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Perfusion of the Underventilated Compartment of the Lungs in Asthmatic Children*

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If some alveoli of the human lungs are not adequately ventilated, the O_2 tension of the blood leaving these elements will be low (1, 2), and these spaces will contribute to the creation of an alveolar-arterial O_2 difference (3). As a consequence, a certain degree of arterial blood unsaturation must be found in every disease where the ventilation of some part of the lungs is low (regardless of the adequacy of the total ventilation) unless a comparable local reduction in blood flow takes place, a decrease that could be triggered by the hypoxia of the pulmonary venous blood. The teleological appeal of such a decrease of blood flow has prompted several studies on the effects of low alveolar O_2 tension on blood flow. The essence of the pertinent work on this question has recently been analyzed in an excellent review (4) in which Fishman concludes that "the bulk of the evidence favors the view that during unilateral hypoxia the resistance to perfusion increases in the hypoxic side."

Beale, Fowler, and Comroe (5) have demonstrated that an underventilated (slow) compartment (in terms of the ratio of ventilation to volume) of significant magnitude is present in the lungs of the asthmatic patient, even in the symptom-free period. More recently, the use of gas chromatography has allowed the study of the relative perfusion and ventilation-perfusion ratio of the slow compartment by following the decrease in inert gas content of the arterial blood when this inert gas is washed out of the alveoli (6).

The first purpose of this study was to determine whether in asthmatic children there was a redistribution of the pulmonary circulation, shifting the blood away from the "slow" compartment, thereby restoring uniformity of the ventilation-perfusion ratio. In addition, patients who had been free of symptoms for some time were studied to assess to what extent these circulatory changes, if they had taken place, progressed or regressed during the attack-free interval.

Methods

Subjects. Subjects for study were four well children, ages 7 to 11, without past history of asthma, and nine children, ages 8 to 13, with a clinical diagnosis or past history of bronchial asthma of varying degrees of severity. The "well children" were the senior author's own healthy children, who cheerfully volunteeered for the experiment, and one 11-year-old boy who was hospitalized for psychological evaluation but was physically well. The asthmatic children were referred by the attending physician at the allergy clinic, where the children, all except one being outpatients at the time they were tested, had been followed for 1 to 4 years. All were examined at the time of the study, and the clinical history was evaluated. Details are given in the appendix, and pertinent data appear in Table I. Clinical severity of asthma in these children was graded as follows: one (+) had only a history of mild seasonal asthma; three (++) had a history of seasonal asthma of moderate severity, but not regularly requiring medication to prevent symptoms, and without wheezing or other signs of bronchiolar obstruction at the time of the study; four (+++) had daily or nearly daily symptoms requiring medication and physical signs of bronchiolar obstruction; one (++++), in spite of continual cortisone orally and frequent Isuprel epinephrine inhalation, had episodes of severe bronchial asthma more than once daily. All children cooperated well. They were instructed to continue medication as prescribed; no sedatives were given.

Procedure. The procedure used is based on the technique of Klocke and Farhi (6), the main difference being that we studied nitrogen instead of helium. These authors' reason for studying He rather than N_2 was to avoid the danger of

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TABLE I

Clinical data in asthmatic children

Patient	Age	Sex	Race	Asthma history					Physical signs	Chest X ray
				Age at onset	Phase	Severity*	Frequency of wheezing	Time since last episode		
	yrs			*yrs*				*mos*		
1) J.M.	13	M	W	11	Seasonal	+	Only with acute episode	9	None	Negative
2) R.H.	12	M	W	7	Seasonal	++	Monthly	7	None	Negative
3) S.P.	11	M	W	5	Seasonal	++	Monthly	2	None	Not done
4) R.S.	13	M	W	5	Seasonal	++	Monthly	9	None	Not done
5) A.M.	13	M	N	4	Chronic	+++	Nearly daily		Musical râles	Accentuated bronchovascular markings
6) M.F.	13	F	N	1	Chronic	+++	Nearly daily	6	Musical râles	Not done
7) P.L.	11	M	W	2	Chronic	+++	Daily	1	Musical râles	Accentuated bronchovascular markings
8) F.N.	8	M	N	1	Chronic	+++	Daily	0	Musical râles	Accentuated bronchovascular markings
9) K.K.	12	M	W	5	Acute and chronic	++++	Daily	0	Intercostal retractions, musical râles, wheezing, cyanosis	Not done

