MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

March 11, 1965

ASTHMA

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   - B. Pathological

II. Classification
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III. Mechanical Derangements
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CASE #1: [redacted]

This 16 year old [redacted] girl had the onset of episodic wheezing and dyspnea at five years of age. For many years she had asthmatic attacks about once a week with no particular relationship to time of day, but the attacks were noticeably worse in the spring and winter. In addition, there were periods of time during the summer when asthmatic attacks were rare. Many things were known to aggravate her problem. Among these, dust seemed to be the most noticeable. She was also known to be allergic to many foods by skin testing, and she avoided all of these foods completely. At one time during childhood she was under a program of allergic desensitization, but this was seemingly to no avail, and was discontinued. Besides this type of treatment, various oral bronchodilators had been used with varying success.

The patient is a member of a family of people with respiratory allergies, and three of her siblings all have varying degrees of asthma. Both of her parents have seasonal rhinorrhea which is felt to be allergic in origin.

At about 13 years of age the episodes of wheezing became more frequent and more severe and she was rarely free of wheezing except for a few days at a time. In [redacted] of 1963 the patient's symptoms became so severe that she was considered to have status asthmaticus and was admitted to another hospital. At that time she was treated with Robitussin, Achromycin, Aristocort 4 mgm. b.i.d., and potassium iodide enseals 5 grains t.i.d. On this regimen she improved considerably over the course of 4 or 5 days, and her total hospitalization was approximately 1 week. The first vitalometry listed was obtained at this time.

Following the hospitalization steroids were withdrawn very slowly over the course of 3 weeks. In addition, the patient was started on a nebulization regimen consisting of 8-10 drops of Aerolone and 60 drops of Tergemist by hand nebulization 4 times a day. The patient was encouraged in slow deep breathing, and in addition she was encouraged to cough and expectorate mucus when this was present. She was also encouraged to take part in physical activity, since iatrogenic restrictions had previously been placed on participation in sports. Over the course of the next three months the patient had only one episode of moderately severe dyspnea and wheezing. She nevertheless maintained her treatment regimen, and in [redacted] of '63 the vitalometry results as listed were obtained.

Since the summer of 1963 the patient has been entirely free of any asthmatic attacks. Most recent vitalometry testing was in [redacted] of '64, and the results after bronchodilators were virtually normal. It is to be noticed, however, that the results before bronchodilators were still modestly obstructed. For that reason the patient was continued on her inhaled bronchodilator therapy although all other methods of treatment have been discontinued.

	Date: [redacted]-63				Date: [redacted]-63				Date: [redacted]-64			
	BBD	%	ABD	%	BBD	%	ABD	%	BBD	%	ABD	%
FVC	2477	95	2764	106	2.765	104	2880	109	3040	113	3078	114
$FEV_{0.5}$	803	32	1222	44	1393	50	1540	54	1371	45	1760	57
$FEV_{1.0}$	1393	56	2041	74	1976	71	2333	81	1951	64	2419	79
$FEF_{0-25\%}$	1.75	40	2.64	60	3.42	75	3.62	80	3.55	77	6.08	132
$FEF_{25-75\%}$	1.02	42	1.76	73	1.53	62	2.26	90	1.20	48	2.01	80
FIF	1.86	55	2.54	76	3.23	94	3.46	100	3.35	95	4.84	130
									0.87	46	1.57	83

Case #2: [redacted]

This 48 y/o [redacted] woman was entirely well except for the usual minor illnesses until [redacted] 1963. At that time she developed a "cold" manifested by rhinorrhea, post-nasal drainage, and a cough that most frequently occurred in paroxysms at night. Although at first the cough was non-productive, over the course of days or weeks it became productive of clear white sputum. These symptoms persisted with varying severity throughout the fall and winter of 1963-64. Because of persistence of these complaints she was seen in the Medicine Clinic on [redacted], 1964. Her exam at that time was entirely normal except for a few expiratory wheezes in both upper lobes. A chest x-ray was normal, as was the CBC, urinalysis and serology. She was treated with antihistaminics.

