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REGIONAL PULMONARY FUNCTION STUDIED WITH XENON^{133} *

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Although there are many tests of pulmonary function in common usage, most of these measure only over-all function and are incapable of describing separately the behavior of different parts of the lung. Pulmonary arteriography has proven to be a valuable procedure for estimating the distribution of blood flow through the lungs but does not provide quantitative results. By bronchospirometry it has been possible to measure separately the ventilation and oxygen uptake of the two lungs or even of individual lobes, but considerable skill is required to obtain valid results, and the measurements must be made under conditions which are quite unphysiological. Both arteriography and bronchospirometry, furthermore, are unpleasant for the patient and are not without hazard.

The use of a radioactive tracer gas for assessing regional ventilation was reported in 1955 by Knipping and co-workers (2). They recorded external counting rate over multiple areas of the chest during breathing of air containing xenon^{133} and were able to show the presence of unventilated or markedly underventilated areas in certain patients. In subsequent publications (3–8), these and other workers extended their observations and described a method of displaying the results pictorially but did not attempt to estimate regional ventilation quantitatively.

More recently, Dyson and co-workers (9) have described the use of oxygen^{15} with external counting for determining the relative ventilation and perfusion in different regions of the lung. The initial counting rates after a single breath of radioactive gas were used to compare ventilation in symmetrically located counting fields, and the rates of removal of isotope from the counting fields were used as a measure of relative perfusion. Findings in normal subjects (10, 11) and in patients with mitral stenosis (12) have been published, and the clinical usefulness of this type of information in patients with pulmonary disease has been clearly shown (13).

This paper will describe and illustrate the application of a method for measuring regional ventilation and perfusion using xenon^{133} and external counting. Quantitative results are obtained by the use of a combined single-breath and rebreathing technique together with the intravenous administration of dissolved xenon^{133}.

METHODS

Xenon^{133} was shipped by air every 3 weeks as 300 mc of the highly purified gas sealed in a 10-ml glass ampule.[1] The gas was diluted to 30 ml with carbon dioxide and transferred into a lead-shielded mercury-displacement reservoir for dispensing in small amounts. Xenon is a chemically inert gas about three times as soluble as oxygen and one-seventh as soluble as carbon dioxide at body temperature ($\alpha = 0.0845$ ml xenon per ml H_2O at 760 mm Hg). The isotope $_{54}Xe^{133}$ decays to stable cesium with a half-life of 5.27 days, emitting a negative beta particle of maximum energy 0.347 Mev. This is absorbed by less than 1 mm of tissue and is therefore of no usefulness in external counting. The nucleus formed by beta decay may reach a stable state either by emitting a gamma ray of energy 0.081 Mev or by the process of internal conversion, which is accompanied by the emission of a *K* X-ray of energy approximately 0.030 Mev. The gamma- and X-ray energy is sufficiently low that adequate protection from radiation and shielding of the detecting instruments can be accomplished with 1/16 inch of

* Presented in part at the Forty-fifth Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 14, 1961 (1). The equipment used in this study was largely paid for by a Dominion Provincial Grant. The investigative work has been supported by a Block Term Grant from the Medical Research Council of Canada, and during the past year by generous support from the John A. Hartford Foundation.

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[1] Produced as a fission product at the Radiochemical Centre, Amersham, England, by neutron bombardment of uranium^{235} (14).

lead, except in the case of the storage and dispensing apparatus, which is shielded with 3/16 inch of lead. The total radiation dosage to the lungs of a normal subject in the complete study to be described does not exceed 40 mrads, although a patient with delayed intrapulmonary mixing may receive a total lung dose of as much as 120 mrads. Both of these amounts are small in comparison with doses received during many ordinary diagnostic roentgenographic procedures.

Apparatus. The subject was seated in a chair with an adjustable seat and head rest. The arms were placed on a horizontal shelf immediately in front of the subject at the level of the manubrium in order to rotate the scapulae outward. Behind the chair were mounted six scintillation counters [2] fitted with 4-inch cylindrical lead collimators and placed for each patient to correspond to fixed positions on a previously taken 6-foot posteroanterior chest film. Measurements on the film and on the subject were made, using the spine of the seventh cervical vertebra as a reference point; the upper zone counters were centered 1.5 inches below the highest projection of the lung, the lower zone counters 0.75 inch above the highest projection of the higher diaphragm leaf, and the middle zone counters halfway between. At each vertical level the counters were placed equidistant from the midline and in the center of the lung projection at that level.

Figure 1 shows the isocount curves in air for the scintillation counters, superimposed in correct position on a drawing of the chest. It will be noted that each counter responds to radiation from a truncated cone of lung, with a sensitivity that decreases quite rapidly with depth.

Pulses from each counter were fed through suitable amplifying and discriminating circuits and were then recorded on separate channels of a multichannel magnetic tape recorder [3] by a nonreturn-to-zero pulse-recording technique. The threshold of each discriminator was adjusted to accept only pulses corresponding to a photon energy of 0.025 Mev or more; hence both gamma rays and X-rays from the xenon[133] were recorded. Outputs from the tape playback heads were fed to counting-rate meters,[4] which were connected to record on a 4-channel Sanborn direct writer. The tape recording was monitored during the study and could later be played back with any combination of tape speed, counting-rate meter range and time constant, and Sanborn gain and paper speed which by trial and error produced the best display of each portion of the data. For the standard study to be described, a counting-rate meter time constant of 1 second was used in all cases. All counting rates were estimated to the nearest 100 cpm from the Sanborn tracing and were corrected for background and dead-time loss. Dead time of the recording system at a tape speed of 7.5 inches per second was found to be 100 microseconds.

The subject breathed through a rubber mouthpiece

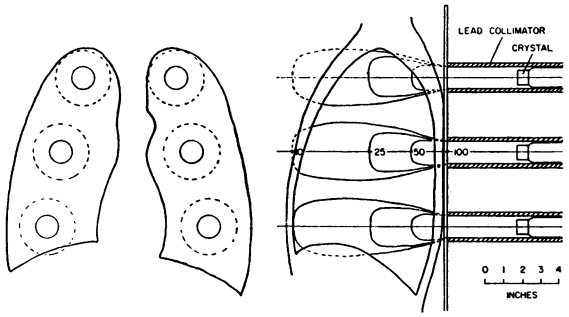

FIG. 1. DIAGRAM ILLUSTRATING POSITION OF THE SCINTILLATION COUNTERS IN POSTEROANTERIOR AND LATERAL PROJECTIONS, WITH ISOCOUNT CURVES SUPERIMPOSED ON THE LATERAL VIEW. Numbers on the isocount curves refer to a counting rate of 100 per cent at the end of the collimator.

