complete, presents some of the developments in counting and shielding techniques that are needed to meet nuclear medicine's increasing instrumental demands. They re-emphasize the need for good spectrometry in the clinical counting of gamma rays.

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4. Radioisotope Methodology in the Study of Respiratory Diseases

Henry N. Wagner, Jr., M. D.*

The respiratory functions of the lung consist of ventilation, diffusion and perfusion, processes which result in the exchange of carbon dioxide for oxygen in the environment. Other functions are of a supporting nature and are non-respiratory. These include cough, ciliary activity, mucus secretion, and alveolar phagocytosis.

The respiratory functions in particular have been studied by a variety of techniques. For example pulmonary blood flow has been measured by direct Fick, dye-dilution and body-plethysmographic methods. A reasonable question is what radioisotope methods provide that is new in the study of pulmonary diseases? What new role do these techniques play in the evaluation of lung function?

The important contribution that these techniques have made is that they permit evaluation of lung function in particular *regions* of the lung. They make possible measurement of regional pulmonary blood flow, regional ventilation and clearance of particulate matter from various regions of the tracheobronchial tree and alveoli, using techniques made possible by the ability of gamma radiation to penetrate the body and be detected by externally-placed scintillation detectors.

Pioneers in the development of these areas have been Knipping [1] in Germany, West, Dollery and Hugh-Jones [2,3] in England and Bates' group in Canada[4]. Five radionuclides have been used: ^{15}O, ^{11}C, ^{13}N, ^{85}Kr, and ^{133}Xe. More recently, ^{131}I, ^{125}I, and ^{51}Cr have been employed as tracers for particulate matter in pathophysiological studies of the lungs.

Measurement of Regional Ventilation

In the measurement of ventilation to different regions of the lung, the subject takes a single breath of a radioactive gas and holds his breath for 10 to 15 seconds. Scintillation detectors in front of and behind

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the chest record the time course of radioactivity in various regions of the lungs. In inspiration the radioactive gas enters various regions of the lung at a rate directly related to ventilation. During the breath-holding period, the radioactive gas is removed at a rate related primarily to the diffusability of the gas into other regions of the lung, diffusability through the alveolar capillary membrane, and perfusion of the particular region.

The choice of the radioactive gas depends upon which parameter of respiratory function one wishes to measure. If, in addition to ventilation, one wishes to measure regional blood flow, one can use a gas, such as CO_2, labelled with ^{15}O, since the transfer of this gas into capillary blood is quite rapid. ^{133}Xe is more readily available than ^{15}O and has been more widely used. The detector used by Bates and his associates for ^{133}Xe consisted of a bank of six crystal scintillation detectors directed toward the upper, middle, and lower zones of each lung. ^{133}Xe was delivered either by a single inhalation or by having the patient breathe xenon from a closed spirometer until there was no change in counting rate over any of the different zones of the lungs. In their initial studies of normal persons, these investigators found that the ^{133}Xe method confirmed the findings of West and Dollery that ventilation is greater in the lower zones of the lung compared to the upper when the subjects were in an upright position, but that this difference disappeared when they were supine. In studies of patients with asthma, the subjects were allowed to breathe the radioactive gas in a closed system and the time required for the lung and breathing circuit to come into equilibrium was determined. It was found that there were zones of the lung with considerable impairment of ventilation, a localization of disease that was not possible by clinical or radiographic examination. Similar data were obtained in patients with pulmonary emphysema.

Venrath and Rink [5] have also used ^{133}Xe to study regional ventilation and have described severe impairment of regional vetilation from lesions causing local stenosis within the bronchial tree while intrapulmonary diseases which did not lead to bronchial narrowing showed only unimportant impairment of regional ventilation. Endler [6] reported the use of ^{133}Xe to study ventilation in over 400 patients.

An important recent advance in nuclear radiation instrumentation makes ^{133}Xe particularly useful. ^{133}Xe decays with emission of a 31 kev K X-ray and an 81 kev gamma ray. These low energy photons interact with the photocathode of an image intensificiation tube and can be amplified to the degree that the light can be detected with photographic film. This instrument, developed by Picker Nuclear in collaboration with Ter-Pogossian, is referred to as a Nuclear Image Amplifier. The two major advantages of this method of imaging the spatial distribution of radioactivity are high resolution and rapid speed. The latter makes possible precise localization of radioactivity within the tracheo-bronchial tree within a few seconds, before the gas can diffuse into other less well ventilated areas of the lungs.

Regional ventilation can also be studied by using fine particles, labelled with ^{131}I, that can be inhaled and are distributed according to regional ventilation. The particles are localized in the alveoli by the process of phagocytosis. To distribute these minute particles throughout the lungs, one must administer them in the form of dry particles. Studies by West and his associates with $H_2{}^{15}O$ indicated that, when radioactive water vapor is inhaled by normal persons, almost no activity reaches the alveoli, most of it being deposited in the upper airways. In our present studies, we have the subjects inhale the fine particles that have been dissolved in volatile liquids under pressure. The vehicle evaporates upon exposure to air and particles penetrate deeply into the lungs.