Late in the summer, the patient's first episode of wheezing and dyspnea occurred, and these were severe enough to cause her to call her family physician. He sent a liquid medicine which caused complete relief of symptoms for approximately 2 weeks. Subsequently, however, she developed frequent severe episodes of dyspnea with wheezing that caused her to seek aid in the [redacted] Emergency Room and Clinic 10 times between [redacted]64 and [redacted]-64. On each of these occasions she was treated with a variety of drugs and mechanical assistance, including inhaled bronchodilators administered by IPPB, intravenous aminophylline, subcutaneous epinephrine, oral aminophylline, rectal aminophylline, and oral ephedrine. Nevertheless, almost continual respiratory difficulty and cough persisted.

On [redacted]-64 the patient developed an episode similar to the preceeding episodes excepting for the rapid progression of symptoms. She was brought to the Emergency Room by her husband, and by the time of her arrival she was completely comatosed, cyanotic, unresponsive to pain, and she had a markedly depressed respiratory rate. Controlled ventilation by IPPB, epinephrine, and intravenous aminophylline caused a rather dramatic reversal of her symptoms. She was admitted for a 19 day period for control of her disease. During that admission the patient was treated with oral and inhaled bronchodilators, frequent assisted ventilation, inhalations of mucomyst, prolonged heated aerosols, and fairly large doses of steroids that were tapered by the time of patient's discharge.

Since discharge the patient has again begun to have frequent episodes of respiratory distress despite treatment with the various measures outlined above. On [redacted]-65 the patient was begun on oral prednisone 60 mgm. daily, and during the ensuing week she noticed marked improvement of symptoms which has been maintained to the present time. On [redacted]65 the dosage of prednisone was reduced to 30 mgm. daily.

The patient has no family history of allergy, nor is she aware of any precipitating allergen in her disease. A program at home to suppress dust has been instituted, rugs have been removed, and she has obtained a foam rubber pillow. This has caused no noticeable benefit.

	Date: [redacted]-64		Date: [redacted]64		Date: [redacted]65		Date: [redacted]-65	
	0200 %	0800 %	BBD %	ABD %	BBD %	ABD %	BBD %	ABD %
FVC	1.40 39	1.50 41	2.60 72	2.85 79	2.40 67	2.70 75	2.25 63	2.60 72
$FEV_{0.5}$	0.30 21	0.40 27	1.10 42	1.20 42	0.85 35	1.00 37	0.80 36	1.30 50
$FEV_{1.0}$	0.60 43	0.70 47	1.60 62	1.70 60	1.40 58	1.50 56	1.25 56	1.70 65

CASE #3: [redacted]

This was the 14th admission for this 35-year-old [redacted] female who had been treated for asthma since age 9. She had been admitted 11 times in the past year out of 30 emergency room visits for asthma which could not be controlled in the emergency room. The present attack had lasted two days with only moderate relief on drug and inhalation therapy at home. No triggering factor could be elicited for this particular episode.

Her asthma history dates back to age 9, when she first developed acute wheezing episodes usually associated with her menses and lasting 8-48 hours, with spontaneous regression. She had no severe trouble until after her first delivery, in 1950. Since, she had never been completely free of shortness of breath or wheezing, with 3-4 attacks yearly requiring medical care. The severity and frequency of attacks progressed during the past 13 years, but especially became more severe and frequent during the past year. The only time she had been relatively symptom-free was during her pregnancies, with the exception of the last one, delivered 3 months PTA. She required hospitalization here during the last trimester of pregnancy for asthma control. Following delivery, she had a tubal ligation.

In 1952, she received an allergic work-up which revealed allergies to ragweed, chicken feathers, cat hair, tobacco, and house dust. A series of desensitization injections were given with only slight if any relief of her asthma attacks. These were subsequently discontinued.