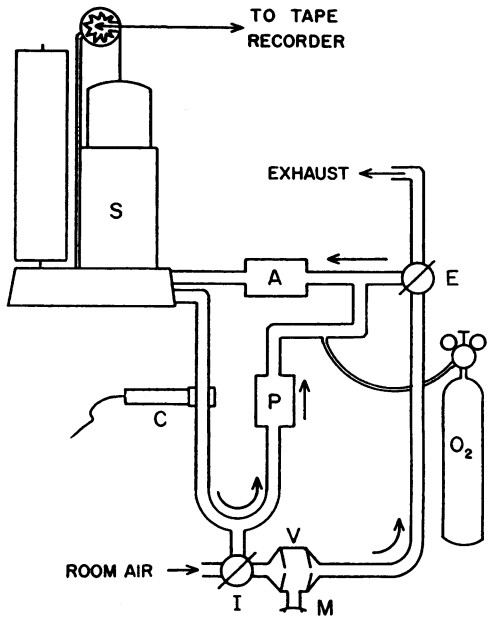

FIG. 2. SCHEMATIC DRAWING OF THE CLOSED SPIROMETER CIRCUIT. M, mouthpiece; V, valve box; I inspired air valve; E, expired air valve; C, scintillation counter for monitoring concentration of xenon in inspired air; P, pump for circulating gas mixture; A, carbon dioxide absorber; S, spirometer. A potentiometer on the spirometer wheel permits a continuous recording of spirometer volume.

[2] Assembled from type 3D2 thallium-activated sodium iodide crystal (Harshaw Chemical Co., Cleveland, Ohio), type K-1716 photomultiplier tube (Du Mont Labs., Clifton, N. J.), and type T-108 linear amplifier (Engineered Electronics, Inc., Santa Ana, Calif.).

[3] Series 3170 30-channel magnetic tape instrumentation system (Minneapolis-Honeywell Regulator Co., Beltsville, Md.).

[4] Tullamore model 2 CRM-2 linear count rate meter (Victoreen Instrument Co., Cleveland, Ohio).

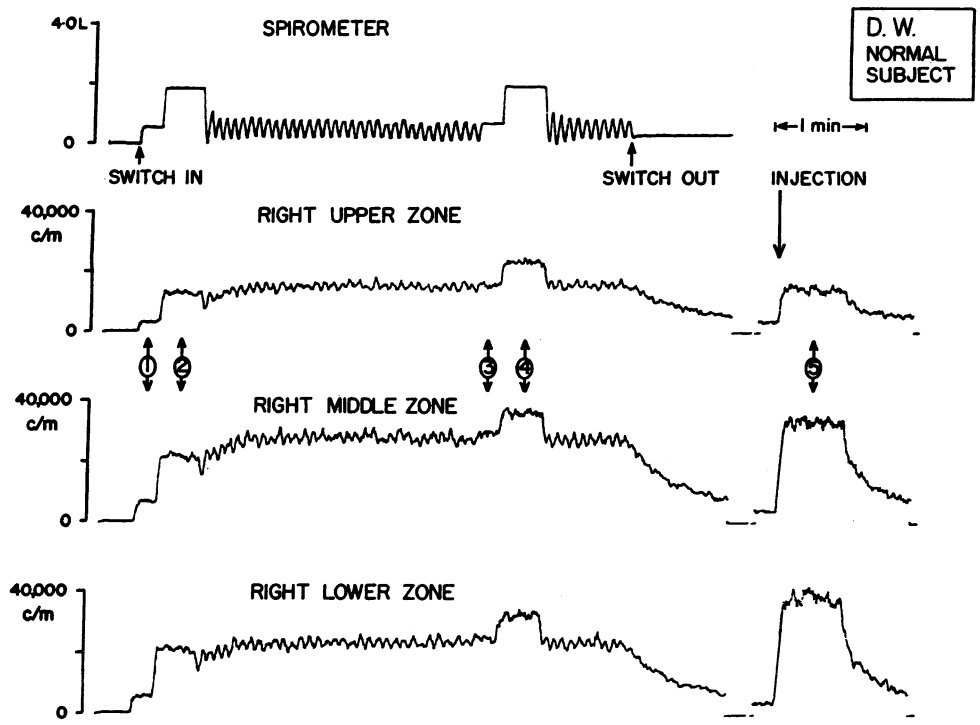

FIG. 3. A PORTION OF THE TRACING FROM A NORMAL SUBJECT, AS PLAYED BACK FROM THE TAPE, SHOWING SPIROMETER TRACING AND COUNTING RATE FROM EACH OF THE THREE CHEST COUNTERS ON THE RIGHT SIDE. Arrows indicate the beginning and end of closed-circuit breathing, and also the intravenous injection of xenon solution. Numbers 1 and 2 refer to the counting rate plateaus which correspond to the small and large initial breaths, numbers 3 and 4 to the plateaus which correspond to the same breath-holding maneuvers after equilibration, and number 5 to the counting rate plateaus during a full inspiration after the intravenous injection. The continuous recording of concentration of xenon in inspired air, together with the counting-rate curves from the left side of the chest are played off separately and are not shown.

and valve box either from room air to an exhaust line for disposal of radioactive waste gas or from a closed spirometer circuit, as shown in Figure 2. The spirometer [5] was fitted with a potentiometer to permit continuous recording of spirometer volume on a channel of tape by means of a standard frequency-modulation technique. The pump circulated the gas mixture on the inspired air side of the circuit at the rate of 36 L per minute to insure rapid mixing. Concentration of xenon in inspired air was monitored continuously by means of a scintillation counter [6] mounted over the inspired air line. Prior to each study sufficient xenon[133] was added to the closed circuit to bring the initial concentration to approximately 0.5 mc per L. During rebreathing, carbon dioxide was removed by a soda-lime absorber and oxygen was added at a rate sufficient to maintain a constant volume.

[5] Stead-Wells 10 L spirometer (Warren E. Collins, Inc., Boston, Mass.).

[6] Similar to those used as chest counters, but containing type 6199 photomultiplier tube (Radio Corp. of America, Harrison, N. J.).

