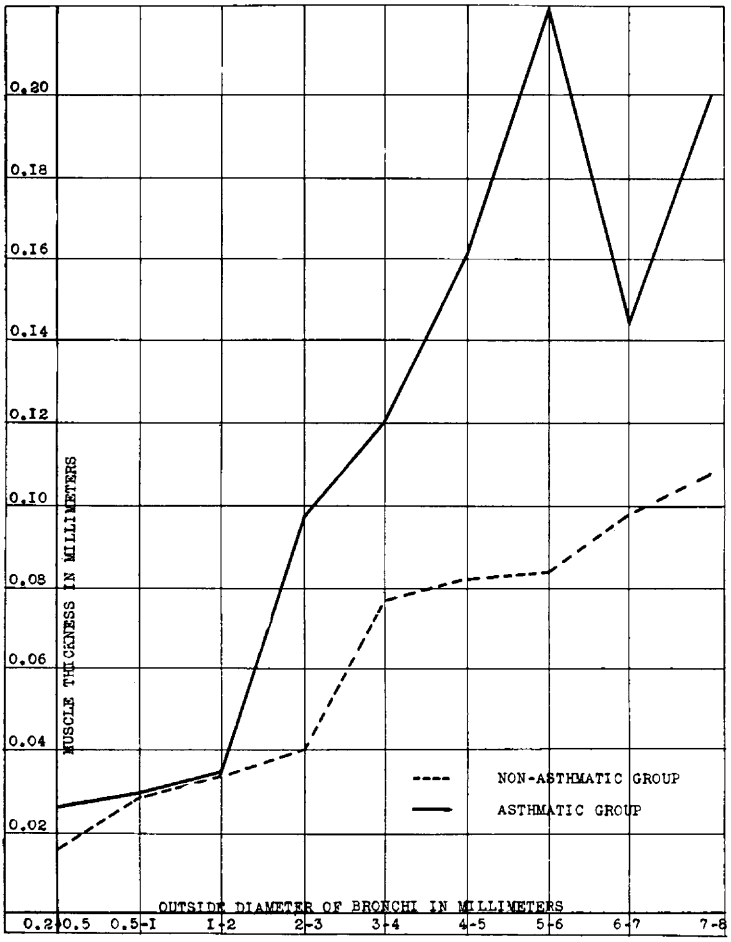

Fig. 17.—Graphs showing comparison of muscle thickness.

main characteristic symptom of the disease, and when associated with an acute stage of emphysema it forms the equivalent to the anaphylactic shock. In three of our cases (Cases 2, 3 and 4) the lumina of many small bronchi and bronchioli are almost occluded by folded epithelium (Plate 2, A and B; Fig. 9). The marked folding of the epithelium in our other cases is present but is not so striking as in the three cases cited.

TABLE 4.—General Summary of Clinical Data of All Cases.

Case	Reported by	Date	Age	Sex *	Occupation	Duration	Heredity	Associated Disorders	Cause of Death
1	v. Leyden	1886	40	♀	.....	From childhood	Not reported	.....	Died during an attack
2	Berkart	1889	37	♀	.....	14 yrs.	Not reported	.....	Died during an attack
3	E. Schmidt	1892	49	♀	Waitress	2-3 wks.	Not reported	Carcinoma in mediastinum; articular rheumatism	Died during an attack
4	A. Fraenkel	1898	63	♂	Carpenter	9-10 mos.	Not reported	Rheumatism; gout; bronchial catarrh (3 yrs.)	Died during an attack
5	A. Fraenkel	1900	48	♂	Not reported	At least 20 mos.	Not reported	.....	Died during an attack
6	Jezierskl	1905	63	♂	Gardener	Probably about 4 yrs.	Father had asthma	Pneumonia	Pneumonia
7	Jezierski	1905	46	♀	Silk-weaver	12 yrs.	Not reported	.....	Died during an attack
8	Ellis	1908	27	♂	Coachman	At least 1 yr.	Not reported	Tachycardia	Died during an attack
9	Mönckeberg	1909	29	♂	Mason	3 yrs.	Not reported	Pneumonia at 12 and 18; psoriasis; anasarca	Died during an attack
10	H. Heizer	1911	2	..	.....	After 9th month	Negative	Eczema	Died during an attack
11	Tichmeneff	1913	29	♀	College student	From childhood	Not reported	Croup; nasal catarrh	Duodenal hemorrhage
12	Marchand	1915	53	♀	.....	23 yrs.	Mother had asthma and bronchitis	Bronchitis since 17th year	Died during an attack
13	Marchand	1915	45	♀	.....	At least 1 yr.	Not reported	.....	Died during an attack
14	Marchand	1918	48	♂	Chemical worker	2 yrs.	Aunt had asthma	.....	Died during an attack
15	Kamchorn and Ellis	1921	52	♂	Actor and fishmonger	From childhood	Father, father's mother, 1 uncle, 1 aunt and 1 child had asthma	.....	Heart failure
16	Huber and Koessler	1922	55	♀	Musician, housewife	5 yrs.	Negative	Bronchitis and coryza	Suicide by drowning
17	Huber and Koessler	1922	55	♂	Real estate	6 yrs.	Mother, 2 sisters, 1 brother and 1 child had asthma	Bronchitis	Died during an attack
18	Huber and Koessler	1922	17	♀	.....	From childhood	Negative	.....	Pericarditis and peritonitis
19	Huber and Koessler	1922	29	♂	Soldier	19 yrs.	Mother had asthma	Head colds	Fatal anaphylaxis
20	Huber and Koessler	1922	32	♂	Car-repairer	From childhood	Negative	.....	Abscess of lung; pneumonia
21	Huber and Koessler	1922	15 mo.	♀	.....	5 mos.	Negative	Eczema; undernourished	Died during an attack

* In this column, ♂ indicates male, and ♀ female.