She was followed in the chest clinic and emergency room since 1956 with 3-4 attacks of acute asthma yearly. These were treated with aminophylline, epinephrine, hand nebulization, antibiotics, sedation and intermittently with steroids both as in-patient and out-patient therapy.

During the past 12 months, she was never free of wheezing and shortness of breath despite vigorous out-patient therapy including prednisone 10-20 mg. daily. She was seen in the emergency room about every 2 weeks and required hospitalization about every month for varying periods of time for in-patient treatment. On several of these admissions it was noted that she became almost symptom-free immediately after admission before in-patient therapy could be started. A psychiatric evaluation was obtained with a diagnosis of passive-aggressive personality trait disturbance, dependent type, and a psychophysiologic respiratory reaction. On occasion an asthmatic attack could be precipitated by suggesting discharge. During the past year essentially no change in vitalometry studies occurred. She was never noted to have more than a mildly productive cough of white sputum during these attacks and no productive cough between acute episodes. No evidence of pulmonary infection was found during the past year which might have triggered her asthma. She had not received steroids for over a month prior to her last admission.

Family and social history: The patient was a 35-year-old unmarried high school graduate, one of 3 siblings and presently living with her grandmother. She had 6 children, all living and well. Her brother has chronic hay fever. She did not smoke.

Physical examination revealed a well-developed, well-nourished colored female in mild respiratory distress, lying quietly in bed, complaining of shortness of breath and audible wheezing. BP 100/70, pulse 110, temperature 98.8°, respirations 30. No cyanosis, clubbing, edema or venous distention was present. Positive physical findings were confined to the thorax, which revealed an overexpanded chest with low diaphragms, audible expiratory wheezing and prolonged expiratory phase. The lung fields were diffusely hyperresonant with scattered wheezing, primarily expiratory, throughout both lung fields. Examination of the heart revealed a sinus tachycardia; otherwise, no abnormalities were noted.

Hospital course: Upon arrival at [redacted] after 8 hours of emergency room therapy including adrenalin, aminophylline and inhalation therapy, the patient was in only mild distress. She was placed at bed rest and started in IPPB with heated mainstream Tergemist and 5% propylene glycol with Alevaire and Aerolone in side-arm. She was given 500 mg. aminophylline suppositories every 12 hours, phenobarbital 1/2 gr. t.i.d., and epinephrine 1/1000 q2h prn for wheezing.

She responded well to this treatment, bringing up only a slight amount of white sputum daily with mixed flora on smear. She remained afebrile. She became almost free of wheezing and had relief of her shortness of breath by the 3rd hospital day. She was considered for discharge, but was to be kept 3 more days because of family problems which were to be solved over the weekend. On the day of expected discharge, she developed another relatively mild attack of asthma which progressed during the day. She was given adrenalin, 500 mg. aminophylline by IV drip, and 60 mg. of seconal, and placed on the IPPB with the above mentioned medications. She developed more dyspnea and air-trapping despite this therapy, which was repeated every 4 hours. She was then given 150 mg. of Solu-Cortef. She seemed to respond somewhat to treatment, only to be found dead a short time later.

At autopsy the classical findings of asthma were found. There was overdistention of the alveolae, but there was no disruption of alveolar septa. Of special importance is the fact that most of the small bronchi from approximately the fourth order of branching down to the terminal bronchioles were filled with a thick, viscid, tenacious, greenish, mucopurulent exudate that was stripped only with difficulty from the bronchi.

LABORATORY DATA

	1952	1957	1962	Last Admission [redacted]/63	[redacted]/63
Hematocrit		40	47	44	41
WBC		10,150	8700	7650	5600
Diff.		80 segs	Normal	9 eos	7 eos
				59 segs	57 segs
$FEV_{0.5}$			0.3 - 0.3	0.4	
$FEV_{1.0}$	0.65		0.4 - 0.7	0.5	
FVC	1.9		1.5 - 2.3	1.7	
% PVC	76%		60% - 80%	64%	
EKG			RAD and normal	RAD	

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2. Criep, Leo H.: Clinical Immunology And Allergy. Grune and Stratton, 1962.