Solutions of xenon[133] for intravenous injection were prepared by agitating a small bubble of a stock xenon-carbon dioxide mixture in a 10-ml syringe fitted with a 3-way stopcock and containing 5 ml of sterile normal saline. Any residual bubble was expelled and the total amount of xenon[133] in the solution determined by counting with the syringe in fixed geometric relationship to a scintillation counter [7] connected to a laboratory scaler.[8] After injection the syringe was again counted, and this count subtracted from the original count. The total amount of xenon[133] injected varied from 0.5 to 1.0 mc.

Procedure. The method of determining regional ventilation and perfusion can be shown with reference to a portion of the tracing from a normal subject (Figure 3). When the subject had been properly placed in the chair and instructed in the breathing maneuvers, the mouthpiece was inserted, a nose clip applied, and the subject allowed to breathe room air from 20 to 30 seconds, during which time background counts were recorded. At the

[7] See footnote 6.

[8] Model 2950 scaler (Picker X-Ray Corp., White Plains, N. Y.).

end of a normal expiration he was quickly switched into the closed spirometer circuit, allowed to inspire a normal tidal volume of air-xenon mixture, and at the end of inspiration was instructed to hold his breath. After several seconds he was instructed to inspire fully and again hold his breath. The counting rates (plateaus 1 and 2, Figure 3) for each lung zone depend upon the amounts of radioactive gas entering the lung within each zone. The subject rebreathed from the closed circuit until examination of the monitored tracings showed that equilibrium had been reached. The breath-holding maneuvers were then repeated, giving two additional counting rates (plateaus 3 and 4, Figure 3) for each zone. Since these external counting rates correspond to known concentrations of xenon within the lung, they can be used in conjunction with the initial breath plateaus to determine the concentration of xenon in each zone after tidal and deep initial breaths (see below). When the pattern of respiration had returned to normal the subject was switched back to breathing room air, and washout curves from each zone were recorded.

After most of the xenon had been washed out of the lungs, a no. 18 needle was introduced into an antecubital vein, and the 5 ml of normal saline containing dissolved xenon^{133} was injected rapidly and flushed in with 20 ml of normal saline. As the injection was made the subject was instructed to take a slow, deep breath and hold it without exerting positive pressure. The solubility of xenon is such that nearly all of the injected dose diffuses into the alveoli on the first circulation, giving a counting rate (plateau 5, Figure 3) for each zone which depends upon the amount of labeled blood brought to the lung within that zone. When the subject resumed breathing of room air, washout curves were again recorded.

Calculations

Because of the complexity of the geometry in body-surface counting, the relationship between concentration of xenon within the lung and the observed external counting rate will differ for different subjects and for different counter positions in the same subject. For each counter, however, with a fixed degree of inflation of the lungs and hence geometry of the system, the external counting rate will be directly proportional to the concentration of xenon within the lung. This relationship is determined for each counter in every subject at two levels of inspiration by means of the breath-holding maneuvers after rebreathing, when the concentration of xenon within the lung is equal to the concentration in the spirometer circuit and can be measured directly. From this relationship it is possible to calculate the concentration of xenon within each lung zone at the time either initial breath plateau is inscribed or within each lung zone after the intravenous injection of xenon. For example, the concentration of xenon, F_2, in a given lung zone after initial full inspiration is given by the equation

$$F_2 = U_2 \cdot \frac{F_4}{U_4}$$

where U_2 is the external counting rate over that zone after the initial breath, F_4 the known concentration of xenon in the lungs after rebreathing, and U_4 the external counting rate during full inflation after rebreathing (subscripts refer to numbered plateaus in Figure 3).

In order to permit direct comparison of data from different studies, each regional concentration as calculated above is expressed as a percentage of the simultaneous mean concentration of xenon in the lungs as a whole or, in other words, as a percentage of the concentration that would have been found if the initial breath of xenon had been uniformly distributed throughout the known lung volume. Thus, for the initial breaths, a "distribution index" Y is defined as

$$Y = \frac{F}{F_I(V_I - V_D)/(V_I + \mathrm{FRC})} \cdot 100\%$$

where F is the calculated concentration of xenon within a zone after initial breath, F_I the concentration in inspired air, V_I the volume of gas mixture inspired, V_D the instrumental dead space (100 ml), and FRC the functional residual capacity determined by closed-circuit helium dilution (15). Using the calculated concentration corresonding to plateau 1 (Figure 3), this equation gives for each lung zone a distribution index for quiet breathing; using the concentration which corresponds to plateau 2, a distribution index for deep inspiration is obtained. Similarly, using the concentration corresponding to plateau 5,

$$Y = \frac{F}{X/(V_I + \mathrm{FRC})} \cdot 100\%$$

where X is the total quantity of xenon injected intravenously, and Y is the distribution index for perfusion.

Each of these indices expresses the total amount of xenon *per unit volume* delivered into the counting field as a percentage of the total amount per unit volume delivered to the lungs as a whole, and hence is a measure of the relative ventilation or perfusion *per unit volume* of lung. If distribution were entirely uniform in relation to lung volume and no dead space were present, all indices should be 100. Since these indices are calculated from the ratio of two external counting rates, they are independent of counter sensitivity, volume of lung within each zone, and absorption of radiation by the chest wall.

It would be anticipated that the rate of washout from areas with reduced ventilation as shown by the distribution index would be delayed in comparison with better ventilated areas. Quantitative analysis of these washout curves is made difficult by the fact that the early portion of the curves is influenced by respiratory movement and the later part by return of dissolved xenon from other tissues to the lung and by radiation from xenon within the chest wall. However, since these regional washout curves, when analyzed in conjunction with the distribution indices for quiet breathing, are theoretically capable of providing information concerning the degree of nonuniformity within a zone, they are currently under further study.

Errors

1. Linearity and precision of calibration of the tape-recording system (after correction for dead-time loss), the counting-rate meters, and direct writer were tested by a pulse generator and laboratory scaler and were found to be within 2 per cent for all measurements.

2. Errors due to the random nature of radioactive decay depend upon the counting rate and the duration of counting. For normal subjects these errors are less than 2 per cent for all plateaus except those corresponding to the small initial breath where, because of low counting rates, the error varies from about 2 to 8 per cent. This fact makes the distribution indices for quiet breathing inherently less precise than those for deep inspiration or perfusion. These errors may be larger in patients, due to shorter periods of breath holding, but rarely exceed 5 per cent for other than the small initial breath plateaus.