The increased thickness of the muscle layer of the bronchi in all of the cases reported is apparent from our measurements. The muscular tissue is well developed, not only in the middle sized and small bronchi but even in the bronchioli. This increase in the size of the smooth muscles surrounding the bronchi may be due to a true increase in the size and quantity of the muscle cells, therefore a true hypertrophy, or it may be due to an increased contraction of the muscle. Increased contraction of a smooth muscle implies with few exceptions [24] increased muscular tonus and the increased thickness of a smooth muscle due

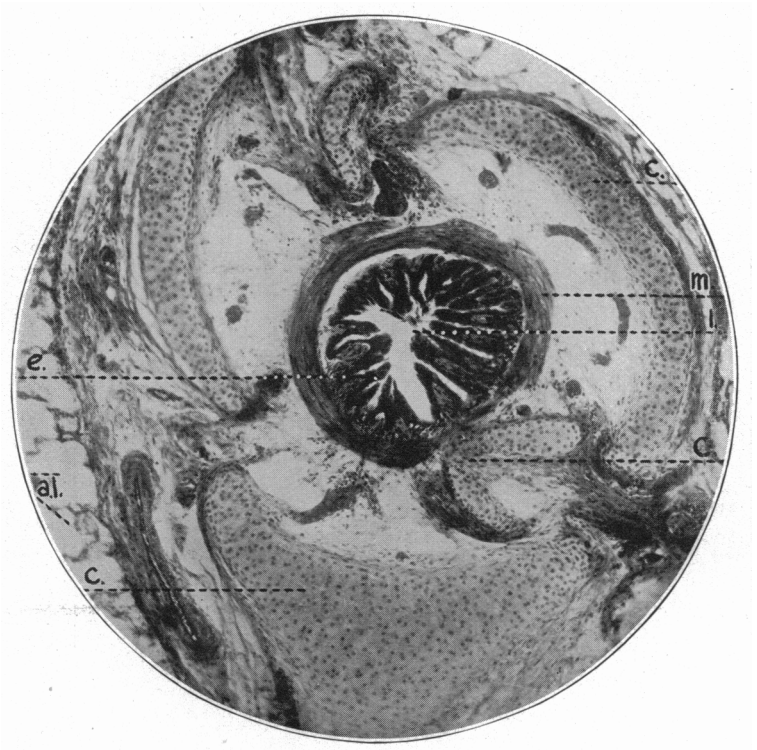

Fig. 18.—Guinea-pig. Fatal horse serum anaphylaxis. Large bronchus. Cross section. Epithelium deeply folded and almost obliterating the lumen. Muscle layer forms a distinct layer. There are no glands. l = lumen; e = epithelium; m = muscle; c = cartilage; al = alveoli. Magnification, 70 diameters.

to contraction is the morphological expression of hypertonus. These factors—hypertonus, repeated contraction, and hypertrophy are closely and functionally related and probably all three are involved in the production of the increased thickness of the muscle tissue in the bronchi of the asthmatic.

24. Bayliss: General Physiology, p. 538.

The deductions which are permissible from the data obtained by than 2 mm. outside diameter is greater in the asthmatic group. (2) these measurements are: (1) The wall thickness of tubes of more This difference is due to increased thickness of the subepithelial layer, of the muscle bundles and of the tissues outside the muscle bundles.

TISSUE EOSINOPHILIA IN BRONCHIAL ASTHMA

Of the cellular elements found in the bronchial secretory system and its product, the sputum, the most interesting are the eosinophil

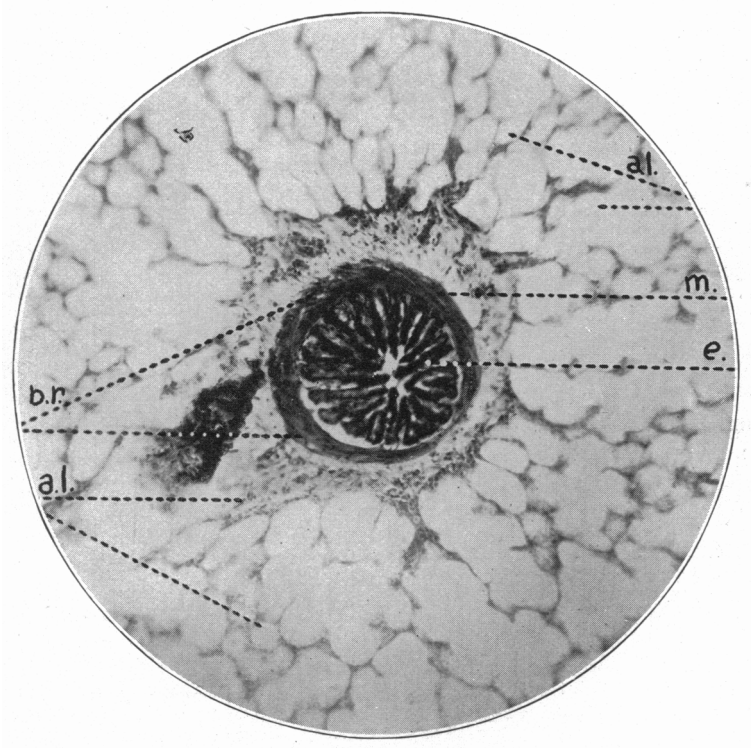

Fig. 19.—Guinea-pig. Fatal horse serum anaphylaxis. Bronchiole. Cross section. Lumen obliterated by folded epithelium. *e* = epithelium; *m* = muscle; *al* = alveoli. Magnification, 90 diameters.

cells. Their numerical increase in the circulating blood and their predominance in the sputum during the attack have been considered for many years a characteristic clinical symptom of asthma. Since the diagnostic value of this finding has been questioned, various observers reporting that in other diseases of the lungs and bronchi an increased number of eosinophils is present in the sputum,[25] we wish to state that