3. Segal, Maurice S., and Attinger, Ernest O.: Bronchial Asthma: Pathophysiology, Pulmonary Function Tests and Therapeutic Aspects. Clinical Cardiopulmonary Physiology. Grune and Stratton, 1960.

The review by Bates and Christie is very good except for treatment; Segal's chapter is better in this regard. Criep's text is a straightforward review of the current concepts of allergy.

CLINICAL DEFINITION OF ASTHMA

4. Terminology, Definitions, and Classifications of Chronic Pulmonary Emphysema and related conditions. A Report of the Conclusions of a Ciba Guest Symposium. Thorax 14:286, 1959.

In 1959 a large group of experts in the field of pulmonary disease met to consider basic definitions of common lung problems, since so many different terms have been used to described the same or similar conditions. One of the categories decided upon was labeled generalized obstructive lung disease. This classification referred to "generalized obstructive lung disease refers to the condition of subjects with widespread narrowing of the bronchial airways, at least on expiration, causing an increase above the normal in resistance to airflow." The first sub-group under this heading was labeled intermittent or reversible obstructive lung disease: asthma. "Asthma refers to the condition of subjects with widespread narrowing of the bronchial airways, which changes in severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease. The clinical characteristics are abnormal breathlessness, which may be paroxysmal or persistent, wheezing, and in most cases relieved by bronchodilator drugs (including corticosteroids)."

PATHOLOGY

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The pathological findings in fatal cases of status asthmaticus as described by all of these authors are fairly uniform, although different authors stress different parts of the pathological picture. On opening the thoracic cage it is apparent that both lungs are acutely distended, and they fill the chest completely covering the pericardium and nearly meeting in the midline anteriorly. They fail to collapse once the negative intrathoracic pressure has been released. On cut surface the lungs show a striking picture with numerous gray, glistening mucous plugs scattered throughout the air passages. These extend from as high as the main bronchi to as distal as the respiratory bronchioles.

In the microscopic exam the most striking feature in any section is the presence of a dense exudate in the bronchial lumen. There is a mass of a basophilic mucoid material, in which spirals of cells are intertwined. The cellular content consists of eosinophiles which are scattered evenly throughout the mucoid portion and some epithelial cells. These cells appear singly or in groups, and they are normal ciliated columnar cells that have been detached from the mucosa. The remaining mucosa may consist only of a few reserve or basal cells. There are areas of regeneration at focal points of the bronchial wall. There is marked mucosal edema with separation of the superficial cells. There is a marked infiltrate of cells which are mostly eosinophiles with very few polymorphonuclear leukocytes. The basement membrane is markedly thickened. Beneath the basement membrane are many eosinophiles, striking dilatation of the capillary blood vessels, and edema of the connective tissues. The mucous glands are very active and smooth muscles in the walls of the bronchi show considerable hypertrophy.

Gough (8) has emphasized that there is no destruction of the alveolar septa. He and his co-worker, Leopold, further emphasize that there is no cellular infiltration in the terminal bronchioles. These findings help to differentiate the asthmatic from the chronic bronchitic or the patient with emphysema.

ASTHMA IN INFANCY

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12. Wittig, Heinz, J., Cranford, M.J., and Glaser, Jerome: The relationship between bronchiolitis and childhood asthma. The follow-up study of 100 cases of bronchiolitis in infancy. J. of Allergy 30:19, 1959.

13. Selander, Per: Asthmatic symptoms in the first year of life. Acta Paedriat. 49:265, 1960.

When various authors speak of asthma during infancy it is difficult to tell how the diagnosis is made. The syndrome of bronchiolitis, which is probably infectious in origin, may not be readily distinguished from subsequent true asthma. Wittig (12) followed 100 children with the syndrome of bronchiolitis with fever for an average of 2.5 years. He found that 32 of these children developed clear-cut recurrent bronchial asthma.