3. During rebreathing, some xenon dissolves in the blood and is carried to other tissues including the posterior chest wall within the counting fields. The extent to which this tissue xenon would contribute to total equilibrium counting rate was estimated by counting over the hand and calf during equilibration. These counting rates rose in roughly linear fashion during the first 10 minutes of rebreathing, reaching approximately 1 and 2 per cent (hand and calf, respectively) of the simultaneous counting rates over the chest. Since the calf is considerably thicker than the posterior chest wall, and since the effect of more remote structures such as heart and anterior chest wall is diminished considerably by their distance from the counters, it was concluded that counts from these extrapulmonary structures would not exceed 2 per cent of the simultaneous counts from normally ventilated lung after as much as 10 minutes of rebreathing. In studies where shorter periods of rebreathing were required, the error would be correspondingly less.

If a counting field contains a large volume of unventilated lung so that the equilibrium counting rate is low, the per cent error due to xenon dissolved in tissues will be greater. However, the likelihood of significant error from this cause will be immediately obvious by comparing the equilibrium counting rate with that obtained from other areas.

Failure to reach complete equilibrium during rebreathing will result in a falsely low value for the equilibrium counting rate and consequently a falsely high distribution index. In patients with poor intrapulmonary mixing, failure to ventilate lung spaces within a counting field during rebreathing will result in an index which describes ventilation and perfusion per unit volume of ventilatable lung.

4. The error due to Compton scatter of radiation from the opposite lung or from an adjacent zone of the same lung was estimated with the use of a pressed-wood model of the thorax, by counting from all zones with a small xenon source placed in various positions within the thoracic cavity. If distribution is uniform there is no error introduced by scatter, but if one lung is underventilated, scatter from a normally ventilated opposite lung produces counts over the underventilated lung sufficient to raise the distribution index by as much as 2 U. Normally ventilated lung in a zone immediately adjacent will raise the distribution index by as much as 5 U. It should be noted that the effect of scatter is always to minimize the degree of unevenness actually present.

5. For the calculation of distribution indices, inspired air volume must be estimated from the spirometer tracing, and an independently determined functional residual capacity must be used. The accuracy of the recorded spirometer tracing is about $\pm$ 40 ml, which may cause error in estimating V_I for the initial tidal volume, especially if this volume is small. Errors of this sort, however, do not alter the relative but only the absolute values of the calculated indices and would therefore not influence the interpretation of results. Similarly, error in estimating the amount of xenon injected, or failure of the entire dose of injected xenon to diffuse into the alveoli, would affect only the absolute values of the perfusion indices and not their relative magnitude.

When tidal volume is small the amount of inspired xenon delivered to the central portion of anatomical dead space will be relatively larger, and the indices obtained for peripheral counting fields will be proportionately reduced without altering their magnitude relative to each other.

6. In the calculation of xenon concentrations within the lung it was assumed that the volume of inspired gas was identical for plateaus 2, 4, and 5, and for plateaus 1 and 3. Some variation in inspired volume occurred, but allowance for this was made by correcting the equilibrium counting-rate plateaus on the assumption that the ratio of external counting rate to total amount of xenon in the lungs remained constant for different degrees of lung inflation. This assumption was tested in normal subjects over a wide range of V_I, and the maximal error in counting rate thus corrected was 5 per cent for variations in inspired volume of as much as 500 ml.

7. The largest potential source of error in this method is gross body movement during the study, especially in dyspneic patients, who tend to move their shoulders during efforts at deep inspiration, and also in patients who equilibrate slowly and are therefore required to remain immobile for longer periods. Every effort was made to avoid changes in body position during the study by the use of head and arm rests, and by making certain that the subject was comfortably seated at the start.

RESULTS

Normal subjects

Twenty-one normal subjects, 17 male and 4 female, ranging in age from 23 to 44, have been studied by the technique described. Indices for quiet breathing were not obtained in two subjects because of equipment malfunction, and perfusion indices were not obtained in three subjects because of leakage or infiltration of the

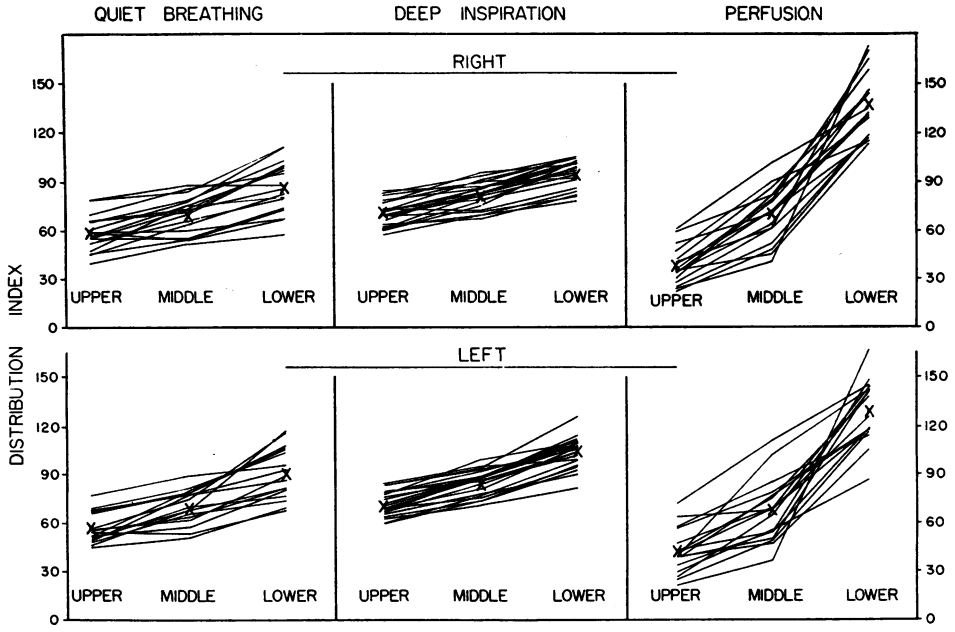

FIG. 4. REGIONAL DISTRIBUTION OF INSPIRED AIR DURING QUIET BREATHING AND DEEP INSPIRATION, AND OF PULMONARY BLOOD FLOW IN 21 SEATED NORMAL SUBJECTS. The distribution indices are computed in such a way that all values would be 100 if distribution were entirely uniform (see text for details). X indicates the mean value for each group of observations.

injectate. In addition, quiet breathing indices have been excluded in one case because the volume inspired (220 ml) was not sufficient to clear instrumental and anatomical dead space, and perfusion indices in another subject were considered invalid because of a shift in body position between the rebreathing and injection parts of the study.