Measurement of Regional Pulmonary Blood Flow

Several techniques have been used to measure regional pulmonary blood flow in man. The rate of clearance of radioactivity following a single breath of radioactive gas may be determined. The rate of fall is a measure of the blood flow in the region toward which the detector is directed, provided the gas is readily absorbed into the perfusing blood. Using $C^{15}O_2$, West and his colleagues investigated the distribution of pulmonary blood flow in several physiologic and pathologic conditions. They found that blood flow wasl ess to the upper regions of the lungs when subjects were erect. In pathologic conditions, such as moderate mitral stenosis and left ventricular failure, where the pulmonary venous pressure is raised, there was a more even distribution of blood flow in the

lung, while severe, prolonged mitral stenosis was associated with a reversal of the normal distribution of flow, that at the base becoming less than at the apex.

Bates and his colleagues introduced the use of a somewhat different technique. Instead of using very soluble gases such as carbon dioxide, a less soluble gas, such as xenon, dissolved in saline, is injected into the pulmonary artery. As it passes through the lung, almost all of it diffuses into the alveoli, and if the lung is held in inspiration, the radioactive gas will remain there for many seconds. Advantage is taken of this to scan the lung rapidly with external radiation detectors, with the result that the counting rate in any particular region will reflect the regional blood flow. A second determination is made after a period of rebreathing to distribute the gas evenly throughout the whole alveolar volume, thus allowing the blood flow per unit lung volume to be derived.

An example of the application of regional pulmonary function studies with ^{133}Xe is the study of patients with bronchial asthma. In half of 12 patients studied, ^{133}Xe inhalation studies revealed significant abnormalities of ventilation that were regional rather than diffuse. In studies of 40 patients with emphysema, the same group of investigators found that in these patients the measurement of regional concentrations of ^{133}Xe after a single breath was not satisfactory, but that procedures involving rebreathing the radioactive gas from a closed-circuit spirometer were. The results suggested that emphysema is probably more focal than had previously been suspected, and that the concept of generalized emphysema may be an oversimplification.

Liese[7] has found that the use of radioactive gases, such as xenon, seemed promising in the early diagnosis of bronchial carcinoma, since changes in the pulmonary circulation occurred early in certain patients with small lesions.

Recently a different technique has been used to measure regional pulmonary blood flow. While this technique has been found to have other uses, its most important contribution to date has been in the diagnosis of massive pulmonary embolism [8]. The diagnosis of massive pulmonary embolism is frequently difficult and always uncertain, primarily because the symptoms and signs may mimic those of some other diseases, such as myocardial infarction or pneumonia. Ancillary examinations, including X-ray study of the chest and electrocardiography, are rarely definitive. The diagnosis can be suspected when sudden dyspnea, pleural pain, hemoptysis, syncope or a blood pleural effusion occur in patients who are predisposed to pulmonary embolism — that is, those who are suffering from congestive heart failure or polycythemia, or who are bedridden, as during the postoperative or postpartum state.

A high degree of suspicion is no longer adequate. When therapeutic measures were relatively nonspecific absolute accuracy in diagnosis was not required. Today, however, the need for improved diagnostic ability has increased because new means of treating pulmonary thromboembolism are available. These include anticoagulant drugs to prevent further thrombosis, proteolytic agents to dissolve thrombi that have already formed and specific surgical therapy, including ligation or plication of the inferior vena cava, to prevent passage of peripheral thrombi into the lungs, and pulmonary embolectomy, the removal of obstructing clots from the pulmonary arteries themselves.

Radioisotope scanning has been found to be a safe and effective way of diagnosing massive pulmonary embolism in man. In addition to its use in thromboembolic diseases, the method has been employed to obtain information concerning regional pulmonary blood flow in other pulmonary diseases.

General Principles in Measuring Regional Pulmonary Blood Flow by Radioisotope Scanning

Despite differences in the details of various methods of measuring regional blood flow most are based on the principle of conservation of material. A known quantity (Q) of material flowing into a region is divided three ways: some (Qi) will accumulate in the region; some (Qm) will be metabolized; and the remainder (Qe) will flow out of the region. This can be described by the equation: $Q = Qi + Qm + Qe$. The inflow (Q) into a region is equal to the blood flow (F) into the region multiplied by the concentration of the substance in the arteries leading to the region (Ca). The basic equation can therefore be written $F \times Ca = Qi + Qm + Qe$. If the injected material is removed from the circulation in a single passage through the region, the result is $Qe = O$, and if the substance is not metabolized during the period of observation, $Qm = O$; therefore, the amount of the

substance found in the region will be proportional to the blood flow to the region -- that is, $F \times Ca = Qi$. The principle has been applied to the meaurement of regional pulmorary blood flow. One injects macro-aggregates of human serum albumin labeled with either ^{51}Cr or ^{131}I and determines their concentration in various regions of the lungs by radioisotope scanning. The concentration of the aggregates in various parts of the lung is directly related to pulmonary blood flow.

Macroaggregated Human Serum Albumin (MAA)

In 1956 Halpern and his associates[9] introduced the use of aggregates of human serum albumin as a type of particle that offered important advantages in the study of phagocytosis. In contrast to other particles, such as carbon, thorium dioxide, saccharated iron oxide, chromic phosphate and colloidal gold, which remain in phagocytic cells almost indefinitely, the albumin aggregates (AA) can be metabolized after ingestion by these cells. This made it possible to administer large quantitites of the albumin aggregates and derive information about the phagocytic capacity of the reticuloendothelial system not obtainable with the use of minute quantitites of nonmetabolizable materials. To study phagocytosis, one uses particles whose average diameter is approximately 10 millimicrons. By altering the conditions under which the albumin particles are aggregated, one obtains much larger aggregates, referred to as macroaggregated albumin (MAA), which vary in size from 1 to 100 microns, and can be labeled with ^{131}I, ^{125}I, or ^{51}Cr.