* Severity was graded as follows: + = history of mild seasonal asthma; ++ = history of seasonal asthma of moderate severity, but not regularly requiring medication to prevent symptoms, and without wheezing or other signs of bronchiolar obstruction; +++ = daily or almost daily symptoms requiring medication and physical signs of bronchiolar obstruction; ++++ = episodes of severe bronchial asthma more than once daily despite continual cortisone orally and frequent Isuprel epinephrine inhalation.

contamination with atmospheric N_2. In the case of abnormal children, where the alveolar and arterial N_2 are maintained at a high level throughout the washout, the error introduced by such a contamination is much less significant. In addition, a simple washout with 100% O_2 did not require the helium prebreathing, and furthermore, it allowed continuous monitoring during the washout. This was accomplished with an N_2 meter,[1] the output of which was fed into a Sanborn recording system. The end-expiratory plateau was assumed to represent mixed alveolar gas. Arterial blood was withdrawn through an indwelling needle placed in a peripheral artery before the study.

The supine subjects were fitted with a mouthpiece, unidirectional valve, and nose clip. The sampling needle of the Nitralyzer was inserted into the airstream through the mouthpiece just outside the lips. A spigot on the inspiratory side allowed switching from room air to 100% O_2 and vice versa. A "dry run" was first made in each case to familiarize the subject with the procedure and check for possible leaks. Arterial samples were withdrawn after the alverolar N_2 curve had shown a definite tendency to plateau and analyzed for dissolved nitrogen by the method of Farhi, Edwards, and Homma (7). The children cooperated well and breathed quietly and regularly during the test with the exception of the sickest patient (Case 9) in whom the tidal volume varied noticeably during the blood sampling procedure. But it was not difficult to estimate the mean concentration of alveolar nitrogen from the record. No test results were discarded, except three technically unsuccessful studies (air contamination, and so forth).

[1] Nitralyzer, model 300A Custom Engineering and Development Co., St. Louis, Mo.

Results

The N_2 content of each arterial sample was converted to a fraction of the control value, Ca/Ca_0; the alveolar N_2 was similarly expressed as the fraction of the initial N_2, F_A/F_{A_0}, and those two values were plotted on a logarithmic scale against time (Figure 1).

In the four normal subjects, the alveolar N_2 decreased rapidly as expected, and a plateau was achieved after 3 to 4 minutes. The level of alveolar N_2 during this phase was so low, however, that accurate readings were not possible, and the only statement that can be safely made is that the ventilation of the slow compartment represented 1% or less of the total alveolar ventilation. In a similar fashion, the N_2 content of arterial blood dropped to 1 to 2% of the control value during the same time. Since the analytical error of the order of 0.5% would represent a con-

siderable relative error, determination of the slow compartment perfusion is inaccurate, although this value appears to range from 1 to 2% of the total cardiac output.

In all patients the gas points obtained after 3 minutes fell on a straight line, indicating that a uniformly ventilated part of the lungs was being washed out. The intercept of this line with the ordinate axis defines $\dot{V}S/\dot{V}A$, the fraction of ventilation of the slow compartment to the total alveolar ventilation. In some of these plots, the blood N_2 points fell on a line parallel to that for the alveolar gas, allowing calculation of a single value for $\dot{Q}S/\dot{Q}t$, the relative perfusion of the slow compartment, and of a single $\dot{V}S/\dot{Q}S$ regardless of time, as was found in normal adults (6). In four patients, however, this was not the case, and the blood washout curve tended to flatten with time, diverging from the alveolar gas washout line. This indicates that some of the perfusion of the lungs was directed to elements