25. Von Hoesslin, H.: Das Sputum, Berlin, Springer, 1921, pp. 114-120.

TABLE 5—General Summary—

Case	Macroscopic Description	Content of Lumen of Bronchi	Epithelium	Basement Membrane	Subepithelial Layer
1 v. Leyden (1886)	Marked vesicular emphysema; bronchial mucosa reddened; small bronchi partially occluded by mucous masses	Small bronchi partially occluded; Mucus adherent to epithelium	.....	.....	.....
2 Berkart (1889)	Right apical adhesions; lungs emphysematous; masses almost occlude right main bronchus and one branch of left; smaller bronchi dilated and partially occluded; heart dilated and hypertrophic; moderate ascites	Masses composed of degenerating cylindrical epithelium; small bronchi contain detritus and fragments of Charcot-Leyden's crystals	Almost all denuded; one deep ulcer extends almost to cartilage	.....	.....
3 Schmidt (1892)	Tumor masses in left side of neck and extending into anterior mediastinum and upper lobes of both lungs; bilateral apical adhesions; lungs contain much blood; small bronchi contain masses of mucus	Many bronchi almost occluded by masses containing cells; these masses form spirals	Well retained	.....	Much dense C. T.; infiltrated by round cells
4 Fraenkel (1898)	Right apical adhesions; lungs emphysematous; nodular hepatization in lower lobe; bronchi contain masses which can be pulled out thread-like; walls of bronchi thickened; dilation of right and left ventricles	Mucous masses contain twisted threads, and epithelial cells which are greatly elongated; no eosinophils	High grade desquamation	.....	Thickened
5 Fraenkel (1900)	Middle-sized and small bronchi occluded by screw-shaped clots	Mucous masses completely occluding many bronchi and made up of layers containing elongated epithelium and eosinophil cells	Cells in small bronchi greatly elongated	.....	Groups of leukocytic cells; many eosinophil cells
6 Jezierski (1905)	Right lung pneumonic; bronchi of left dilated; mucosa hyperemic	Middle-sized and small bronchi of left partly occluded by mucus containing desquamated epithelium, neutrophils, eosinophils and lymphocytes	Fairly retained and infiltrated by round cells	.....	Infiltrated by round cells; elastic tissue increased; many engorged blood vessels
7 Jezierski (1905)	Fluid in both pleural cavities; left lung emphysematous	Small bronchi of left occluded by mucous plugs containing elongated epithelial cells, round cells, eosinophil cells	Mostly intact	Interrupted by accumulations of round cells	Contains many round cells
8 Ellis (1908)	Lungs emphysematous; right adhesive pleuritis; many bronchi occluded by greenish colored mucus	Most of smaller bronchi occluded by mucous plugs containing some degenerated epithelial cells, neutrophils and a few eosinophils; mucous plugs show spiral arrangement	Mostly intact in smaller bronchi; desquamated in larger	Hyalinized in the larger bronchi	Contains many polynuclear cells, some being eosinophil cells
9 Mönckeberg (1909)	Ascites; anasarca; bilateral adhesive pleuritis; mediastinal and peribronchial lymph glands enlarged; lungs air-filled; walls of bronchi thickened; lumen of most of smaller bronchi occluded by mucus; right heart enlarged, aorta narrowed	Small bronchioles empty; larger bronchioles occluded by mucous plugs containing desquamated epithelial cells and round cells; mucus shows spiral arrangement; Charcot-Leyden's crystals in larger bronchi	Mostly intact	Hyalinized and thickened in larger bronchi	Infiltrated by round cells and many eosinophil cells; contains diverticula-like protrusions of epithelium
10 H. Heizer (1911)	Lungs distended; many bronchi almost occluded by mucus; right ventricle thickened	Contains leukocytes and epithelium	.....	.....	Thickened by infiltrating cells and distended capillaries
11 Tichmeneff (1913)	500 c.c. fluid in left pleural cavity; left adhesive pleuritis; cavity in left upper lobe; mucopus in bronchi; ulcer in duodenum	Mucus containing round cells and leukocytes in many bronchi	Greatly elongated; hyperplasia	.....	Thickened; marked round cell infiltration
12 Marchand (1915)	Lungs emphysematous; occlusion of many small bronchi; slight hypertrophy of right heart	Plugs in bronchi composed of epithelium, round cells and crystals	Contains many goblet cells; infiltrated by cells	.....	Infiltrated by round cells; some eosinophil cells

Muscle	Mucous Glands	Fibrocartilaginous Layer	Blood Vessels	Nerves	Alveoli	Lymph Glands	Other Tissue
.....	.....	.....	.....	.....	Some dilated; most filled by a granular material containing many large cells		
.....	Mucous glands small and atrophic	.....	.....	.....	Emphysematous; some contain a fibrinous exudate		
.....	Mucous glands in active secretion	.....	Periarteritis obliterans in vessels of upper lobe	.....	Some dilated and some filled by mucus; no spirals; bronchopneumonic areas about some bronchi		
.....	.....	Thickened; infiltrated by round cells	Extremely dilated in mucosa of bronchi	.....	Some dilated, some contain blood	Large and pigmented	
Eosinophil cells between muscle bundles	Marked cellular infiltration; many eosinophil cells in glands	.....	Bronchial capillaries markedly distended	.....	Patchy emphysema; alveoli contain a few eosinophil cells		
.....	.....	Contains many round cells	Many newformed engorged blood vessels in walls of bronchi	Phrenic nerve contains degenerating fibers	.....	Numerous groups of round cells in wall of bronchi	
.....	.....	Contains many round cells	Surrounded in many cases by round cells	.....	No change	Bronchial glands anthracotic	
Not changed	Contains many mononuclear cells, some being eosinophil cells	.....	Vessels in bronchial well engorged by blood	.....	Many distended; some contain many eosinophil cells	.....	Not changed
Increased in lobular septae; increased in bronchi and larger bronchioles	Large	Contains many mononuclear and polynuclear cells	Pulmonary artery sclerotic; pulmonary veins thickened	.....	Some occluded by granular precipitate	Prominent lymphoid nodules in larger bronchi	
.....	Greatly enlarged and filled by mucus	.....	Distended	.....	Some distended	All enlarged	
Hypertrophied; infiltrated by round cells	Enlarged; infiltrated by round cells	.....	.....	.....	Some contain leukocytes		
Infiltrated by round cells	Contain many round cells	.....	.....	.....	.....	Distinct nodes formed in walls of middle-sized and smaller bronchi	