Toxicity Studies

Radioisotope-labeled macroaggregated albumin is potentially toxic in three ways: alteration in the structure of the albumin molecule might render it antigenic to man; obstruction of pulmonary capillaries and arterioles might have deleterious cardiovascular effects; and, lastly, there might be a radiation hazard. Consequently, extensive testing for potential toxicity was carried out before its initial use in human beings. Before the study of MAA, we administered AA in more than 1,200 studies in over 300 subjects and were unable to detect any evidence of antigenicity, although human-albumin aggregates were antigenic to foreign species (dogs, rabbits, and guinea pigs), and cross-reacted with normal human serum albumin. Studies with MAA similarly failed to give evidence of antigenicity to man. Testing included skin reactions, albumin clearances and careful evaluation of symptoms or signs after repeated injection.

In studies of cardiovascular toxicity, the LD_0 was determined in rats and found to be of the order of five thousand times the dose used to perform lung scans in man — that is, over 10 mg per kilogram of body weight. Doses as high as 10 mg per kilogram were also administered to dogs without increases in pulmonary-artery pressure or respiratory rate, and without a decrease in femoral arterial pressure. Rats that received up to 10 mg of MAA per kilogram of body weight were indistinguishable from control rats in histologic examination of the lungs, immediately and one week after injection.

When radioiodinated MAA was used the thyroid gland was blocked by the administration of 0.5 *ml* of Lugol's solution per day for four days to prevent accumulation of radioactive iodine. When this was done, over 80 per cent of the radioactivity appeared in the urine within 48 hours, and the entire dose could be accounted for within a period of several weeks. When ^{51}Cr labeled MAA was used the excretion into the urine was slower, approximately half the dose remaining in the liver. With both ^{131}I and ^{51}Cr the limiting organ from the standpoint of radiation dose was the lungs, the dose being 0.3 and 3.0 rads, respectively, for 300 microcuries of ^{131}I and one millicurie of ^{51}Cr.

Characteristics of the Lung Scan in Normal Man

In all cases, a dose of 300 microcuries of ^{131}I-labeled MAA or 1,000 microcuries of ^{51}Cr was injected while the patient lay supine. To obtain more quantitative data than that provided by the scanning procedure, the output of the detection system could lead to either a ratemeter or scaler as well as to the photorecorder.

The scan performed by means of a detector anterior to the chest was characterized by an area of decreased radioactivity corresponding to the cardiac silhouette. The superior mediastinum was also visualized as an area of decreased concentration of radioactivity. When the scan was performed from the posteroanterior projection the cardiac area was diminished in size in relation to that seen in the anterioposterior projection,

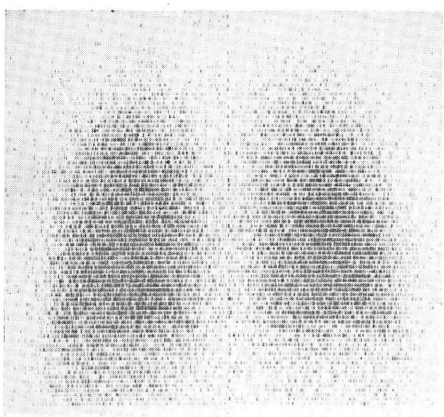


Fig. 1. Normal lung scan.

and a larger area of lung could be visualized (Fig. 1 and Fig. 2).

Massive Pulmonary Embolism in Man

In the present series of over 300 patients autopsy, operation or selective pulmonary arteriography confirmed the diagnosis of regional pulmonary avascularity in cases in which filling defects were observed in the lung scans. The size of the smallest lesion that could be detected is not known with certainty although it is likely that lesions less than a few centimeters in diameter would be missed with present scanning equipment. Examples of massive pulmonary emboli are shown in Figures 3, 4, and 5.

Is the scanning procedure sufficiently definitive to permit the diagnosis of massive pulmonary embolism on the basis of the scan alone? The answer to this question is a qualified no, because, as we have previously reported [9], most parenchymal lesions of the lungs result in avascularity of the pulmonary circulation, the blood supply presumably being provided by the bronchial circulation. On the other hand, in a large number of patients, a characteristic pattern has been observed in massive pulmonary embolism. This pattern consists of crescent-shaped defects, particularly at the lateral borders of the lungs.

In the studies in dogs we found that the right lower lobe is by far the most commonly involved lobe when large emboli pass into the lungs. Frequent involvement of the right lower lobe has also been reported in pathological studies in man, and in the present series of patients we have confirmed this finding.