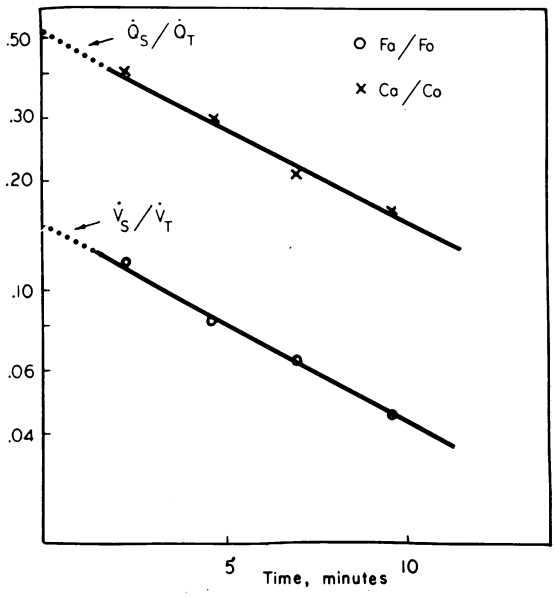

FIG. 1. CHANGES IN N_2 IN ALVEOLAR GAS AND IN ARTERIAL BLOOD IN ONE PATIENT. The intercept of the extrapolated alveolar gas washout line gives the fraction of the ventilation to the slow compartment ($\dot{V}S/\dot{V}T$); the intercept of the arterial blood washout line gives the fraction of the perfusion to this compartment ($\dot{Q}S/\dot{Q}T$). The ratio of these two values gives the ventilation-perfusion ratio of this compartment in relation to the total ventilation-perfusion ratio. Note that the two lines are parallel. Fa/Fo = alveolar N_2 expressed as the fraction of initial N_2; Ca/Co = N_2 content of arterial sample converted to a fraction of the control value.

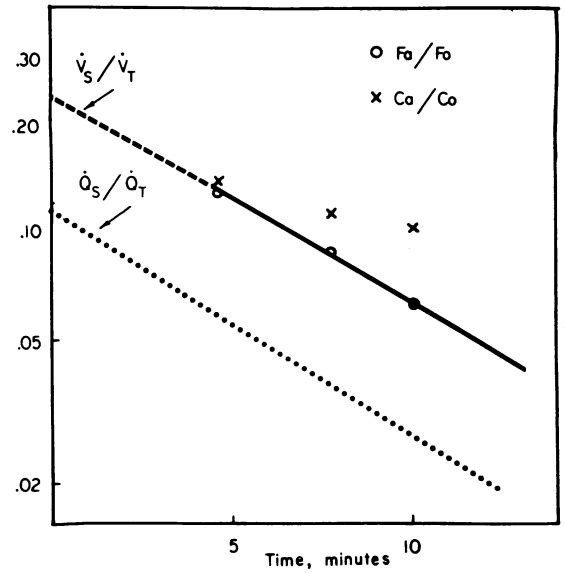

FIG. 2. CHANGES IN N_2 IN ALVEOLAR GAS AND IN ARTERIAL BLOOD IN ONE PATIENT. The alveolar washout line is still a straight line, and its intercept determines the relative ventilation of the slow compartment. It is possible to resolve the arterial blood washout into a line parallel to the alveolar gas washout (dotted line) plus a fixed value. The latter represents the perfusion of the unventilated compartment.

that did not contribute enough to the mixed expired alveolar gas to produce a similar distortion in the alveolar N_2 tracing. The ventilation of this additional compartment can be calculated to be essentially zero, which would result in a constant contribution to the arterial N_2. By trial and error, it is possible to determine in each case the value that must be subtracted from every Ca/Ca_0 value in order to yield a "corrected" blood washout line parallel to the alveolar gas washout line (Figure 2). The vertical intercept of this new line indicates $\dot{Q}S/\dot{Q}t$, whereas the subtracted value defines $\dot{Q}U/\dot{Q}t$, the fraction of the perfusion to the unventilated areas. The results obtained in all subjects appear in Table II.

Like any other description of the lung as an organ that can be divided into a number of homogeneous compartments, the above division is an oversimplification of a system in which there is probably in fact a gradation from normal alveoli to completely unperfused elements (8). Therefore, the results given in this paper (as well as in all the others where the lungs are divided into compartments) really describe an "equivalent"

lung, the behavior of which is identical to the one studied, the latter being too complicated to be visualized easily.

The fraction of the expired alveolar gas originating in the slow compartment was small in normal children (1% of the total on the average) and somewhat increased in the asthmatic children. There was no striking correlation with the severity of the disease, and with the exception of Patient 9, who was studied during the attack, this fraction varied between 0.9 and 3.7% of the total.

The relative perfusion of the slow compartment in the sick children is higher than that estimated to exist in normals. In addition, in all children classified as +++ who had pathologic physical signs on examination of the chest, 7 to 13% of the pulmonary blood flow was directed to unventilated areas.

Finally, the ventilation-perfusion ratio of the slow compartments of asthmatic children varied between 0.10 and 0.33, denoting unequal change in the ventilation and in the perfusion of this slow compartment.