TABLE 5—General Summary—

Case	Macroscopic Description	Content of Lumen of Bronchi	Epithelium	Basement Membrane	Subepithelial Layer
13 Marchand (1915)	Pulmonary emphysema; some bronchi almost occluded by exudate; bronchial mucosa swollen and reddish; peribronchial lymph glands enlarged	Arranged in layers and contains many polynuclear leukocytes; a part contain strands of fibrin	Well retained; a few goblet cells	Thickened and hyalinized	Contains many eosinophil cells, some lymphoid cells, and a few polynuclear leukocytes
14 Marchand (1918)	Lungs distended; smaller bronchi occluded by yellowish masses; left antrum of Highmore filled by secretion; walls of right and left ventricle thickened	Mucous masses in bronchi contain leukocytes, round cells and eosinophils; mucus forms spirals in smaller bronchi	.....	.....	Capillaries engorged; infiltrated by cells; many eosinophil cells
15 Kamchorn and Ellis (1921)	Left adhesive pleuritis; all other serous cavities contain fluid; left lung collapsed; right upper and middle lobes distended; tenacious mucus in middle-sized bronchi; hypertrophy of right ventricle	Mucus contains epithelial cells, leukocytes and a few eosinophil cells and is arranged in spirals	Mostly desquamated	.....	Capillaries engorged; infiltrated by mononuclear cells
16 Huber and Koessler (1922)	Coroner's inquest; report not available; lungs distended; most bronchi, except larger, occluded by mucous masses	Mucous masses in bronchi contain desquamated epithelium, round cells, neutrophil and eosinophil leukocytes; mucus in layers and twisted; some bronchioles contain many eosinophil cells	Partially desquamated	Thick and hyalinized	Infiltrated by many round cells and a few eosinophil cells
17 Huber and Koessler (1922)	Emphysema of lungs; bronchi contain a small amount of mucus	Mucus in small bronchi is scanty and contains only a few epithelial cells	Mostly intact	Not conspicuous	Not uniformly thickened; contains many dilated capillaries
18 Huber and Koessler (1922)	Peritonitis, right adhesive pleuritis, pericarditis; small amount of mucus in smaller bronchi	Small amount of mucus containing a few epithelial cells and a few eosinophils	Mostly intact; goblet cells numerous in large bronchi	Thick and hyalinized	Infiltrated moderately by cells; some eosinophils
19 Huber and Koessler (1922)	Right fibrous pleuritis; marked emphysema; cut surface of lungs dry	Smaller bronchi contain a granular precipitate	Mostly intact; many goblet cells	Thick and hyalinized	Cellular infiltration marked
20 Huber and Koessler (1922)	Abscess of left lung; pulmonary emphysema; pneumonia of right lung; bronchial walls thickened; hypertrophy of right heart	Contains fragments of epithelium and neutrophil leukocytes	Partially desquamated	Indistinct	Markedly infiltrated by mononuclear cells
21 Huber and Koessler (1922)	Moderate emphysema of both lungs; small firm nodules in both lungs; some bronchi occluded by mucus; lymph glands large	Contains fragments of epithelium, neutrophil and eosinophil cells	Mostly intact; some goblet cells	Not conspicuous	Contains a few round cells and eosinophil cells

on the basis of the examination of several hundred patients suffering from true bronchial asthma and other respiratory disease associated with dyspnea, we can say that the coincidence of sputum and blood eosinophilia in the same individual seems to be a pathognomonic symptom of the asthmatic state. Exceptions to this statement are pulmonary distomatosis and hydatid disease.

In our work we are mainly concerned with the local accumulation of eosinophil cells in the tissues of the bronchi a localization which has

—OF PATHOLOGY OF ALL CASES—(*Continued*)

Muscle	Mucous Glands	Fibrocartilaginous Layer	Blood Vessels	Nerves	Alveoli	Lymph Glands	Other Tissue
Tissue between muscle bundles contains round cells and some eosinophil cells	Large cells filled by mucus; gland duct epithelium contains many goblet cells	Contains many lymphoid cells	Distended and many contain numerous polynuclear neutrophils	.....	Some areas completely consolidated	Some small lymph nodules contain a few eosinophil cells	
Hypertrophied	Enlarged	.....	.....	.....	No change	One contains a small tubercle	
No change	.....	.....	Sclerotic				
Thickened	Enlarged; structure altered by many foci of round cells; infiltrated by eosinophil cells	Some cartilages calcified	No change	No changes	Irregular in size	Anthracotic	
Thickened	Small; contain many foci of round cells and areas of areolar tissue; ducts form distinct ampullae	No change	Walls of bronchial arteries thickened	No changes	Irregular in size; some contain a granular precipitate	Anthracotic	No changes
Thickened; forms a distinct ring in some bronchioles	Large and containing many foci of round cells; gland ducts form distinct ampullae	Ossified cartilages	Walls of bronchial arteries moderately thickened	No changes	Vary in size	No changes	No changes
Not prominent	Small and densely infiltrated by round cells	Calcified and ossified cartilages	Walls of bronchial arteries markedly thickened	No changes	Patchy obliteration of alveoli; these areas contain hyperplastic epithelium	No changes	Spleen contains many eosinophil cells
Structure altered by round cell infiltration	Small; ascini separated and composed of compact masses of cells	Calcified areas in cartilages	Walls of bronchial arteries thickened	No changes	Obliterated in patches by pneumonic foci	No changes	No changes
Eosinophil cells between muscle bundles	Enlarged; contain foci of round cells and eosinophil cells	Many eosinophil cells between cartilages and muscle layer	Walls of bronchial arteries thick	No changes	Some areas of absorption atelectasis	Contain eosinophil cells	Spleen and thymus contain many eosinophil cells

been previously observed by others. This tissue eosinophilia is a phenomenon of far-reaching bearing, which it seems to us, if completely understood, would undoubtedly greatly elucidate the pathogenesis of asthma.

In the normal adult the bone marrow is the chief place of formation of the eosinophil cells (Ehrlich). This conception is substantiated by the frequency with which mitotic cell divisions of these cells are found in this locality. Additional evidence is furnished by the increased

number of these cells in the bone marrow in cases of high blood eosinophilia.[26]

From this viewpoint any increase of the eosinophils in the circulating blood and in the tissues is to be considered as a (protective?) reaction of the leukopoietic centers of the bone marrow to the stimulus of an unknown toxic substance. In bronchial asthma this eosinophilotactic substance is either actually formed in the tissues of the respiratory system or it has, wherever formed in the organism or wherever introduced to it from without, an elective affinity for this system. Such an elective organ localization of chemical substances is not to be considered as a special postulate for this problem but constitutes the basis of most pharmacodynamic actions.