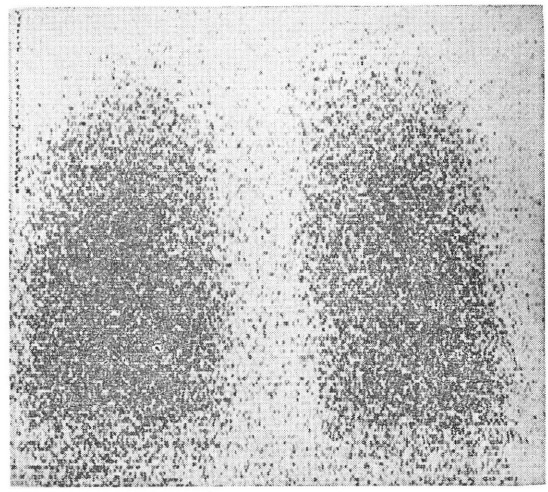
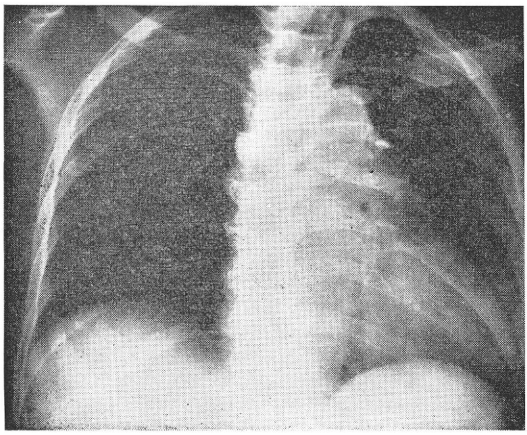


Fig. 2. Normal lung scan performed with a posterior detector. The patient was injected with MAA while standing, thereby decreasing the concentration of particles at the apices of the lungs.

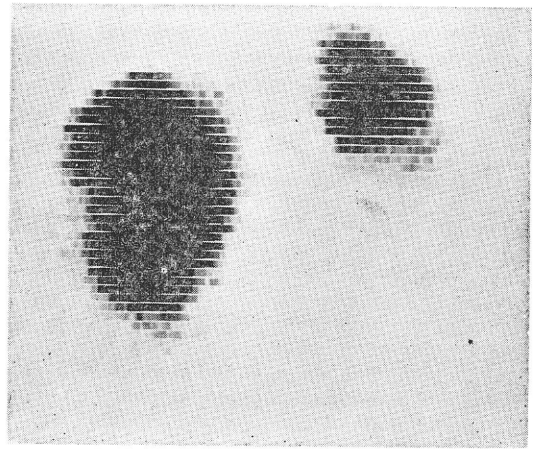
Even in the absence of the characteristic pattern, one should suspect pulmonary embolism if one finds multiple avascular areas on the scan, particularly if no parenchymal lesions are seen on the X-ray film of the chest. This has usually been the case, both in the experimental emboli in dogs and in patients subsequently proved to have massive embolism. Particularly helpful is the finding of a corresponding zone of increased radiolucency, initially reported by Westermark [10] and recently extended by Torrance [11].

On the other hand, if there is a lesion on the X-ray of the chest, from our past experience, regardless of whether the lesion is the result of an infarct, pneumonia, atelectasis, abscess or tumor, the area will be avascular so far as the pulmonary arterial blood flow is concerned, and an area of decreased radioactivity will be found on the lung scan. In these cases, although of considerable academic interest, the information is of no diagnostic value.

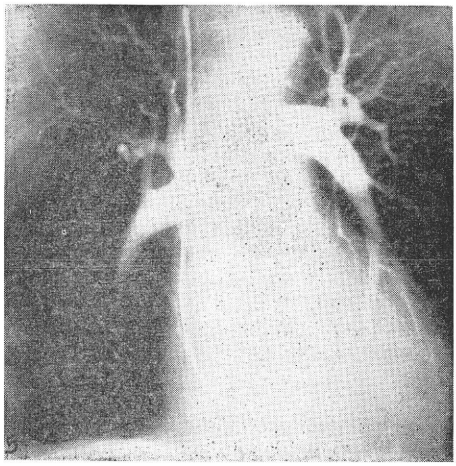
Since we have used selective pulmonary arteriography as a means of confirming the diagnosis of pulmonary embolism in the patients who were not studied at autopsy, a reasonable question is what lung scanning offers in the diagnosis of pulmonary embolism that pulmonary arteriography does not. Each technic has its own particular strong points and deficiencies. To be completely satisfactory, pulmonary arteriography must be performed by injection of relatively large



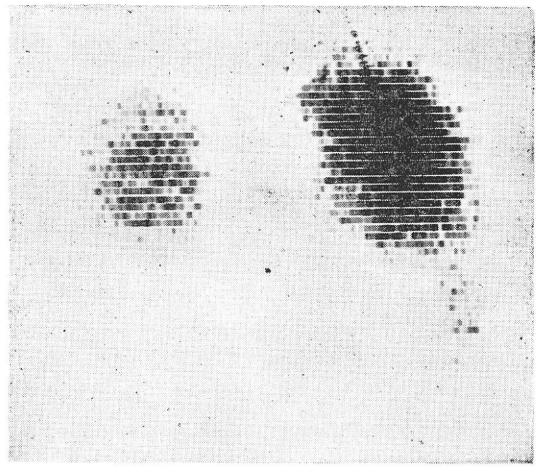
3 A.



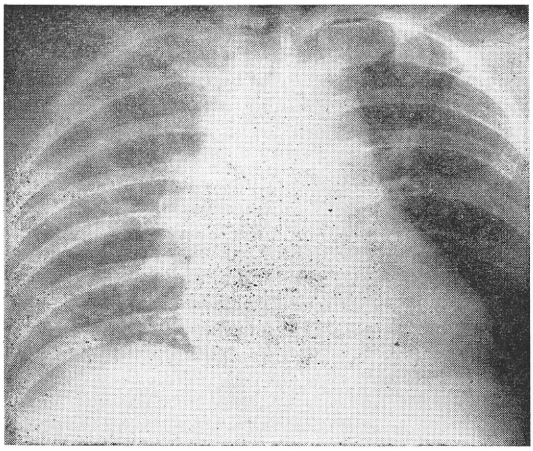
3 B.