Discussion

One of the basic assumptions made in the analysis of the data is that all the inert gas present in the arterial blood during the measurement period after the first 3 minutes of O_2 inhalation is contributed by the perfusion of the slow compartment. Venous admixture to the pulmonary circulation could invalidate this assumption by introducing into the arteries blood that would not have equilibrated in the lungs. In order to test to what extent this should be taken into account, inert gas washout in the mixed venous blood was studied in three children who were undergoing cardiac catheterization, for evaluation of semilunar valve obstruction. No intracardiac or great vessels shunts were found. In all these the inert gas content of the pulmonary artery blood fell to 20% of its control value after 10 minutes. Thus, if the venous admixture constituted 2% of the total flow, it would raise arterial inert gas content by 0.004. This would not affect significantly the results obtained in patients, since the samples were obtained up to 15 minutes after initiation of washout, but it may have raised the blood values obtained in normals since they were assessed at an earlier phase of the washout. In fact, a shunt of 5% of the total cardiac output would be required to give an error in the estimated perfusion of the slow compartment of 1% of its value.

The data obtained can be used to calculate the effects of uneven distribution on alevolar oxygen in patients. This is done by plotting a $\dot{V}_A/\dot{Q}$ line (1, 2) and reading on its Ss, the O_2 saturation of the blood leaving the slow compartment. If we assume complete saturation of the blood returning from the rest of the lung, the mixing equation allows us to calculate Sa, the arterial saturation, as

$$Sa = 1 - \frac{\dot{Q}s}{\dot{Q}t}(1 - Ss). \qquad [1]$$

This equation underlies the fact that the decrease in arterial saturation, which appears as the second term of the right side of the equation,

TABLE II

*Distribution of alveolar ventilation and perfusion in asthmatic children**

Patient	$100 \times \frac{\dot{V}s}{\dot{V}t}$	$100 \times \frac{\dot{Q}s}{\dot{Q}t}$	$100 \times \frac{\dot{Q}u}{\dot{Q}t}$	$100 \times \frac{\dot{Q}s + \dot{Q}u}{\dot{Q}t}$	$(\dot{V}/\dot{Q})s/(\dot{V}/\dot{Q})t$
1) J.M.	0.9	3.0	0	3	0.30
2) R.H.	1.2	12.0	0	12	0.10
3) S.P.	1.4	10.0	0	10	0.14
4) R.S.	1.8	8.0	0	8	0.23
5) A.M.	2.2	8.0	9	17	0.33
6) M.F.	3.7	8.0	13	21	0.31
7) P.L.	1.2	4.0	13	17	0.31
8) F.N.	2.7	8.5	7.5	16	0.24
9) K.K.	15	50	0	50	0.30

* $\dot{V}s$ = ventilation of the slow compartment; $\dot{V}t$ = total alveolar ventilation; $\dot{Q}s$ = perfusion of the slow compartment; Qt = total alveolar perfusion; $\dot{Q}u$ = perfusion of the unventilated compartment.