There are, however, many histologists who consider the local eosinophilia in the bronchi as a true primary autochthonous tissue eosinophilia. They believe that the eosinophil cells are formed in the bronchial tissue through myelocytic metaplasia from the perivascular connective tissue cells over the "lymphocyte." The secondary blood eosinophilia may be due, then, to the passage of the eosinophil cells from the bronchial tissues through the bronchial capillaries into the general circulation, or it may be due to a simultaneous stimulation of both the pulmonic perivascular tissues and the bone marrow. The faculty of forming new myelocytic cells in the adult organism we usually concede only to those organs which in the development of the embryo possess the property of leukopoiesis, i. e., the bone marrow, liver, spleen, lymph glands, kidneys and thymus. In certain pathologic conditions (e. g., leukemia), and others associated with severe infections and toxemias (e. g., congenital syphilis) the remnant foci of the embryonic leukopoiesis in these organs are stimulated to proliferation and renewed activity in the direction of their original function. The difficulty that such preexisting myeloid tissue is not known in the bronchial mucosa and submucosa is removed by the assumption that all perivascular adventitial connective tissue is a latent hematopoietic and leukoblastic organ. This conception, based on the early studies of Virchow and later studies of Marchand on the cellular products of inflammation and on the perivascular lymphoma formation of Ribbert, has been especially adopted by Pappenheim, Weidenreich and by G. Schwarz.

As far as the bronchial mucosa in asthma is concerned, the idea of the autochthonous local eosinophilia is mainly based (1) on the occurrence of mononuclear eosinophil cells in the sputum and the bronchial tissue; (2) on the complete absence of such unicellular elements in the circulating blood, and (3) on the enormous number of the eosinophil

26. Opie, E.: Cells with Eosinophil Granulations, Am. J. M. Sc. **127**:217, 477, 988, 1904.

cells, polymorphonuclear as well as mononuclear, in the tissue, far too many, as is argued, to have been accumulated from the blood even if it showed a considerable eosinophilia.

The last quantitative argument might be first considered. It is well known that a very marked local tissue eosinophilia does frequently exist without eosinophilia of the blood. This is very often to be observed, for instance, in the periphery of malignant tumors, and then—a rarer incidence—in the pleura and exudate of eosinophilic pleuritis. It is just this discrepancy of the normal amount of eosinophils in the blood and of their abundance in the tissue which is taken as one proof for their local genesis. But it could be shown by a simple calculation that in bronchial asthma enough eosinophil cells can be removed from blood with a normal content of these cells to account even for their most extensive accumulation in the respiratory tissue. Thus Heineke and Deutschmann [27] observed during an asthmatic attack a decrease of the eosinophilic polymorphonuclear cells in the blood from 2.1 to 0.4 per cent. Calculated for 1 liter of blood, this means that 126,000,000 eosinophil cells have disappeared from the circulation and could have accumulated by chemotactic emigration in the tissues. J. G. Taylor, in his studies in leukemia, has made a similar calculation.[28]

What now regarding the occurrence of mononuclear eosinophilic cells ("myelocytes") in the tissues of the asthmatic patient?

Our material furnished us an unusual opportunity for studying this special phase of the question. The tissue eosinophilia was very marked in the first case, bacterial asthma (asthmatic bronchitis), in the fourth case, anaphylactic horse serum asthma, and excessively so in the sixth case—food asthma in an infant. The accumulation of eosinophil cells in the wall of and in the tissues about some of the bronchial capillaries is very striking but in the same section of the same bronchus the walls of and the tissues about many capillaries are free of eosinophil cells. Again, the location of the eosinophil cells varied greatly; in Case 6 they were most numerous between the muscle tissue and the cartilages, while in the other cases they were most numerous in the subepithelial layer. In some cases (Cases 1 and 6) the mucous glands contain many of these cells. In the wall of a blood filled bronchial vein (Case 6), which lies between a cartilage plaque and a muscle bundle, there are three migrating eosinophil cells, each of which lies between adjoining endothelial lining cells and partly inside the vessel. Immediately surrounding the vessel there are many polymorphonuclear eosinophil cells and a few small round cells. Many

27. Heineke und Deutschmann: Das Verhalten der weissen Blutzellen während des Asthmaanfalles, München. med. Wchnschr. **53**:797, 1906.

28. Taylor, J. G.: Studies in Leukemia, Contribution from the William Pepper Laboratory of Clinical Medicine, Philadelphia, 1900.

similar pictures are seen on further careful study of these tissues. The sinuses of the bronchial lymph glands (Case 6) contain many polymorphonuclear eosinophil cells but the sinuses of the mesenteric lymph glands contain only an occasional eosinophil cell. The spleen (Cases 4 and 6) shows very many eosinophil cells, almost all of which are polymorphonuclear.

Most of the eosinophil cells are polymorphonuclear cells with usually two or three nuclear fragments. On closer focusing and study, fine chromatin threads can be seen which connect the parts of the nucleus with each other. There are many cells which on first inspection give one the impression of possessing a single nucleus, but most of these, when studied in different planes of depth, with powerful magnification, are seen to have nuclei with two or three fragments. There remain, however, a few eosinophil mononuclear cells, whose nucleus cannot be separated by the eye in such a manner (Plate 3, C). These mononuclear eosinophilic cells are plainly not larger than the polymorphonuclear elements and are of the same type. Their nucleus is small, opaque, more deeply stained than in the polymorphonuclear cells immediately surrounding them, and its chromatin is very homogenous and pyknotic. The protoplasm surrounding this deeply stained nucleus is completely filled with acidophilic granules and no cells were observed where a transformation of granulopoiesis was suggested by a slightly basophilic stained protoplasm containing only a few eosinophilic granules. We could find no cells, however carefully we searched our preparations, which suggested a mixture of basophilic granulations with the eosinophilic as is found frequently in young alpha myelocytes. There was nothing to suggest transitional or intermediate stages between the many "lymphocytes" ("myeloic lymphoidocytes") and acidophilic cells. Nor were we successful in demonstrating any eosinophilic cells which showed evidence of mitotic division. There were no immature embryonic cell forms such as erythroblasts, promyelocytes or meta myelocytes or megakaryocytes. One would expect to find some of these cells if true myeloic metaplasia was taking place.

On the basis of these studies we reach the conclusion that these mononuclear eosinophil cells are not alpha myelocytes but degenerative forms of polymorphonuclear eosinophil cells whose nuclear substance has undergone a regressive metamorphosis. This conclusion became most suggestive when we studied the thymus in Case 6. Here we were able to find many large mononuclear eosinophilic cells with a loose structured, more pale nucleus, encircled by a wide protoplasm containing abundant eosinophilic granulations of varying size, i. e., true eosinophilic myelocytes. The presence of such cells in the thymus, of a

2-year-old child is a normal occurrence.[29] Autochthonous tissue eosinophilia in the thymus can be accepted as proved, for this organ contains active myeloid tissue and is, therefore, capable of metaplastic activation. Mitotic cell divisions, erythroblasts, eosinophilic as well as neutrophilic myelocytes have repeatedly been described in this organ.