Buffum (10, 11) and Selander (13) each followed large groups of children who had the onset of what was felt to be true asthma in infancy. It was found that 80% of these children were symptom-free by the age of 6-11 years. Those children that had clear-cut skin sensitivity to egg were found by Buffum to be less likely to be free of symptoms by the end of the follow-up period.

ASTHMA IN CHILDHOOD

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16. Smith, J. Morrison: Prevalence and natural history of asthma in school children. Brit. Med. J. 1:711, 1961.

According to Rackemann (14, 15) the prognosis for childhood asthma is good. In his 20 year follow-up of asthmatics with the onset of disease before 13 years old, 30% of the patients were virtually cured, another 20% had no trouble as long as they avoided the offending cause, and another 21% no longer had asthma but had developed hay fever. This made 71% who had done very well. Fifteen percent still had mild symptoms, but only 11% of the total were having any real trouble. Eleven patients, or 2.4% of the total series, had died from their disease. That is to say, 0.88% of the children with asthma had died of this disease.

During childhood the incidence of asthma in boys is about twice that of girls. Thus Smith (16) found the incidence of asthma in school children in Birmingham, England, 2.85% in boys and 1.02% in girls during the early school years. In both groups, however, the incidence had fallen to 0.9% by young adulthood.

ADULT ASTHMATICS

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The classification of adult asthmatics is much more difficult. However, everyone agrees that the older the age of onset of asthma the more important infection is likely to be and the less important allergy is likely to be. Although the estimates of the number of adult asthmatics caused by allergy varies considerably, that of Fagerberg (19) of 17% seems very reasonable.

Most authors would estimate that at least 40 to 50% of all asthmatics have the onset of their disease in childhood. The onset of asthma after 55 years of age is infrequent. Furthermore, early age of onset and intermittent asthma are associated and have a more favorable prognosis. Asthma beginning in middle age is likely to be very severe and run a rather short course.

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From the various available series one finds that 90% of the patients dying of status asthmaticus are over 30 years old. Most of these patients have had their disease for a number of years, but about 20% of the patients dying have had asthma for 5 years or less at the time of death. The average decade of death is from 50 to 60 years old.

All authors stress the importance of the airway obstruction caused by viscid secretions. Quiet breath sounds in the presence of dyspnea indicate the ability to move little air, and hence are a serious prognostic sign. Hypercapnia is likewise a poor prognostic sign.

THE PHYSIOLOGY OF ASTHMA

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The hallmark of asthma is the reduction in the velocity of airflow or an increased resistance to airflow; these findings are present both during inspiration and expiration, but as might be expected are more severe on expiration. The most widely used indices of reduced airflow are the volume exhaled during a specific time period ($FEV_{0.5}$, $FEV_{1.0}$) or the total amount of air that a patient can ventilate in a 20 second interval (MBC). The former tests are easier to perform, and they correlate better with the amount of disease present, but it should be noted that both of these tests are relatively crude and severe degrees of airway obstruction may be present despite a relatively normal test. For research work a more sensitive test is the measurement of airway resistance. This may be increased in asthmatics from a normal value of 1 to 2 cm. H_2O/L./sec. to values over 50 cm. H_2O/L./sec..

The total lung capacity (TLC) is increased in many asthmatics, and the volume of air remaining in the lung after a complete exhalation (RV) is usually increased. The RV/TLC ratio is likewise increased. The amount of air remaining at the end of a normal tidal volume (FRC) may or may not be increased. The actual stiffness of the lungs (compliance) is normal, but the lung may appear stiffer during respirations (dynamic compliance) because fewer lung units are being ventilated and because of the increased airway resistance. The diffusion capacity is usually normal indicating that there has been no loss of lung capillaries. The oxygen saturation and PCO_2 are usually normal unless the patient is in a severe asthmatic attack (status asthmaticus).