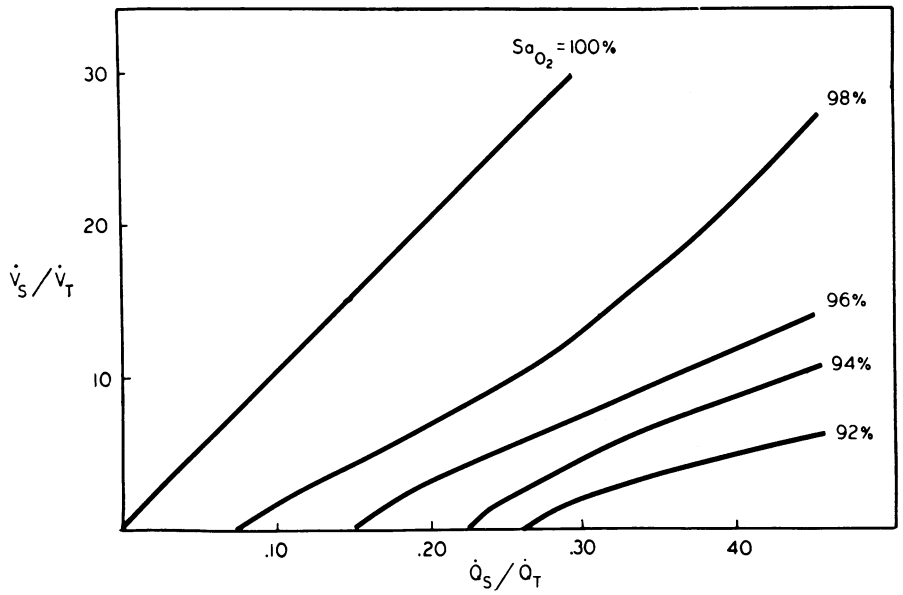

FIG. 3. EFFECTS OF VENTILATION AND PERFUSION OF THE SLOW COMPARTMENT ON ARTERIAL BLOOD SATURATION (SaO_2). The fraction of perfusion can be read on the abscissa; the fraction of the ventilation on the ordinate. The isopleths give the mixed blood saturation.

depends on two factors: the portions of blood flow perfusing the slow compartment as well as the $\dot{V}_A/\dot{Q}$ of that compartment which determines the saturation of the blood it contributes. This relationship is the base of Figure 3, which allows rapid estimation of the arterial saturation that can be expected to result for uneven distribution of $\dot{V}_A/\dot{Q}$ when $\dot{V}_S/\dot{V}_A$ and $\dot{Q}_S/\dot{Q}_t$ have been determined. Although this figure assumes a venous O_2 saturation of 75% and a venous CO_2 content of 52 vol per 100 ml, it is a reasonable index unless the $S\bar{v}$, the venous saturation, drops to less than 50%, or the venous CO_2 content is higher than 70 vol per 100 ml.

When an unventilated compartment can also be demonstrated, Equation 1 changes to

$$Sa = 1 - \frac{\dot{Q}s}{\dot{Q}t}(1 - Ss) - \frac{\dot{Q}u}{\dot{Q}t}(1 - S\bar{v}). \quad [2]$$

In patients 5 to 9, who had evidence of airway obstruction at the time they were tested, the relative perfusion of the "slow compartment" (plus that of the unventilated compartment, when the latter could be demonstrated) was much higher than its relative ventilation. This indicates clearly that if any readjustment of the pulmonary circulation is taking place and producing a shift away from the underventilated areas, it is incomplete, since the total flow to these two compartments is still 3 to 7 times the "ideal" perfusion that would match perfectly the ventilation.

The same is true in Patients 1 to 4, who had been symptom-free for 2 to 9 months. In these a considerable relative overperfusion of the slow compartment persisted, indicating that there had been no permanent adjustment of blood flow to ventilation in underventilated areas. From clinical experience and the natural history of bronchial asthma, it is conceivable that the slowly ventilated or unventilated areas do not remain the same over long periods of time but probably vary in extent and location in the course of days or hours. Reduction of perfusion in proportion to the reduction in ventilation might not occur in such an unstable system.

Study of the unevenness of distribution by the alveolar gas washout method alone will invariably underestimate the severity of the disease. This is especially true in cases where perfused unventilated elements exist, since such a compartment can be detected only by its contribution to the arterial blood. Although arterial puncture is involved, the procedure is not formidable and

seems justified in view of the additional information gained.

The determination of $\dot{V}s/\dot{V}A$ and $\dot{Q}s/\dot{Q}t$ requires monitoring of the alveolar gas and serial arterial sampling, but it is possible to derive from the above data a simpler screening procedure. In Figure 4 all the analytical points for blood have been plotted, and they show that 4 minutes after washout was started, the blood of normal subjects contained 1.5 to 2.5% of the control amount of N_2, whereas in patients this varied from 3 to 30%. We would suggest that any figure above 5% can be considered as definitely abnormal, and values between 3 to 5%, on a single 4-minute check, can be regarded as warranting further investigation.

Summary

The distribution of the pulmonary circulation was studied in four normal children and in nine children suffering from asthma. The perfusion of the underventilated compartment of the lungs was less than 2% of the total in normals and as high as 12% in the others. This is more than the fraction of the ventilation to this compartment, which has therefore a relatively low alveolar ventilation-perfusion ratio. In addition, in patients with more severe forms of the disease, there were findings that could be ascribed to the presence of a perfused but virtually unventilated compartment. Even patients who had been free of symptoms for as long as 9 months did not show a readjustment in perfusion of the slow compartment that would restore its ventilation-perfusion ratio to normal values.