Whether the mononuclear eosinophilic cells in the bronchial mucosa, as Schwarz [30] and also Marchand believe, are derived from the binuclear polymorphonuclear cells through amitotic direct cell division is impossible to decide.

Our studies, therefore, contain little evidence which would prompt us to abandon the view that the local tissue eosinophilia in the bronchial structure is due to emigration of alpha granulocytes from the blood in favor of the theory of their autochthonous ontogenesis from the perivascular tissue and transformation of the histogenous lymphocytes. The chemotactic toxin, fixed (or formed?) by the tissue of the bronchi, exerts simultaneously a stimulus upon the bone marrow in the direction of increased new formation of eosinophilic cells which through the way of the blood reach the bronchial tissue. The question of the nature of this eosinoplastic and eosinotactic toxin is closely allied with the physiologic and pathologic significance of the eosinophilic cells in general. Ehrlich [31] suggested nearly twenty-fve years ago that eosinophils seem to appear especially in such places in the organism at which many cells are destroyed, especially cells of epithelial type (e. g., in carcinomatous tissue). There can be little doubt that certain relations exist between proteolytic digestive processes in the tissues and organs and the accumulation of alpha cells. Eosinophilia appears to be a response, a reaction to a stimulus produced by certain substances derived from the catabolism of proteins. It has been shown that the eosinophils increase markedly in the tissues of the intestinal tract during the process of digestion, but disappear completely in animals that have been starved.[32]

Neusser held that eosinophilia is produced in response to the increased activity of glands supplied by the sympathetic nervous system. Eppinger and Falta,[33] and their co-workers, on the other hand, see in

29. Schaffer, J.: Ueber das Vorkommen von eosinophilen Zellen in der menschlichen Thymus. Zentralbl. f. med. Wissensch., 1891, 401-417. Dudgeon, L. S.: A Contribuion to the Pathology of the Thymus Gland, J. Pathol. & Bacteriol. **10**:173, 1905. Fortescue-Brickdale, T. M.: Observations on the Thymus Gland in Children, Lancet **2**:1029, 1905.

30. Schwarz, E.: Die Lehre von der allgemeinen und örtlichen Eosinophilie, Lubarsch und Ostertag Ergebn. d. allg. Path. **17**: 1913.

31. Ehrlich, P.-Lazarus: Die Anaemie, Nothnagel's spec. Pathol., Ed. 1, 1898, p. 113.

32. Opie: Loc. cit.

33. Bertelli, Falta and Schwerger: Ztschr. f. klin. Med. **71**: 1907. Eppinger, H., and Hess, L.: Die Vagotonie, Berlin, 1910, p. 60.

eosinophilia a symptom of increased vagus tonus. They attempted to show that substances like pilocarpin, pituitary extract and nitrites, which increase the tonus of the autonomous nerves, produce an experimental eosinophilia.[34] Their work, however, could not be corroborated by Schwenker and Schlecht.

The whole problem of blood and tissue eosinophilia, in general, but especially in relation to bronchial asthma, reached an entirely new phase since it has been considered from the point of view of anaphylaxis.

There are some scattered observations in immunologic literature which suggest that blood and serum injections into animals are often followed by a considerable increase in the number of eosinophils in the blood.[35] But the true connection between eosinophilia and the anaphylactic process was first clearly recognized by Schlecht.[36] He had observed previously that serum injections were sometimes associated with a marked increase in eosinophilic cells in the blood and he ascribed this phenomenon to the introduction of the foreign protein. Later he and his collaborators,[37] found that eosinophilia developed regularly on reinjection of sensitized animals. He examined many proteins and their derivatives in this regard and found egg albumin, serum albumin and globulin, and especially, fibrin, efficacious in producing eosinophilia. Peptone acted less promptly and amino-acids (leucin, alanin, phenylalanin, glycin and asparagin) were without action. Schlecht and Schwenker discovered also the eosinophilic infiltration of the bronchi in the lungs of anaphylactic guinea-pigs and in the perivascular tissue in the edema of the Arthus phenomenon. On the basis of this work, eosinophilia is to be considered as a protective reaction of the organism against certain definite decomposition products of heterogenous and even homologous proteins. We are in complete agreement with

34. Schwenker, G., and Schlecht, H.: Ueber den Einfluss sympathico- und autonomotroper Substanzen auf die eosinophilen Zellen, Ztschr. f. klin. Med. **76**:77, 1912. Bertelli, Falta and Schwerger: Ueber die Wechselwirkung der Drüsen mit innerer Sekretion S. Mittheilung über Chemotaxis, 1910, p. 23.

35. Stschastnyi: Histogenese der eosinophilea Granulationen, Beitr. z. path. Anat. u. z. allg. Path. **38**:456, 1905. Schwarz, E.: Loc. cit.,[36] p. 431.

36. Schlecht, H.: Ueber experimentelle Eosinophile u. basophile Leukocytose **27**: Congr. f. inn. Med., 1910. Ueber die Einwirkung von Seruminjectionen auf die Eosinophilen, etc., Deutsch. Arch. f. klin. Med. **2**:308, 1910. Ueber experimentelle Eosinophile nach parenteraler Zufuhr artfremden Eiweisses und über die Beziehungen der Eosinophilie zur Anaphylaxie, Arch. f. exper. Path. **67**:137, 1912. Ueber lokale Eosinophilie beim anaphylactischen Versuche, Verhandl. Congr. f. inn. Med., 1912, p. 416. Ueber allgemeine und locale Eosinophilie bei Ueberempfindlichkeit gegen organische Arsenpraeparate, München. med. Wchnschr. **60**:800, 1913.

37. Schlecht, H., and Schwenker, G.: Ueber lokale Eosinophilie in der Lunge anaphylactischer Meerschweinchen, Arch. f. exper. Path. **68**:163, 1912. Ueber die Beziehungen der Eosinophilie zur Anaphylaxie, Deutsch. Arch. f. klin. Med. **108**:405, 1912.

this point of view and believe that most clinical eosinophilias have to be considered as the reaction of a person in the state of allergy.