The individual results, expressed in terms of the distribution index, are plotted in Figure 4. Despite the variability among different subjects, there occurred for nearly every subject a progressive increase in the magnitude of the distribution index from upper to middle and from middle to lower zones, indicating that both the ventilation and perfusion per unit lung volume increased progressively from apex to base.

Mean values for these indices with their standard deviations are shown in Table I. It will be noted that the mean indices are all lower for quiet breathing than for deep inspiration; this is due to the fact that a larger fraction of the total amount of xenon inspired lies within the major airways, where it does not contribute to the external counting rates. Variations in the ratio of anatomical dead space to tidal volume are also a major factor in increasing the variability of the indices for quiet breathing among different subjects.

From the mean indices it will be seen that for quiet breathing the ratio of ventilation of the lower zones to ventilation of the upper zones is 1.55, while the corresponding ratio for deep inspiration is 1.41. Although this difference is small it was present in nearly every subject, and by statistical analysis of the paired data was shown to be significant (right lung, $p < 0.001$;

TABLE I

Mean distribution indices and their standard deviations in 21 normal subjects

	Quiet breathing		Deep inspiration		Perfusion	
	R	L	R	L	R	L
Upper	58 ±11	57 ±9	71 ±8	71 ±7	38 ±12	42 ±14
Middle	70 ±11	70 ±10	81 ±8	85* ±8	70 ±17	67 ±20
Lower	87 ±16	91 ±16	95 ±9	104* ±10	137* ±20	129 ±19

* Significantly greater than the corresponding index on the opposite side.

left lung, $p < 0.05$). In addition, the index for deep inspiration for the left lower zone was greater than the corresponding index on the right in all 21 subjects and, although the mean difference is only 9 per cent, this is highly significant ($p << 0.001$). Similarly, the index of 85 for ventilation of the left middle zone on deep inspiration is significantly greater than the index of 81 on the right side ($p < 0.001$), and the index of 137 for perfusion of the *right* lower zone is greater than the index of 129 on the *left* side ($p < 0.01$). The indices for ventilation of the lower zones during quiet breathing do not differ significantly ($0.3 < p < 0.4$). In contrast to the relatively small difference in ventilation of lower versus upper zones, the perfusion indices indicate that the lower zones were 3.3 times as well perfused as were the upper zones.

Technically satisfactory duplicate studies on different days have been performed on four of the above subjects. The mean difference between the paired distribution indices varied from 3 to 8 U (over-all mean 6 U) for different zones, indicating a high degree of repeatability in normal subjects.

Patients

Forty patients have been studied, including 20 patients with pulmonary emphysema, 5 with bronchiectasis, 4 with mitral stenosis, and 11 with various other cardiac or pulmonary lesions.

A few patients were unable to cooperate adequately, either because they could not do the breathing maneuvers properly or because they were unable to hold a full inspiration for a sufficient length of time. In four of the patients with emphysema, wash-in was so slow in one or more areas that true equilibrium on rebreathing was never attained. In most instances the procedure was carried out without difficulty and, except for the venipuncture, imposed no discomfort upon the patient.

Four illustrative cases have been selected and are described below. Methods used for routine pulmonary function testing in this laboratory are as given by Bates, Pare and Meakins (16).

Patient 1. Mr. A.G. was a 57 year old man with a 20-year history of productive cough and progressively increasing exertional dyspnea. He had had repeated hospital admissions for pneumonia. During the 5 years prior to admission he was unable to work, and at the time of study was virtually bedridden and unable to bathe himself because of dyspnea. On physical examination his chest was hyperinflated, breath sounds were diminished, especially at the bases, and expiration was prolonged and wheezing. The plain chest film and a pulmonary arteriogram are shown in Figure 5. Tomograms revealed loss of vasculature in both lower lung fields, and a selective bronchogram of the left lower lobe showed advanced changes of chronic bronchitis. The patient's vital capacity was 1.62 L, functional residual capacity 3.53 L, $FEV_{0.75}{}^{\times 40}$ 15.0 L per minute,[9] maximal midexpiratory flow rate 0.24 L per second, and steady-state diffusing capacity at rest 5.9 ml CO per mm Hg per minute. Arterial P_{CO_2} was normal, and arterial oxygen saturation was 96 per cent.

TABLE II

Distribution indices in Patient 1 *

	Quiet breathing		Deep inspiration		Perfusion	
	R	L	R	L	R	L
Upper	72	110	79	87	70	104
Middle	32	48	102	68	47	78
Lower	7	3	29	20	26	34

* A.G., pulmonary emphysema. See Table I for normal values. During quiet breathing there is a gross reduction in ventilation of both lower zones and some reduction in ventilation of both middle zones, and the fraction of total inspired air delivered to these areas is increased by deep inspiration. Perfusion of both lower zones is also strikingly impaired. There is relative preservation of function in the left upper zone.

Radioactive xenon studies (Table II) showed greatly reduced ventilation of both lower zones and significantly reduced ventilation of both middle zones. Perfusion was similarly disordered. On deep inspiration a much larger fraction of the inspired air was delivered to the middle and lower zones, but the distribution was still distinctly abnormal. Equilibration and washout curves showed striking delay over both lower and middle zones, and less marked but definite delay over the right upper zone. It will be noted that the left upper zone is better ventilated and perfused than any other area, and washout curves from the left upper zone appeared essentially normal.

A left lower lobectomy was performed. At operation the left lower lobe was overdistended, and pathological study showed that it was almost completely destroyed by severe panacinar emphysema. Some normal alveolar tissue was present in the lowest part of the lobe. At thoracotomy the upper lobe, including the lingula, showed some evidence of emphysematous change, but there were no bullae present. The patient's postoperative exercise tolerance was markedly improved.

[9] An indirect estimate of the maximal breathing capacity obtained by multiplying the 0.75-second forced expiratory volume by 40.