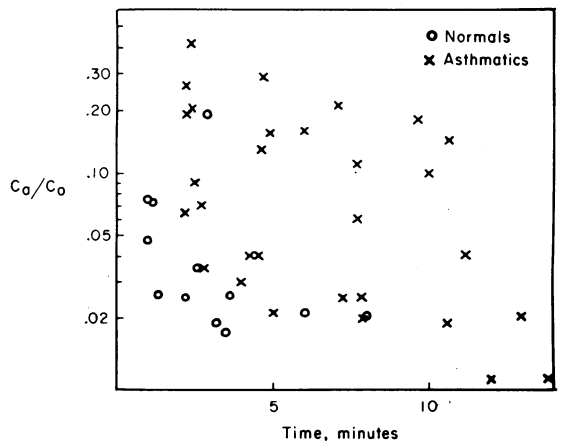

FIG. 4. INDIVIDUAL VALUES FOR ARTERIAL BLOOD N_2 IN NORMALS AND IN PATIENTS.

Appendix

Case 1: K. Mc.C., no. 333 450, born 3/16/49, studied 5/2/62. This patient had onset of wheezing in October 1960. Wheezing, coughing, sneezing, and vomiting recurred August 1961. He was first seen in the clinic October 23, 1961. Chest was clear to percussion and auscultation, but X rays showed heavy markings along lower heart borders on two occasions. On 5/2/62 chest X ray was clear throughout. The patient was found sensitive to several inhalants and fish. Desensitization injections were started February 9, 1962. The patient had no symptoms except local reactions. On the day of the test, the lungs were clear to percussion and auscultation. The child was apprehensive and hyperventilating.

Case 2: R.H., no. 331 720, born 10/23/49, studied 6/21/62. This boy had a history of wheezing on exertion, and running nose between July and October since the age of 4 years. These symptoms were not very severe; he was able to play football and baseball, and at the age of 12 years was 64 inches tall and weighed 154 lbs. On physical examination he had allergic rhinitis, but his chest was clear on many occasions including the day of the study. Chest X ray showed normal lungs on 8/30/61 and 6/21/62. He had positive skin tests for many allergens and had received desensitization injections regularly since November 1951.

Case 3: S.P., no. 239 539, born 2/2/52, studied 6/25/62. Since the age of 2 years, this boy had had attacks of coughing, usually in July to August, which lasted 4 to 6 days. Sometimes the cough continued into winter. Wheezing occurred only in summer. In addition he had perennial allergic rhinitis. Skin tests were done in 1956 and gave positive reactions to various inhalants but not to house dust. He has been treated in the allergy clinic of Children's Hospital with grass and alternaria extracts. His asthma was never completely controlled. He frequently had wheezing and cough at night and required ephedrine and sedatives on many occasions. He had never been hospitalized and had never received steroids. His weight was always in the 50th percentile and height in the 75th percentile for his age. Chest X rays in 1956, 1959, and 1961 showed "heavy markings," which were thought to be indicative of chronic bronchial disease. Roentgenograms were interpreted as showing slight evidence of "emphysema" in October 1959 but not in August 1961. At the time of the study, the patient was asymptomatic, and his chest was clear to percussion and auscultation.

Case 4: R.S., no. 303 563, born 6/23/49, studied 7/9/62. This very cooperative white boy had had severe asthmatic attacks, lasting for about a week, one a month from 1954 to 1960. When first seen at the Children's Hospital in February 1960, his exercise tolerance was impaired, the AP (anterior-posterior) diameter of his chest was increased, diaphragm was low, and there were marked wheezing and musical râles. The lungs, however, were clear by X ray. He responded very well to aminophylline. Skin tests were positive for several inhalants. In September 1960 and

again early in October 1961, he required hospitalization for severe acute asthmatic attacks with dyspnea and mild cyanosis. He also had hay fever every fall. Desensitization therapy was begun in October 1960. Outside of the ragweed season the child had been very well, with full exercise tolerance and normal physical findings except for slightly increased AP diameter of the chest. Pneumotachograms were normal in March 1960 and October 1961. Maximal breathing capacity was normal [66.6 L per minute BTPS (body temperature, pressure, saturated with water)] in March 1960 and 86.6 L per minute BTPS in January 1964. At the time of study, the patient was asymptomatic, and his chest was clear to percussion and auscultation.