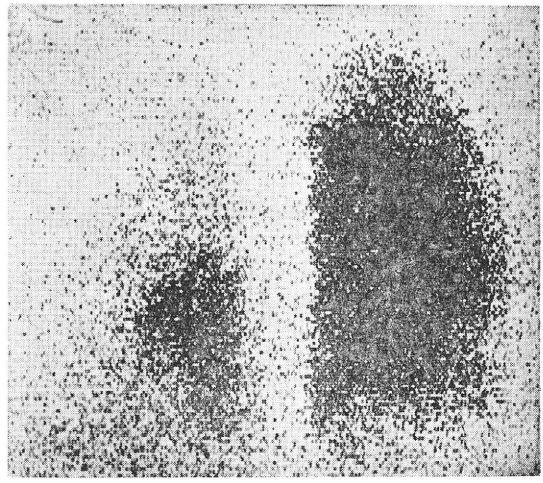
4 A.



4 B.



5 A.



5 B.

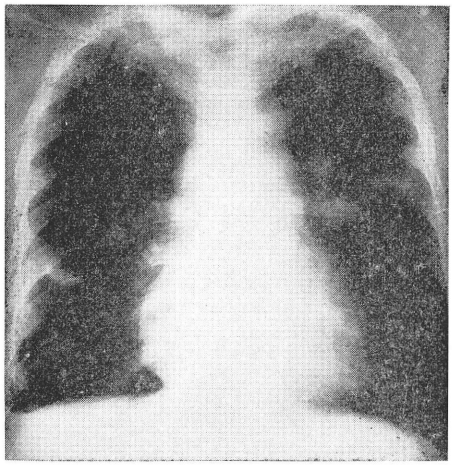
Fig. 3 (A, B), Fig. 4 (A, B), and Fig. 5 (A, B). Lung scans and chest radiographs in patients proved to have had massive embolism.

volumes of radiopaque material directly into the pulmonary artery. Intravenous injections usually do not give sufficiently good definition of the vasculature. Therefore, cardiac catheterization is required, which is cumbersome at best and may result in the dislodgment of venous thrombi at worst. Furthermore, experience has shown that patients with pulmonary hypertension tolerate injections of X-ray contrast material very poorly. Up until now, lung scanning has not been associated with any known toxicity and does not result in any morbidity. An important advantage is that serial studies can be performed at frequent intervals in the same subject, thereby providing follow-up information at intervals that would not be possible if one had to perform repeated pulmonary arteriography. Examples of follow-up studies now in progress are an evaluation of the natural history of pulmonary embolism, evaluation of the incidence of recurrences of pulmonary embolism after plication or ligation of the vena cava and determination of the efficacy of thrombolytic drugs.

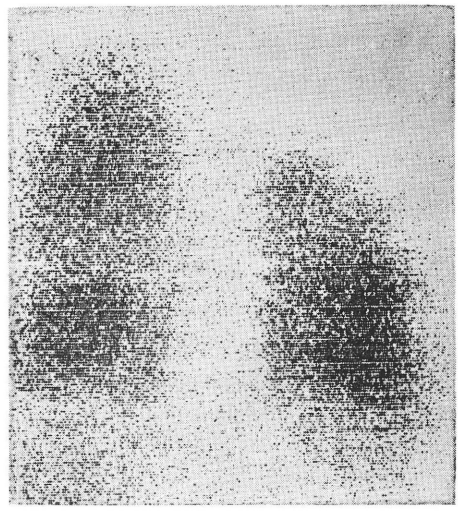
The scanning procedure is technically simple, and, at present, we have a scanner available for immediate use as soon as the diagnosis is suspected. In many patients serious consideration of the diagnosis of massive pulmonary embolism was discarded when lung scans revealed normal pulmonary vasculature. On the other hand, whenever we obtained strong evidence of multiple areas of pulmonary avascularity, selective pulmonary arteriography was performed if the possible necessity of pulmonary embolectomy was considered.

In a series of over 300 lung scans carried out in patients with a variety of diseases, we encountered four patients with bronchogenic carcinoma in whom the scan indicated obstruction of pulmonary blood flow to a degree not suspected from the size of the lesion on the radiograph of the chest. An example is shown in Figure 6. The radiograph of the chest showed a left hilar mass and an area of linear atelectasis in the right mid-lung field. The scan revealed nearly complete avascularity of the left upper lobe as well as a band of decreased blood flow on the right. These observations led us to perform experiments in dogs which indicated that partial bronchial obstruction decreases regional pulmonary blood flow to a degree that can be readily visualized by scanning techniques.

Foley catheters (urethral retention catheters) were inserted through the larynx into the bronchus of the right lower lobe of seven dogs anesthetized with pentobarbital. Four to six *ml* of radiopaque contrast media were injected into the balloon. Air flow through the lumen of the catheter remained adequate throughout the study. An example with the inflated balloon in the right lower lobe bronchus is shown in Figure 7A. The catheter had no effect on pulmonary blood flow when the balloon was not inflated. In contrast, pulmonary blood flow was markedly impaired (Fig. 7B), as indicated by the distribution of the radioactive macroaggregates injected intravenously after the balloon had been inflated.