Probably the clearest example of protein sensitization in the human is pollen disease.[38] Morphologic studies of the blood of many patients lead us to the conclusion that blood eosinophilia is a constant symptom during the attack. In the months of the year in which the patient is free from hay-fever his eosinophilic cells in the blood are, as a rule, not increased. If the eosinophilia perists outside of the six or eight weeks of the hay-fever season and a few weeks following it, the patient is usually the subject of multiple sensitization, i. e., he is sensitized to other proteins, e. g., horse dander, or he is subject to eczema or urticaria, i. e., he is sensitized to certain food proteins. In the autumnal type of pollen disease due to the pollen of ragweed, sunflower and other compositae, the eosinophilia begins almost immediately on the day when the catarrhal symptoms begin and increases usually progressively until the third week. The asthmatic symptoms, however, usually do not become evident until from twelve to twenty days after the yearly resensitization with pollen has begun.

These clinical data are mentioned here in this connection because they show how the human organism acts in regard to the emigration of eosinophilic cells from the bone marrow into the blood on yearly parenteral introduction of a foreign protein. The eosinophilia of pollen asthma is a reaction of the organism sensitized to pollen protein. For most other types of asthma there exists no difficulty in accepting this point of view; they are cases of special protein sensitization either to food, animal or plant proteins. Less evident is the meaning of eosinophilia in the bacterial type of asthma, the eosinophilic bronchitis. Here the eosinophilic reaction in its relation to protein katabolism and allergy is not at once entirely evident. It is certain that bacterial protein possesses antigenic and anaphylactogenic properties and it would be a simple explanation to assume that the infective organism had sensitized the subject in the same manner as the pollen protein. This is a possibility. But it should be remembered that at least all acute bacterial infections, with the one exception of scarlet fever, are invariably associated with hypo-eosinophilia which, in the convalescence, is followed by hypereosinophilia. Aside from the eosinophilia, the evidence for the assumption that micro-organisms produce asthma through sensitization with their own body substance—the evidence for the existence of a true allergic asthma of bacterial origin—is very meagre. Skin sensitization tests with bacterial antigens made according to Woodehouse from stock cultures, as well as autogenous cultures, grown from

38. Koessler, K. K.: The Specific Treatment of Hay-Fever (Pollen Disease), Billings-Forschheimer Therapeusis of internal Diseases **5**:671-706, 1914.

the bronchial expectoration and including anaerobic as well as aerobic organisms, have proved of very little diagnostic value in our hands. After using them in many hundred instances we have scarcely three or four reactions which we could call positive.[39] Shall we conclude from this failure of obtaining skin reactions to bacterial antigens that all cases of bacterial asthma are in reality cases of true allergic asthma due to sensitization with an undiscovered protein, which we might discover if we would increase the scope of our tests? It is undoubtedly certain that the group of allergic asthmas will steadily increase with improved methods for the preparation of antigens, with increasing their numbers used in the tests and thus detecting new etiologic factors.[40] Yet on the basis of our clinical observations and studies we are led to believe that there remains still a definite group of cases of asthma, between 25 and 30 per cent. of all cases, which are of true bacterial origin. Blood eosinophilia in this group of cases is of exceedingly varying degree; it is sometimes very marked, sometimes slight and may even be absent completely.

The production of an eosinophilia through stimulation of the leukopoetic organs is not restricted to intact proteins of antigenic properties. Lower decomposition products of proteins, as albumoses and peptones, too, have the faculty of producing eosinophilia as well as bronchiolar spasm and arterial hypotonus with capillary stasis, the three cardinal symptoms which constitute the syndrome "asthma."

Bacterial asthma may thus be considered as being due to the products which micro-organisms form by their action on the proteins of the body's own tissues or on the proteins of the food in the intestinal tract. It is a peptone intoxication or amine intoxication (aminosis).

Other peptones and amines, while possessing bronchospastic activity, do not exert any eosinotactic stimulus upon the blood forming organs. The study of the formation of these toxic products (amines) by micro-organisms has been the subject of our investigations for many years. Our evidence for the relation of amines to asthma is, while not conclusive, very suggestive, and will form the subject of a special report. Here, we wish merely to point out that the production of amines of bronchospastic and hypotonic action, of which histamin is the chief representative, is mainly dependent on a particular type of otherwise common species of micro-organisms. Thus, of twenty-nine strains of *B. coli* studied, six were able to form histamin on a synthetic medium and no other chemical reaction, as fermentation of sugars, etc., could be

39. A detailed account of the clinical phases of our work will be published in the near future.

40. Cooke, R. A.: New Biologic Factors in Bronchial Asthma, J. Immunol. **7**:147, 1922.

found which would set this group of colon bacilli aside, except their faculty of decarboxylating amino-acids with the formation of amines.[41]

From our viewpoint, then, eosinophilia, if present, is a very important symptom of bronchial asthma. It is evidence of (1) the allergic type of asthma due to sensitization with proteins of antigenic character, or (2) of an intoxication with higher peptones. If constantly absent it forms, together with other clinical symptoms, strong evidence that the asthma is due to an intoxication with lower peptones or with amines or that the bronchospasm is produced by extraneous factors, pressure on the vagus by tumors or aneurysm (symptomatic asthma).

ABSORPTION ATELECTASIS IN BRONCHIAL ASTHMA

If the passage of gases (air) through a bronchiole or small bronchus is interrupted for some time, either through bronchiolar spasm or through obturation with secreted mucus, the air contained in the alveoli connected with that occluded tube is gradually absorbed by the blood of the pulmonary capillaries and an area of atelectasis is formed. In two of our cases, the infant with food asthma (Case 6) and the adult male (Case 4), who succumbed to an injection of horse-serum, definite areas of this character were shown. In the infant there are two distinct groups of areas scattered rather diffusely and which may be interpreted as representing two stages in the production of areas of absorption atelectasis. In one group of areas, apparently the newer stage, there is an obliteration of the alveoli by an exudate containing only a few cells, chiefly polymorphonuclear neutrophils. In these areas the bronchioles are completely occluded by a mucous exudate. In the other group of areas, apparently the later stage, there is such a complete obliteration of alveoli, that all vestiges of lung structure, except contracted bronchioles, are absent. Both of these areas are sharply defined and are separated from normal appearing alveoli only by the normal amount of fibrous tissue which separates the units of lung tissue in the child. We can think of these areas as representing two distinct end-results of different asthmatic attacks. In one, the newer, the occlusion of a small bronchus cut off temporarily that portion of the lung which connects with it and the exudation resulted; in the other, the older stage, the occlusion of a bronchus or bronchiole, occurred in a previous attack and lasted long enough so that complete organization of the lung connected with it resulted. In the adult (Case 4) we find also areas of lung tissue in which there is complete obliteration of all alveoli. In these areas, which are less sharply defined than in the infant's lung, there is a larger amount of fibrous tissue which surrounds, zonelike, all blood vessels