In a symptom-free interval many patients have entirely normal pulmonary function studies, but some patients continue to exhibit the derangements

listed above. Symptoms are a poor guide to the amount of functional derangement present. Pulmonary function testing is therefore of considerable benefit in determining whether the patient should be continued on treatment during prolonged symptom-free intervals.

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It is somewhat difficult to determine the role of allergic hyposensitization in the treatment of asthma. Everyone seems to agree that skin sensitivity to specific allergens does not necessarily indicate that these are the cause of respiratory symptoms. Inhalation tests are much more specific, and they have been shown to correlate better with clinical findings; however,

they are too complex and time consuming for routine clinical use. When evaluating the benefits of hyposensitization, most authors fall back on "a considerable body of clinical evidence" (64). In this limited review I have found only two semi-objective evaluations of hyposensitization. Citron (57) showed a clear-cut decrease in bronchial obstruction to allergens after hyposensitization. His study, however, was of a carefully selected group of patients with clear-cut precipitation of asthma by pollen. Johnstone (59) was unable to detect any benefit clinically in a group of children treated for four years with hyposensitization by a low dosage method. More objective evaluation is clearly indicated in this area.

Various studies of bronchodilator drugs have indicated that the old standbys of epinephrine, isuprel, ephedrine, and theophyllines are all excellent bronchodilators when used correctly. Sedatives have a clear-cut place in the treatment of asthma, since the slowing of respiration is a major therapeutic aim. When one utilizes sedatives, however, in the presence of status asthmaticus, one should be prepared to perform artificial respiration should respiratory efforts cease. Steroids are clearly beneficial in severe cases; it should be noted, however, that it requires several hours for the beneficial effects of these agents, and dramatic effects should not be expected in status asthmaticus.

In all cases dying of status asthmaticus, the major factor is the obstruction of airways with a thick, viscid, tenacious mucus. For this reason the use of bronchodilator drugs and steroids cannot be relied on alone. Correctly administered inhalation therapy to maintain oxygenation, thin viscid secretions, promote better distribution of ventilation in the patient's chest, and relieve the work of breathing is the key to success in such situations.

SURGERY IN ASTHMA

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101. Segal, Maurice S., and Dulfano, Mauricio J.: Glomectomy in the treatment of chronic bronchial asthma, a report of 15 unsuccessful cases. N. Eng. J. of Med. 272:57, 1965.

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103. Takino, Masuichi, and Takino, Yoshitada: Surgical removal of the carotid body and its relation to the carotid chemoreceptor and baroreceptor reflex in asthmatics. Dis. of Chest 47:129, 1965.

Various surgical approaches have been attempted in asthma since the 1920's, and carotid glomectomy is only the latest in this series of approaches. The bronchial mucosa is supplied by both sympathetic and para-sympathetic nerves, and the relationship of these to bronchoconstriction has not entirely been worked out. Surgical approach has included disruption of the sympathetics, disruption of the para-sympathetics, and disruption of both types of nerves both unilaterally and bilaterally. These operations have been discarded because of their lack of long term benefit and the high incidence of complications. Carotid sinus removal was introduced by Nakayama in the early 1940's, but it was not noted in this country until 1961 when Overholt reported his experience with several hundred cases. In the series reported by Nakayama, Overholt, and Phillips (who also has a large series of operated cases) there has been no attempt at controlled evaluation of results. Marschke (100) has the only double-blind study reported on this operation. Of his three operated cases and five sham controls, 100% of the patients felt that they had been improved by the operation; of even more interest, 100% of their physicians felt that the patients had been improved by surgery. Takino (103) reports that the operation has been abandoned in Japan because of lack of long term benefit. It seems quite likely that this same fate awaits the operation in the United States.

MISCELLANEOUS

104. Gandevia, Bryan: The prevalence of an abnormal breathing mechanism in cases of respiratory allergy. Med. J. Austral. 2:52, 1953.