Case 5: A.M., no. 341 146, born 9/29/48, studied 4/4/62. This colored boy was first seen at the Children's Hospital at the age of 5 months, and his condition was diagnosed as bronchitis. At the age of 8 months, he was hospitalized because of severe respiratory infection with cough, wheezing, and severe dyspnea. In June 1952, after another episode of "asthmatic bronchitis" he was referred to the allergy clinic. He also had allergic rhinitis and several episodes of contact dermatitis. Skin tests at that time were mostly negative except for caddis fly and peanuts. Nothing was done about this. The patient continued to do fairly well with rare attacks of bronchitis but marked rhinitis, sinusitis, and hypertrophied adenoids until 1959. In November 1959 he again developed severe bronchitis with dyspnea, orthopnea, and productive cough. Blood count showed up to 23% eosinophils. Skin tests were repeated and again were essentially negative. He continued to have wheezing and cough throughout 1960 and was treated with expectorants, Quadrinal, and Aminet suppositories. He got steadily worse and in August 1961 was started on small doses of cortisone acetate. His condition improved temporarily, except for the rhinitis, and cortisone was reduced and then discontinued entirely in November 1961. In January 1962, skin tests were repeated again and now showed marked reaction to dust and caddis fly and moderate reactions to ragweed. His adenoids and tonsils were removed in February 1962, and in March 1962 desensitization to housedust was begun. He had several severe upper respiratory infections during the winter of 1961 to 1962, but in April and May 1962 improved considerably, and had no wheezing by the end of May. Chest X rays on September 5, 1958, and November 27, 1959, showed clear lungs. On March 23, 1952, lungs were clear except for slight accentuation of markings. At the time of study, the patient had no respiratory distress, but musical râles were heard over his chest both on inspiration and expiration. The patient's height was at the 50th percentile, and his weight in the 25th percentile for his age.

Case 6: M.A.F., no. 191 753, born 10/23/48, studied 4/11/62. This colored girl was born in Florida, and her mother states that she noticed wheezing shortly after the baby's birth. She had her first acute asthmatic attack at the age of 4 years in 1952. She was treated symptomatically and had two to three severe attacks a year until 1959 when she came to the Buffalo Children's Hospital. The tuberculin test was positive. Since April 1959 she had four admissions to the hospital and innumerable clinic visits for asthma or "fainting spells," or both. In October 1959, skin tests were performed and gave positive reactions to several foods and many inhalants but not to dust. Desensitization against grasses and alternaria was begun in July 1960; a diet eliminating eggs in any form and nuts was recommended, but recommendations were not always carried out. The patient also took ephedrine and other medication occasionally and between September to November 1959 received steroids. She was never completely controlled for any length of time and had frequent asthmatic attacks of moderate severity until 1960, and much less severe attacks in 1961. Her last severe attack had occurred in October 1961. Chest X ray in April 1959 showed evidence of a probably inactive tuberculous focus that subsequently disappeared. On August 18, 1959, December 14, 1959, February 2, 1961, and April 11, 1962, heavy markings and prominent hilar markings of the lungs were noted in the X ray. The patient is in the 25th percentile for her age for height and weight. At the time of the study she had no respiratory distress, but coughed occasionally. Musical râles were heard over both lungs.

Case 7: P.L., no 217 827, born 1/2/51, studied 4/25/62. This white boy was first seen at the Children's Hospital in December 1954 with complaints of wheezing with respiratory infections on several occasions since the age of 2½ years and three severe asthmatic attacks that responded to adrenaline. Ephedrine, antihistamines, and expectorants did not relieve his condition. He was found to be allergic to dust, feathers, and other inhalants as well as several foods. Dust and feather precautions and desensitization against dust, feathers, grasses, and hormodendron were begun in September 1955. After several months he improved, but he was rarely completely free of wheezing for more than a few weeks at a time and usually wheezed after his desensitization injections, which he took regularly. He usually required Quadrinal, aminophylline, and so forth. In December 1961, skin tests were repeated with similar results as in 1955, but they were negative for feathers and hormodendron and positive for dog hair and a few other inhalants. Autogenous dust extracts were prepared and used for desensitization beginning in February 1962. In March 1962 he was better than he had been for years, but in April he again had considerable wheezing. He continued to take Quadrinal twice a day and to use Medihaler with epinephrine occasionally. Chest X rays showed moderately increased markings in December 1954. These were less prominent in December 1958 and only slightly accentuated on February 13, 1959, and December 9, 1961. Height and weight were in the 50th percentile for his age. At the time of study, the patient exhibited slight barrel shape of the chest, square shoulders, and musical râles throughout the lungs both on inspiration and expiration. At the end of the procedure, he developed mild wheezing.