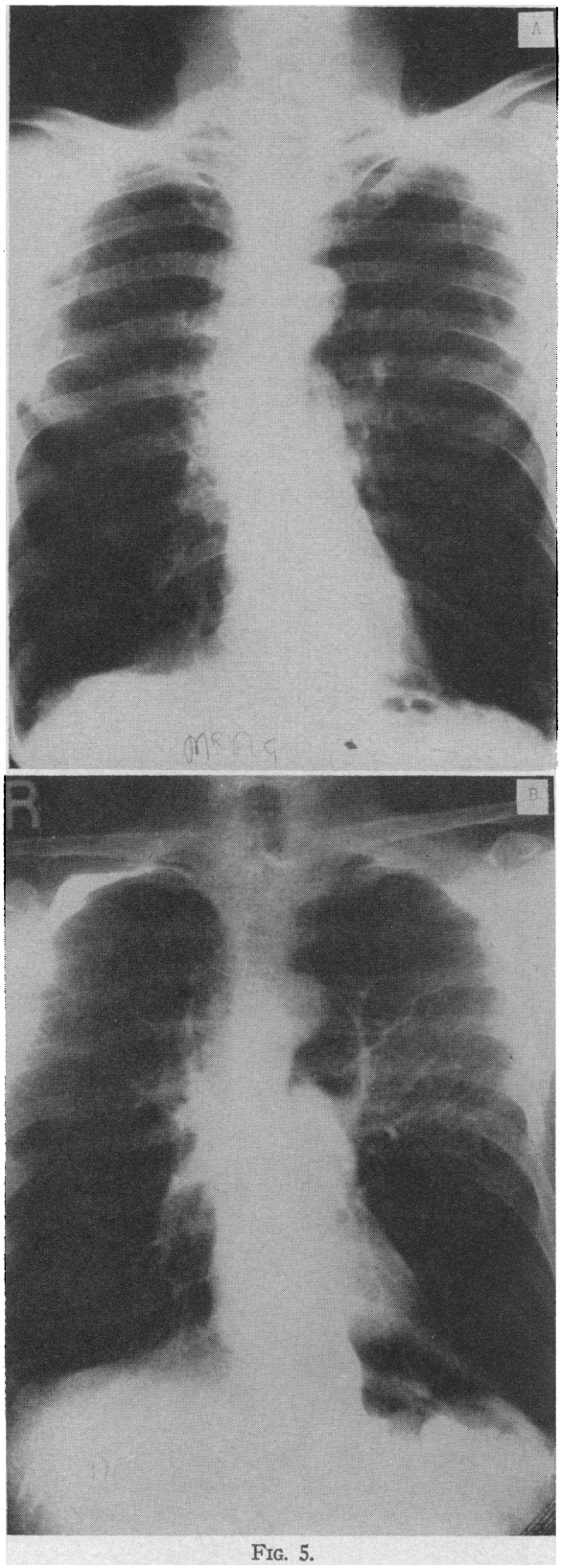

FIG. 5.

Patient 2. Mr. L.T. was a 36 year old mechanic with a strong family history of bronchitis. He had had chronic cough for 15 years and for 7 years had noted gradually increasing dyspnea on exertion. During the 4 years prior to study, cough had become productive of moderate amounts of greenish sputum, and dyspnea had become severe. Physical examination showed that the chest was hyperresonant to percussion, with diminished breath sounds and occasional rhonchi at the bases. There was no clubbing. The chest film is shown in Figure 6. Tomograms showed a moderate degree of loss of vascularity which appeared to be generalized, and bronchograms showed no abnormality. At the time of study his vital capacity was 1.67 L, functional residual capacity 4.50 L, $FEV_{0.75}{}^{\times 40}$ 16 L per minute, and maximal midexpiratory flow rate 0.30 L per second, with no improvement after bronchodilators. The diffusing capacity at rest was 7.9 ml CO per mm Hg per minute.

TABLE III

Distribution indices in Patient 2 *

	Quiet breathing		Deep inspiration		Perfusion	
	R	L	R	L	R	L
Upper	74	116	70	89	98	74
Middle	77	66	68	60	112	70
Lower	76	61	84	77	123	86

* L.T., pulmonary emphysema. Ventilation and perfusion are distributed relatively uniformly among the six counting fields, with virtual loss of the normal lower-to-upper-zone perfusion gradient. The records showed gross delay in equilibration and clearance of xenon from all zones, indicating uniformly distributed diffuse disease.

Arterial P_{CO_2} was 47 mm Hg and oxygen saturation 93 per cent. Exercise diffusing capacity measured a year earlier was only half the predicted value.

Radioactive xenon studies (Table III) showed rather even distribution of ventilation and perfusion among the six counting fields, with slightly greater perfusion on the right side than on the left, and somewhat better ventilation of the left upper zone than of other areas during quiet breathing. The normal perfusion difference between upper and lower zones was virtually abolished. The striking feature of the records was the gross delay in equilibration and washout over *all* zones, indicating uniformly distributed diffuse disease.

FIG. 5. CHEST FILM (A) AND PULMONARY ARTERIOGRAM (B) IN PATIENT 1. The chest film shows low and flat diaphragms, increased radiolucency of both lung fields, and decreased vascular markings at the bases. The arteriogram shows a marked deficiency in peripheral vasculature in the whole right lung and lower part of the left lung. The left upper lobe was better perfused than any other area but still showed abnormally rapid tapering of the vessels.

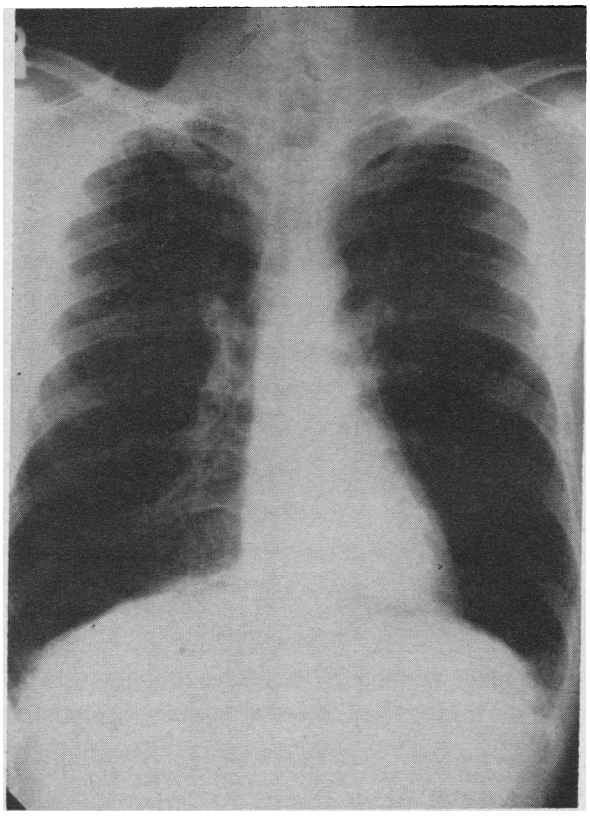

FIG. 6. CHEST FILM IN PATIENT 2. The plain film shows only flattening of the diaphragms and increased radiolucency of both lung fields.