41. Hanke, M. T., and Koessler, K. K.: Studies on Proteinogenous Amines, XII, J. Biol. Chem. **50**:131, 1922.

and small contracted bronchioles. These areas we interpret as representing old lesions following previous asthmatic attacks. No other lungs, whether normal, asthmatic or nonasthmatic, showed such areas. The presence of absorption atelectasis has heretofore not been observed in bronchial asthma. Pathogenetically it is, like the acute emphysema, the result of the bronchiolar obstruction and represents the ultimate stage of the emphysema in an area of lung tissue in which the normal gaseous exchange through the bronchi has become completely interrupted.

Some authors [42] have attempted to set apart certain forms of paroxysmal dyspnea in children as a new morbid entity, which they call "bronchotetany." This, according to its originator (Lederer), is a symptom complex fundamentally distinct from bronchial asthma, though also due to bronchiolar spasm. The distinction is based first on the clinical observation that bronchotetany is found usually only in children who show some definite symptoms of spasmophilia, such as laryngeal spasm, carpopedal spasms or eclampsia, and second, on the evidence of the pathologic anatomy that all fatal cases of bronchotetany are associated with the formation of areas of atelectasis. For after studying the published reports of twelve postmortem examinations of bronchial asthma, all of which we have cited in our historical review, this investigator reaches the conclusion that "intense bronchospasm leads in asthma only to emphysema, never to the formation of atelectasis; in bronchotetany always to atelectasis." From the clinical description it is not clear to us how the cases cited as bronchotetany differ from true (allergic?) asthma in children. The presence of definite areas of absorption atelectasis in our two cases of bronchial asthma, shows that also the specific pathologic criteria evoked for the existence of this new entity, bronchotetany, do not hold true.

SUMMARY

The pathologic histologic examination of the finer structure of the bronchi and their branches in our six cases of bronchial asthma suggests a certain parallelism between the clinical picture and the structural changes. Of those cases developing seemingly on a bacterial basis, one was during life a well defined exudative type (Case 1), characterized by an abundant secretion (bronchorrhea) which was one of the chief clinical symptoms associated with the paroxysmal attacks. The anatomic parallel of this picture is furnished by the striking hypertrophy of the mucous gland system of the bronchi.

42. Lederer, R.: Ueber Bronchotetanie, Ztschr. f. Kinderh. **7**:1, 1913, and ibid. **23**:79, 1919. Chronische Bronchitis, Bronchial Asthma und Bronchotetanie, Ergebn. d. inn. Med. u. Kinderh. **19**:564, 1921. Rietschel, H.: Bronchotetanie, Bronchialasthma und Asthmatische Bronchitis, Monatschr. f. Kinderh. **12**:261, 1913.

One other case of bacterial asthma (Case 2) was characterized clinically by a more or less unproductive cough which led to the attacks of bronchospasm. The chief pathologic changes seen in this case are the hypertrophy of the smooth muscle system and the atrophy of the mucous glands.

The two cases of food asthma (Cases 3 and 6) are characterized pathologically by hypertrophy of both glandular and muscular systems, both of which undoubtedly played a rôle in the production of the stenosis.

One case of true allergic asthma (Case 4) in a person hypersensitive to horse serum, calls to mind the picture seen in the lungs of the guinea-pig in the classical anaphylactic experiment, i. e., the acute emphysema and the marked contraction of the bronchi and bronchioli by the well developed muscle layer. The irregular thickening of the walls of the bronchial arteries recalls the nodal arrangement of these arteries described by Schultz as occurring in the guinea-pig.

The outstanding finding in our study is the evidence that the actual thickness of the walls of bronchi and of bronchioli of more than 0.2 mm. outside diameter is increased, as compared with similar structures in nonasthmatic persons. This difference is due to increased thickness of all layers from the epithelium to the outer fibrocartilaginous layer. Hyperemia and cellular infiltration of the wall and increased activity of the glands lead to swelling and thickening and this can produce, mechanically as well as chemically, irritation of the peripheral nerve endings in the tube, which may indirectly cause bronchospasm. The abundant secretion of the epithelium and the hyperactive glands obstruct, in some instances completely, the already narrowed lumen of the middle-sized and small bronchi and the 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. Even in the purely allergic asthma of the infant 16 months old, which at that age already showed definite thickening of the bronchial wall as compared with an infant of the same age, the exudation into the bronchi and bronchioli with complete obstruction of some is proof of this combined involvement. These observations make it plain that in man, at least, the allergic reaction of the tissues is not confined alone to the smooth muscle fiber system, but involves also the whole organ system which serves exudative processes, endothelium, epithelium, capillaries and glands.

The increased thickness of the wall, the hyperactivity of the glandular system, the bronchoconstriction, as well as the emphysema, are not present to the same degree in all parts of the lungs but often involve one lobe or part of a lobe to a greater degree than others.

The anatomic substrate of the bronchospasm is mainly furnished by the hypertrophy of the smooth muscle fiber system. The evidence of a narrowed lumen and the folding of the epithelium while present has to be interpreted with great care.

The chief cellular symptom of the allergic reaction in man is the eosinophilia. In only one disease, bronchial asthma, does a blood, sputum and tissue eosinophilia occur simultaneously. The eosinophilic infiltration of the bronchial wall in asthma is a characteristic histologic criterion of bronchial asthma, but if absent it does not exclude asthma. Since eosinophilia is regarded as one of the chief clinical and pathologic symptoms of allergy, its constant absence in certain forms of bacterial asthma is regarded as one important part of evidence that there are types of asthma which may not be of allergic origin. This form may be regarded as due to an intoxication with peptones or amines, bronchospastic poisons, which are formed by the action of micro-organisms on tissues.

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