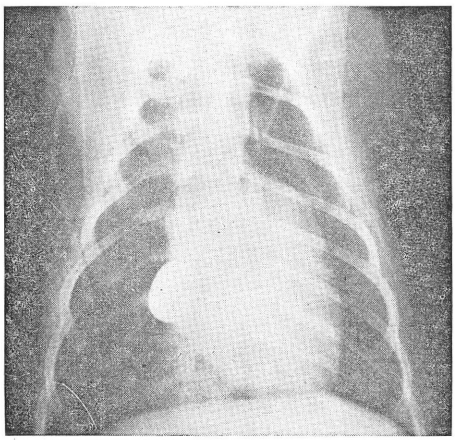


A.

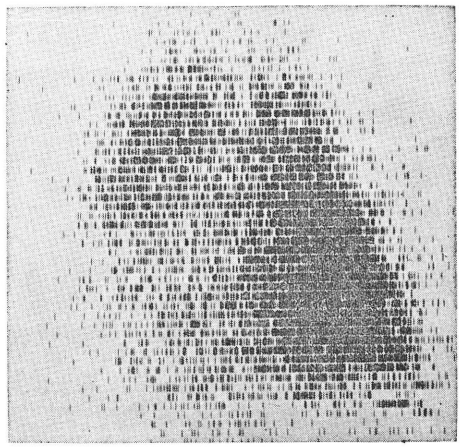


B.

Fig. 6 (A, B). Chest radiograph and lung scan of a patient with proven carcinoma of the lung.



A. Radiograph of a dog showing balloon inflated with radiopaque contrast medium in the right lower lobe bronchus.



B. Lung scan in the same dog, showing marked avascularity of the right lower lobe.

Fig. 7.

This technique of measuring regional pulmonary blood flow measures only that flow from the pulmonary arteries. Since the systemic circulation does not contain macroaggregates, the bronchial arteries do not deliver radioactivity to the lungs. Therefore absence of radioactivity does not indicate a decrease in *total* blood flow but rather a decrease in *pulmonary arterial* blood flow.

At present we are investigating the possibility that lung scanning may be helpful in the early diagnosis of bronchogenic carcinoma and are studying patients with unexplained hemoptysis, hilar masses of unknown cause, and chest pain in whom the chest radiograph is unrevealing.

Comparison of Radioisotope Scanning and Differential Oxygen Uptake of the Lungs[13)]

Differential spirometry is an accepted method for evaluating the distribution of pulmonary blood flow between the right and left lung. It has been found to be particularly useful prior to surgery in patients with unilateral and bilateral pulmonary disease. With this technique an index of the vascular perfusion to each lung is obtained by measuring the percentage of the total oxygen uptake which is taken up by each lung. A study was undertaken to compare the estimates of pulmonary blood flow to each lung obtained by bronchospirometry and by lung scanning. Eighteen patients with unilateral and bilateral lung disease were studied. Sixteen of them had tuberculosis and two had bronchiectasis. Differential spirometry was performed at rest in the supine position using a modified Gaensler-Collins bronchospirometer. The two bells of the bronchospirometer were filled with 100 per cent oxygen and each contained a soda lime carbon dioxide absorption canister.

After topical cocaine anesthesia, a Carlens catheter was placed in the trachea. When the balloons on the catheter were inflated, this double lumen catheter separated the ventilation from each lung. The oxygen uptake of each lung was determined simultaneously and was expressed as a percentage of the total uptake. A scan was obtained three to ten days after the differential spirometry. During this interval there were no appreciable changes in the chest X-ray. Radioisotope scanning of the lungs was performed following the intravenous administration of 0.5 *ml* of one per cent macroaggregated human serum albumin tagged with 300 microcuries of ^{131}I. The majority of the particles ranged in size from 20 to 100 μ, and presumably were retained in pulmonary vessels of similar size. Once deposited, the distribution of radioactivity could be determined at any time over the next several hours. Scanning of the lungs was performed with the detector over the anterior chest in six cases and posteriorly in twelve cases.

An estimate of the percentage of vascular perfusion to each lung was determined from the radioisotope scan in the following manner: the central portion of

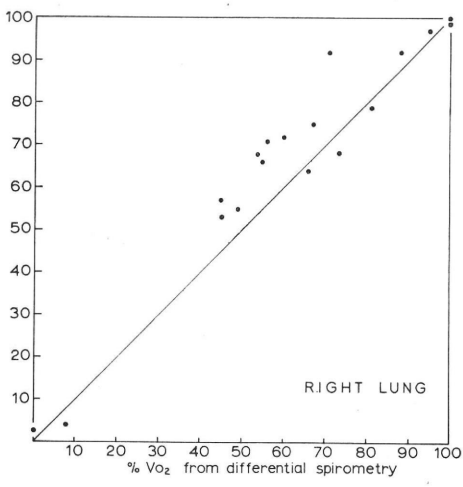


Fig. 8.

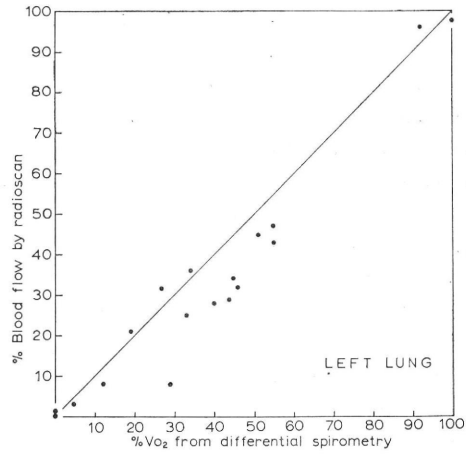


Fig. 9.