Case 8: F.N., no. 223 757, born 6/27/54, studied 6/13/62. This colored boy had his first attack of wheezing at the age of 9 months and was hospitalized at the ages of 12 and 16 months for severe respiratory infections with wheezing and iron-deficiency anemia. Attacks of wheezing recurred

once to three times every week until he was referred to the allergy clinic at the age of 23 months in May 1956. Complete skin testing resulted in positive reactions to most antigens except milk, soybeans, trees, and timothy, but including cotton seed, rice, barley, eggs, and all meats other than beef. An elimination diet was recommended, but because of very poor home conditions, it is doubtful that it was ever carried out. Desensitization injections against dust, feathers, ragweed, and other grasses were begun in October 1956. The patient continued to have many respiratory infections and many attacks of wheezing that finally became milder and less frequent about a year later. He always required medication. Between attacks, his chest usually was clear to percussion and auscultation. He also developed perennial allergic rhinitis. During the winter of 1960 to 1961, he was worse than ever with many episodes of wheezing and productive cough, with and without infections. He was treated with antibiotics as well as usual asthma therapy. Blood count showed 28% eosinophils, nasal smear, 14%. Skin tests were repeated in 1961 with similar results as in 1956, i.e., many strong reactions. Desensitization to alternaria, hormodendron, and trees was added to his previous therapy in December 1961. In February 1962, prednisone therapy was started and resulted in considerable improvement. When steroids were discontinued in March, wheezing recurred; therefore prednisone was resumed, and dosage was increased in April, then gradually reduced. At the time of the study, the patient was receiving 2.5 mg of prednisone twice a day. All X-ray films of the lungs showed distinct accentuation of the lung markings; the last one, in January 1962, also showed a few small areas of bronchopneumonia.

Case 9: K.K., no. 232 769, born 7/28/50, studied 7/2/62. This highly intelligent white boy had been well until the age of 5 years. After a severe respiratory infection in September 1955, he developed severe asthmatic attacks with cough, choking, dyspnea, and cyanosis. He occasionally responded well to adrenaline or Isuprel, but because of frequency of attacks, he received steroids for 10 days in December 1954 and had another short course of steroids in March 1955. From September 1956 up to his admission in June 1962, the patient had been taking steroids continuously in varying dosage. On this therapy his asthma was well controlled, but whenever the steroids were decreased, severe asthmatic attacks recurred. He was admitted to the hospital on June 23, 1962, for the purpose of weaning him off steroids because of growth retardation. (He had not grown in height at all in 2½ years.) On admission the patient had marked Cushingoid appearance with a "barrel chest," but good respiratory excursions. His lungs were clear to percussion and auscultation on admission. His height was 50 inches, weight 83 lbs. Because of the respiratory infection, the patient was treated with penicillin, and steroids were reduced to half his previous dosage on June 23, 1962, and discontinued completely on June 26, 1962. Two days later the patient began to develop severe asthmatic attacks with extreme cyanosis that did not respond to aminophylline and sedation and responded only transiently to adrenaline and isoproterenol. During the attacks, there were marked wheezing and musical râles; however, 2 minutes after isoproterenol inhalation the chest was completely clear to percussion and auscultation. On June 26, 1962, vital capacity was 2.20 L BTPS, and the maximal breathing capacity was 42.4 L per minute BTPS (both within normal limits). Pneumotachogram showed a normal pattern with quiet breathing. X ray of the chest showed normal lungs on June 25, 1962. On the day of the test, the patient had isoproterenol before coming to the laboratory. He had short, labored breaths and many musical râles that cleared up after isoproterenol. After the arterial puncture and before administration of oxygen, he became apprehensive and cyanotic. Cyanosis was relieved slowly during the inhalation of oxygen for the nitrogen washout, but the patient coughed frequently and was dyspneic. However, he cooperated well. Four to five minutes after the oxygen was removed, another sample of arterial blood had a pH of 7.28, P_{CO_2} was 41 mm Hg, buffer base, 42 mEq per L, and P_{O_2}, 84 mm Hg.

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