Patient 3. Mr. H.L. was a 34 year old man who had been subjected to exploratory thoracotomy 6 months previously because of an egg-sized mass near the right hilum found on routine chest X-ray. At operation he was found to have a bronchial adenoma arising from the superior segmental bronchus immediately adjacent to the right lower lobe bronchus. The right lower lobe and a major portion of the intermediate stem bronchus were resected in order to provide an adequate margin, and the distal stump of the middle lobe bronchus was anastomosed to the proximal stump of the intermediate stem bronchus. Postoperative bronchoscopy and bronchograms demonstrated patency of the grafted airway, but the patient was referred for radioactive xenon studies to determine the degree of function of the transposed middle lobe, which on bronchography appeared to be hyperinflated and to occupy much of the inferior and posterior portion of the right hemithorax. Results (Table IV) showed ventilation and perfusion in the right middle and lower zones to be reduced by one-third to one-half in comparison with the normal lung, but provided conclusive evidence that the transposed lung was functioning.

TABLE IV

Distribution indices in Patient 3 *

	Quiet breathing		Deep inspiration		Perfusion	
	R	L	R	L	R	L
Upper	81	80	95	110	34	62
Middle	66	88	78	111	40	83
Lower	65	99	72	136	74	162

* H.L., surgical transposition, right middle lobe. Studies performed 6 months after right lower lobectomy and anastomosis of the middle lobe to the intermediate stem bronchus. There is a moderate reduction of function of the lung in the right middle and lower zones, but the study provides conclusive evidence that the transposed lobe is functioning.

TABLE V

Distribution indices in Patient 4 *

	Quiet breathing		Deep inspiration		Perfusion	
	R	L	R	L	R	L
Upper	74	62	74	71	145	128
Middle	77	86	83	91	141	165
Lower	87	91	99	101	58	73

* A.McA., mitral stenosis. Despite the striking reduction in perfusion of lung in both lower zones, the distribution of ventilation is entirely normal.

Patient 4. Mrs. A. McA. was a 22 year old housewife with a history of recurrent chorea during childhood and exertional dyspnea gradually increasing since age 17. She had one episode of frank congestive failure complicating a respiratory infection at age 20, and had recently developed orthopnea, bouts of paroxysmal nocturnal dyspnea, and intermittent ankle edema. At the time of study she was unable to climb one flight of stairs at a normal pace. Physical examination revealed murmurs of mitral stenosis, mitral insufficiency, and aortic insufficiency, but with a loud mitral first sound and early opening snap. It was confirmed at cardiac catheterization and later at operation that the predominant valvular lesion was mitral stenosis.

Xenon studies (Table V) showed the distribution of inspired air in the six zones to be entirely normal, both on quiet breathing and on deep inspiration. Perfusion in both lower zones was considerably reduced, however, and relative perfusion of the upper zones was correspondingly increased.

DISCUSSION

It has been recognized for many years that there is significant nonuniformity of ventilation and perfusion in the lungs of the normal subject in the erect posture. The study of foreign-gas equilibration and washout curves by a variety of techniques, and also the continuous analysis of gas concentrations during a single expiration have provided clear evidence of unevenness in ventila-

tion (17), but until recently there was no direct evidence that this unevenness was regionally distributed.

Regional unevenness of perfusion was suggested by the studies of Martin, Cline and Marshall (18), who found that the concentrations of oxygen and carbon dioxide in expired air from upper and lower lobes differed significantly in the erect subject. By lobar bronchospirometry Mattson and Carlens (19) demonstrated a substantial decrease in oxygen uptake by the upper lobe when the subject assumed the erect posture, and attributed this finding to changes in the distribution of blood flow through the lung under the influence of gravity. Further indirect support for this interpretation was provided by Riley and colleagues (20), whose studies showed a significant increase in physiological dead space in normal subjects on changing from the supine to the erect position.

The recent work by West and Dollery (10) has provided more direct and quantitative data concerning regional ventilation and perfusion in the normal seated subject. By the use of externally placed scintillation counters they were able to measure the rate of removal of oxygen^{15}-labeled carbon dioxide from different regions of the lung after a single breath of the radioactive gas, and have shown this to be a measure of regional perfusion. From the initial counting rates over different regions after a single 900-ml breath of radioactive gas, ventilation was compared in symmetrical areas, and by the use of cadaver measurements and volume calculations an approximate comparison of ventilation per unit volume was made for different levels. Comparison of a lower counting field (at the level of the fifth rib anteriorly) with an upper counting field (at the level of the first rib interspace) in 16 normal subjects showed the ratio of the mean values for ventilation to be approximately 1.4 : 1 and for perfusion approximately 8 : 1.

Corresponding ratios for a comparable vertical separation of counting fields in the present study were 1.55 : 1 for ventilation during quiet breathing, 1.41 : 1 for inspired air on deep inspiration, and 3.3 : 1 for perfusion. The ventilation results are in excellent agreement with those of West and Dollery, and confirm that the lower portions of the lung are better ventilated than the upper portions in the seated subject. Regional differences in the mechanical compliance of the lung and chest wall may be in part responsible for this observation. An alternative explanation, however, is suggested by the work of Swenson, Finley and Guzman (21), who demonstrated a marked and almost immediate decrease in the ventilation of one lung when the pulmonary artery on that side was obstructed, and showed further that this effect could be abolished by allowing the nonperfused lung to breathe 6 per cent carbon dioxide. Regional differences in gas tensions resulting from nonuniform blood flow in the seated subject might thus be responsible for the regional differences in ventilation that were observed in the present study.

The ratio of lower zone to upper zone perfusion measured with radioactive xenon was smaller than that found by West and Dollery (10), but this is in part due to the much narrower counting fields made possible by coincidence counting with oxygen^{15} (9), and to the effect of scattered radiation on counting rates observed over the upper zones in our studies (see Methods). It is also possible that the taking of a full inspiration at the time of injection may have increased perfusion in the upper lung zones. Preliminary observations of the effect of different respiratory maneuvers on the distribution of pulmonary blood flow have produced inconclusive results, but in some apparently normal subjects quite striking changes in distribution have occurred with a deep inspiration or with a Valsalva maneuver. Further study of this problem is clearly necessary.