Relationship between oxygen uptake measured by differential bronchospirometry and quantitative lung scanning in patients with lung disease. Figure 8 refers to the right lung while Figure 9 refers to the left.

a standard X-ray viewbox was used as the light source in a darkened room. A photometer with a one inch diameter porthole was placed in direct contact with the radioisotope scan film. A control reading in foot-candles was obtained from a clear area of the film. Each lung was divided into an upper, middle, and lower zone and three readings were taken from different areas in each zone. The reciprocal of each reading was calculated, since this number corresponds to the density of the film at each site. The average value from each lung was calculated. The increase in density over the control value was calculated for each lung by subtracting the average of the nine readings from the control reading. The increase in density for each lung divided by the increase in density for both lungs was then taken as an index of the percentage of vascular perfusion to each lung.

The correlation between radioisotope scanning and differential oxygen uptake to estimate the percentage of the total blood flow to the right and left lungs was excellent (r=.96, P .001) (Figs. 8, 9).

An important advantage of the radioisotope scanning technique was its usefulness in estimating the differences in pulmonary arterial perfusion between regions of the same lung. Radioisotope scanning of the lungs appears to be a safe, rapid, and reliable method for estimating the relative distribution of pulmonary artery blood flow to each lung.

Clearance of Particulate Matter from the Tracheobronchial Tree in Patients with Tuberculosis [14]

The importance of physioiogical mechanisms for clearing dust and other particulate matter from the lungs and tracheobronchial tree is illustrated by the fact that, while a coal miner may in his lifetime inhale 6,000 grams of coal dust particles less than 4 micra in size, only 100 grams will be found in his lungs at post-mortem examination. In a typical English industrial town, a person inhales about 100 grams of carbon during a lifetime, but only 0.5 to 1.0 grams are found in his lungs and bronchial glands at autopsy. From experimental studies of the behavior of particulate matter in the respiratory tract, it is known that larger particles, 10 micra or more in size, are trapped in the nose, while smaller particles penetrate further into the lungs and settle upon the mucus blanket lining the tracheobronchial tree. About 90 per cent of particles less than one micron in size penetrate through to the lungs.

One mechanism by means of which foreign particles are eliminated from the lungs is the activity of cilia which line the bronchial tree as far down as the respiratory bronchioles. Riding on the mucus blanket which covers the cilia, particles are propelled up to the oropharynx, where they are swallowed. A second

mechanism is coughing. In the past, quantitative study of these mechanisms to determine their relative importance and degree of derangement under various physiological and pathological conditions has been difficult, particularly in human subjects. Recent advances in the field of external radiation detectors combined with the ability to label a variety of particles with gamma-emitting radioactive isotopes have made possible a new approach to these problems.

In the present studies 0.1 to 0.3 *ml* of a solution containing less than 0.1 mg of aggregated albumin labelled with 20–100 microcuries of ^{131}I was injected at various positions along the tracheobronchial tree in man by means of a fine radiopaque catheter inserted through a needle in the crico-thyroid membrane. Local anesthesia was used at the site of injection, but no other medication was necessary. The patients lay quietly in the supine position.

The rate and pattern of movement was measured in two ways, by means of serial radioisotope scanning of the chest and by means of two stationary crystal scintillation detectors with slit collimators (3.0×0.3 cm). Studies were carried out in afebrile male patients with chronic pulmonary tuberculosis in various stages of activity at the time of study. The thyroid gland was blocked with 0.5 *ml* of Lugol's solution because of eventual deiodination of the albumin aggregates.

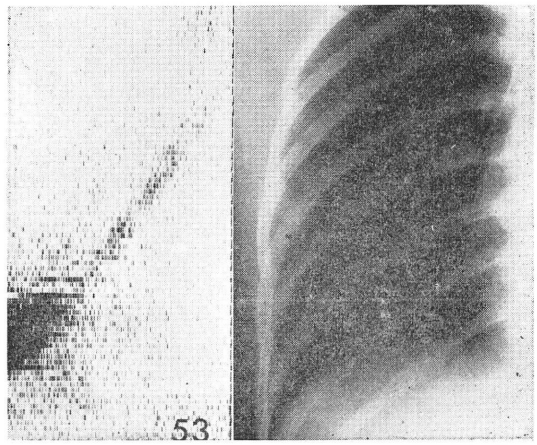


Fig. 10. Scan of the distribution of aggregated albumin (AA) particles, 53 minutes after their injection into the lung through a catheter extending into the right main bronchus. On the right the catheter can be seen in the X-ray of the chest.