105. Bolton, J.H., Gandevia, Bryan, and Ross, Muriel: The rationale and results of breathing exercises in asthma. Med. J. Austral. 2: 675, 1956.

106. Williams, D.A.: Asthma and bronchitis with emphysema. Acta Allerg. 16:400, 1961.

These are interesting clinical observations by two outstanding clinicians.

107. Rakower, Joseph, Wayl, Pinkhas, and Halberstadt, Herman: Massive asthmatic atelectasis. Dis. of Chest 27:573, 1955.

108. Shaw, Robert R., Paulson, Donald L., and Kee, John L., Jr.: Mucoid impaction of the bronchi, a study of 36 cases. Amer. Rev. of Tuber. and Pulmon. Dis. 76:970, 1957.

These authors emphasize the fact that patients with tenacious sputum that do not cough and produce the sputum may develop atelectasis. In addition the sputum may form a radiodensity that can be mistaken for other types of lesions.

109. Frankland, A.W.: The pathogenesis of asthma, hay fever and atopic diseases. Clin. Aspects of Immunology. F.A. Davis Co., 1963.

110. Brocklehurst, W.E.: Pharmacological mediators of hypersensitivity reactions. Clinical Aspects of Immunology. F.A. Davis Co., 1963.

111. Parish, W.E., and Pepys, J.: Allergic reactions in the lung. Clinical Aspects of Immunology. F.A. Davis Co., 1963.

Excellent reviews of the different types of pulmonary allergies and their patho-physiological mechanisms by authors who have done much to elucidate these mechanisms.

112. Widdicombe, John G., Kent, Donald C., and Nadel, J.A.: Mechanism of bronchoconstriction during inhalation of dust. J. of Appl. Physiol. 17:613, 1962.

113. Rosa, L.M., and McDowall, R.J.S.: The action of the local hormones on the isolated human bronchus. Acta Allerg. 4:293, 1951.

Widdicombe shows that there is reflex bronchoconstriction during inhalation of dust in animals and humans, and that this reflex bronchoconstriction depends on the cervical-vagosympathetic nerves. Rosa shows, however, by working with isolated human bronchi shortly after their removal from the body that histamine can cause bronchoconstriction without any exogenous nervous enervation. In addition, in a bronchus from a patient with allergic asthma he showed that the addition of wheat antigen caused marked contraction that did not occur in the bronchus from normal subjects.

114. Cohen, Edward P., Petty, Thomas L., Sventivanyi, Andor, and Priest, Robert E.: Clinical and pathological observations in fatal bronchial asthma. Report of a case treated with immunosuppressive drug, azathioprine. Ann. of Int. Med. 62:103, 1965.

These authors have shown that atopic individuals react abnormally when given an infusion of epinephrine intravenously. Instead of the expected tachycardia, atopic subjects develop bradycardia. These observations have been interpreted as an indication of the malfunction of the autonomic nervous system in atopic individuals.

115. Harter, John G., Reddy, William J., and Thorn, George W.: Studies on an intermittent cortico-steroid dosage regimen. N. Eng. J. of Med. 269:591, 1963.

This study indicates that the same benefit may be obtained in asthma by administering a given dose of cortico-steroids every 48 hours as by administering the same dosage divided throughout the 48 hours. The side effects, however, are much fewer in number.

116. Loveless, Mary Hewitt: Repository immunization in pollen allergy. J. of Immuno. 79:68, 1957.

This study is the only one that I have found dealing with hyposensitization treatment that utilizes placebo controls. Unfortunately, it deals with hay fever instead of asthma, and these are highly selected patients with clear-cut history of pollen allergy. The study demonstrates a statistical improvement in the patients with desensitization therapy. However, it should be noted that about 1/3rd of their patients responded well to placebo therapy for at least a year.

117. Criep, Leo H.: The march of allergy. J.A.M.A. 166:572, 1958.

Although this is frequently listed as an article indicating the percentage of patients responding to allergy hyposensitization treatment, it is a completely subjective paper. It is therefore open to considerable doubt.