It is of interest that on deep inspiration the ventilation of the middle and lower portions of the lung was found to be significantly greater on the left side than on the right (Table I). This is presumably due to the difference in resistance to diaphragmatic descent offered by the abdominal contents on the two sides, and correlates well with the fluoroscopic observations of Wade (22), who found that the left diaphragm descends more than the right during deep inspiration. The possibility that a similar but less marked difference is present in the lower zones during quiet breathing is not excluded by our data, and our failure to show a significant difference may be the result of the somewhat greater variability of the quiet breathing indices due to lower counting rates.

The mean distribution index for perfusion was significantly greater for the *right* lower zone than for the *left* lower zone (Table I). Although it is possible that this small difference is the result of a systematic error in equilibrium counting rates over the left lower zone because of dissolved xenon in the heart, this seems unlikely in view of the distance between the heart and the chest counters, as well as the relatively slight solubility of xenon. West and Dollery (10) found clearance rates to be considerably greater at the right base than at the left in normal subjects, but this difference appeared to be due largely to interference with counting rates on the left by the presence of radioactive blood within the heart.

The cases presented illustrate some of the clinical applications of this method. It will be noted that the measurements of regional perfusion are in good general agreement with the qualitative estimates provided by tomography and pulmonary arteriography in Patient 1 and by tomography in Patient 2. The measurements of regional ventilation provide information not obtainable by other techniques and distinguish clearly between Patient 1 with regionally localized emphysema and Patient 2 whose emphysema is generalized. It is of particular interest that in Patient 1 the relative ventilation of the most severely affected areas was greatly reduced during quiet breathing, but that these areas received a much larger fraction of the inspired air on deep inspiration. This discrepancy in distribution has been observed repeatedly in patients with localized emphysema and demonstrates the importance of making measurements with an inspired volume equal to the patient's tidal volume if information concerning distribution during steady-state conditions is desired.

It seems clear that precise knowledge of regional function will be necessary for the development of a more rational approach to surgery in patients with chronic lung disease. In Patient A.G., as well as in other patients with emphysema treated surgically at this hospital, the radioactive xenon studies have been of considerable assistance in preoperative appraisal, permitting both an estimate of the amount of function in the portion of lung to be removed and an estimate of the functional integrity of the portions to be left behind.

Briscoe and co-workers (23) have analyzed ventilation-perfusion relationships in patients with pulmonary emphysema by measurement of nitrogen clearance, oxygen uptake, and arterial saturation. Such studies demonstrate the nonhomogeneity that may exist in such patients, but the extent to which the computed volumes of "poorly ventilated space" have spatial significance is uncertain. Patients 1 and 2 described above illustrate quite different situations in two patients with pulmonary emphysema whose tests of overall lung function were similar. In Patient 1 (A.G.) the pathological change was much more marked in the lower than in the upper lobes, while in Patient 2 (L.T.) all areas were approximately equally affected.

The finding of reduced perfusion at the lung bases in Patient 4 is in agreement with the findings of Dollery and West in their study of patients with mitral stenosis (12). It is of additional interest that despite the gross abnormality of perfusion the distribution of inspired air was entirely normal.

Several facts may be pointed out concerning differences between the oxygen[15] and xenon[133] methods of assessing regional pulmonary function. The oxygen[15] single-breath method requires less cooperation from the patient and is more quickly done, making body movement less of a problem and permitting repeated determinations at one sitting. Since oxygen[15] is a positron emitter, it is possible by the use of coincidence counting to achieve a very narrow and sharply defined counting field. For the measurement of regional perfusion, radioactive carbon dioxide has the advantage that clearance rates are related to absolute blood flow, whereas with xenon[133] only the relative distribution of flow can be measured. Furthermore, by the use of radioactive carbon monoxide it has been possible to study regional diffusion (11).

Oxygen[15] compounds are taken up by the red cell, however, and rapidly appear in the heart and other extrapulmonary structures, where they may interfere with external counting. With data from a single inspiration, relative ventilation can be determined only for geometrically symmetrical counting fields or by estimating relative lung volume within different counting fields whereas, by the use of a rebreathing technique with

xenon^{133}, it has been possible to make accurate comparisons of ventilation in different regions independent of the volume of lung within the counting fields. It is also possible from the shape of the xenon^{133} washout curves to make some assessment of mixing within a single counting field. The most serious obstacle to the general use of oxygen^{15} for the study of patients is its half-life of only 2 minutes, which requires that studies be done in close proximity to a cyclotron or other powerful particle accelerator capable of producing this isotope.

SUMMARY AND CONCLUSIONS

1. A radioactive isotope of the inert gas, xenon, has been used in conjunction with externally placed scintillation counters to estimate separately the function of six different regions of the lung. By comparison of external counting rates after a single breath and after rebreathing an air-xenon mixture, it has been possible to compute an index of relative ventilation that is independent of the volume of lung within the counting field. Determinations were made at two levels of inspiration in order to compare the distribution during normal quiet breathing with the distribution after a single full inspiration. By the intravenous injection of dissolved xenon^{133} during breath holding, the relative perfusion of lung in different regions has been determined.

2. In 21 seated normal subjects, it was found that *a*) the lower portion of the lung is somewhat better ventilated than the upper portion, but receives a much greater fraction of the total pulmonary blood flow; *b*) the distribution of inspired air is slightly more uniform on deep inspiration than during quiet breathing; *c*) the middle and lower portions of the lung are better ventilated on the left than on the right during deep inspiration; and *d*) the lower portion of the lung is probably better perfused on the right than on the left.

3. Forty patients with various cardiac or pulmonary disorders have been studied, and four illustrative cases are presented. Two of these illustrate the differences in regional distribution of disordered function that may occur in patients with pulmonary emphysema. The third patient demonstrates the value of the technique in assessing lobar function after transposition surgery, and the fourth patient illustrates normally distributed ventilatory function despite a disturbed distribution of perfusion in uncomplicated mitral stenosis.

4. The advantages and disadvantages of this method in comparison with the oxygen^{15} technique of West and co-workers (9–13) are discussed.

5. It appears that the xenon technique described is capable of extensive application to both investigative and clinical problems.

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