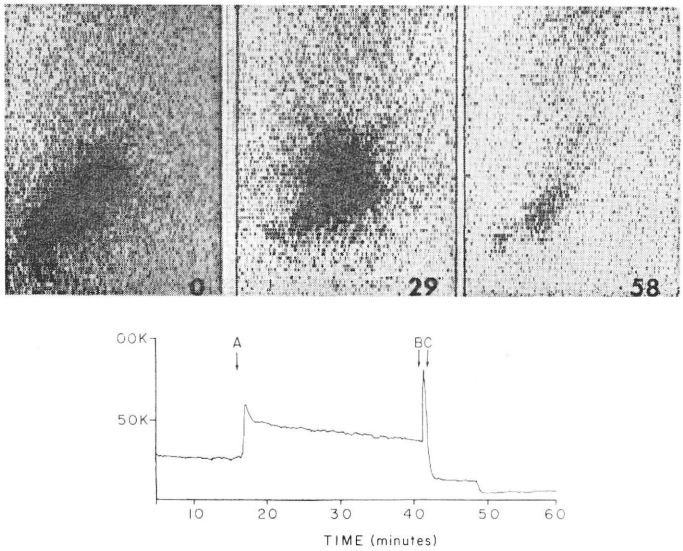


Fig. 11. Seria scans of the distribution of AA particles. The numbers 0, 29, and 58 refer to the time in minutes after injection of the particles into the right main bronchus. The area of increased radioactivity in the scan performed 29 minutes after injection of the particles was at the carina. The lower graph indicates the time course of radioactivity at the carina. At point A the patient coughed and the amount of radioactivity increased suddenly, presumably the result of particles being propelled upward to the carina. Thereafter the radioactivity decreased up to point B where the patient again coughed. This resulted in a further increase in activity; at point C the patient again coughed and the amount of radioactivity fell precipitously. The final decrease in activity occurred at 58 minutes and was also due to a cough.

Figure 10 illustrates the position of the catheters in the right lung of one patient. The scanning image of the distribution of the particles was obtained in this study 53 minutes after injection of the AA particles. The large area of increased activity at the most distal point remained unchanged at least as long as two hours presumably because of the location of the particles in alveoli or terminal bronchioles where cilia are absent. The rest of the particles lining the bronchi were moved slowly toward the larynx at a rate of approximately 1–2 cm per minute.

In many patients, foci of accumulatian of the particles were observed to form as the particles moved. Most often these were at the carina, but also in other regions along the tracheo-bronchial tree. An example is shown in Figure 11. The graph in the lower part of the figure represents the rate of clearance of the radioactivity, as measured by a detector at the carina. There was a net decrease in concentration of radioactivity as the particles were being moved by ciliary activity. At point A the patient coughed with the result that the particles moved from lower in the tracheobronchial tree up to the carina; ciliary activity then moved the particles at a steady rate for approximately the next 20 minutes; then at point B, the patient coughed a large number of particles up to the carina, followed by another cough at point C, which resulted in a great decrease in activity, related to movement of the particles up to the oropharynx. Serial scans performed at the numbers (minutes after the injection of the particles) gave a visual image of the processes being monitored with the stationary detectors.

In the patient shown in Figure 12, the second scan shows a typical focal concentration of radioactivity. The tracing at the bottom of the figure was obtained by a stationary detector over the lower end of the area of distribution of the AA particles. In this patient there was a continual decrease in concentration of the radioactivity, presumably entirely due to ciliary activity since the patient did not cough throughout the study. In all subjects the radioactivity could be detected eventually in the stomach, arriving there when the particles in the oropharynx were swallowed. Insignificant amounts of radioactive iodine were detectable in the blood until after the particles had been swallowed, thus indicating that the phagocytic process did not participate significantly in the movement of the particles up the tracheobronchial tree to the pharynx.

LaBelle and Brieger have reported that the physiological events following the intratracheal injection of particulate matter is the same as that seen after the inhalation of the same particles. Consequently we chose to use this simple method in our initial studies. The effect of ciliary activity and cough could be readily quantified. Both were of considerable importance in clearing the lungs of this type of particle. Studies of other types of particle are in progress.

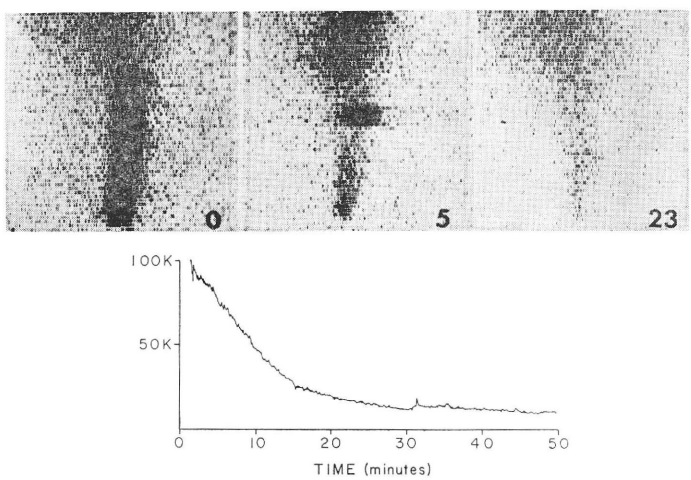


Fig. 12. Serial scans of the distribution of AA particles after injection into the right main bronchus. The numbers 0, 5, and 23 indicate the time in minutes that the scan was begun after injection of the particles. The lower graph is the time course of radioactivity as measured by a stationary radiation detector at the lower end of the area of maximum radioactivity.

The frequent finding of areas of decreased ciliary activity where the particles seem to gather is of interest since these may indicate areas where cilia or ciliated cells have been destroyed or where changes of the type described by Hilding may be found. He reported areas of squamous epithelial cells scattered throughout the lower respiratory tract, particularly at the carina. It has been known for many years that islands of metaplasia of ciliated columnar epithelium result from chronic inflammation. In these areas squamous epithelium replaces the ciliated, mucous covered epithelium, and the regions of diminished motility may correspond to such areas.

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