

# USING XENON-133 AND A SCINTILLATION CAMERA TO EVALUATE PULMONARY FUNCTION

Merle K. Loken and Hugh D. Westgate

*University of Minnesota Hospitals, Minneapolis, Minnesota*

During the past several years considerable attention has been given to evaluating pulmonary disease using radioisotopic techniques. The majority of the radioactive preparations used for these studies can be divided into two general categories: colloidal aggregates of albumin and radioactive gases. Macroaggregates labeled with  $^{131}\text{I}$  or  $^{99\text{m}}\text{Tc}$  have been used extensively for determining regional pulmonary perfusion and, as such, are useful for evaluating patients with suspected pulmonary emboli (1-5). The distribution of these macroaggregates in the lung is usually determined by conventional rectilinear scanning although the scintillation camera has also been used effectively (4,5).

To obtain information on ventilation and diffusion one of the radioactive gases—oxygen, carbon dioxide, krypton or xenon—must be used. The half-lives of gamma-emitting oxygen and carbon radioisotopes are extremely short so that the cyclotron used for their production must be very close to the pul-

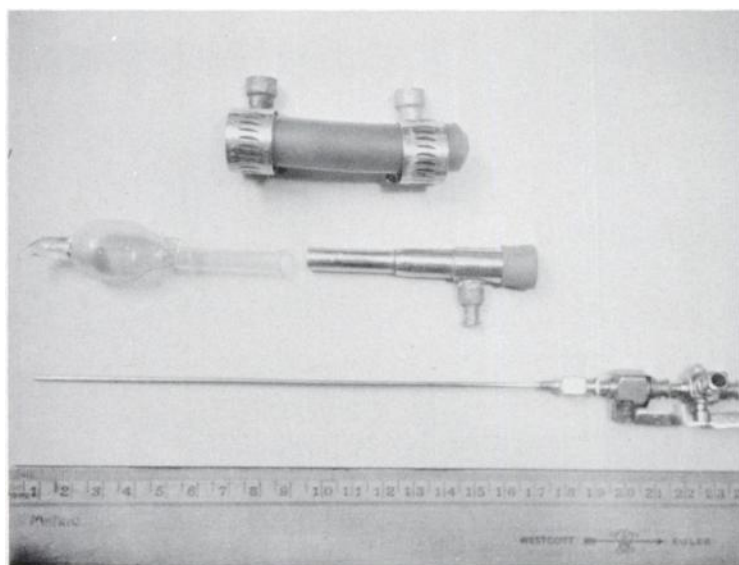
monary-function laboratory (6-9). Thus because of their universal availability, the noble gases are being used more extensively, and, of these gases,  $^{133}\text{Xe}$  has the best physical characteristics (5, 10-13).

In this paper we report our preliminary experience using an Anger scintillation camera to record pulmonary uptake and clearance of  $^{133}\text{Xe}$  in patients referred to our service for pulmonary-function evaluation. The radioactive xenon was administered either by inhalation or intravenous injection.

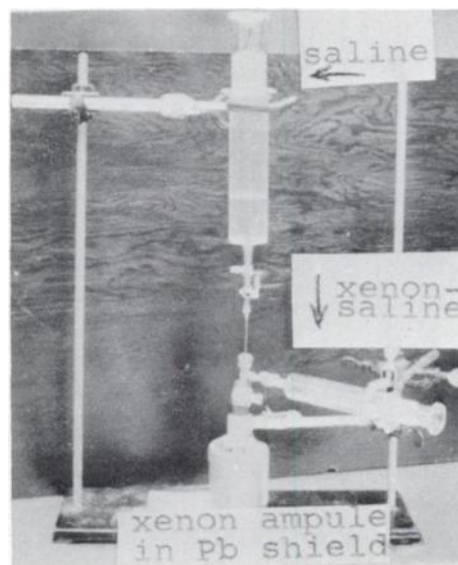
## MATERIALS AND METHODS

We obtain  $^{133}\text{Xe}$  in 1-curie ampules at approximately biweekly intervals from Oak Ridge National Laboratory. The gas is contained in a volume of about 5 cc at a pressure of about 10 mmHg (Fig. 1). For most of our work we need the xenon in solution with saline, and we have devised a special technique for making this transfer (Fig. 2). After unpackaging

Received Nov. 10, 1966; accepted March 8, 1967.



**FIG. 1.** Xenon ampule from Oak Ridge National Laboratory, shown with rubber connector, metal adaptor and long plunger needle.



**FIG. 2.** Apparatus assembled for transferring xenon into saline solution.

the xenon ampule and assaying it for radioactive content, we sterilize it in zephiran solution and then immobilize it in a hollow lead cylinder with plaster of Paris. A 2-in. length of rubber vacuum tubing with a 1/4-in. inner diameter is then fitted over the ampule and clamped. After clamping, a specially designed metal adapter is inserted on the other end of the rubber tube and secured with a clamp (Fig. 1). A rubber cap is placed over the open end of this metal adapter, and a 50-cc glass syringe with two stop cocks is attached to its side arm. All components of this system are sterilized before use. The assembly procedure is then carried out aseptically. The entire system is fixed in place as shown, and sterile saline is added to replace all the air in the system. Because the solubility of xenon in saline is much less than in air, it is of utmost importance to remove all air from the system to obtain an acceptable concentration of xenon in saline.

A 100-cc syringe filled with sterile saline is fitted with two stop cocks and a long needle. The needle is inserted through the rubber cap and advanced carefully through the glass seal on the xenon ampule. The plunger of the syringe is advanced slowly so that sterile saline is flushed through the ampule. The xenon then enters into saline solution which is flushed through the system daily for three or four days until essentially all the xenon has been removed from the ampule.

The extremely short biological half-life of inert gases such as  $^{133}\text{Xe}$  makes it possible to administer rather large quantities of radioactivity to patients without significant radiation hazard. Calculations show that an intravenous or intra-arterial injection of 40 mc  $^{133}\text{Xe}$  dissolved in saline results in a gonadal

dose of about 10 millirads which is only a small percentage of the gonadal dose from a conventional radiograph of the pelvis and is considered safe for routine diagnostic radioisotope work (14). Administration of this amount of  $^{133}\text{Xe}$  results in counting rates over the lungs which are considerably higher than can be recorded optimally by any gamma camera available at this time. Therefore we conclude that in practice the upper limit for  $^{133}\text{Xe}$  activity used for pulmonary-function studies is governed more by the resolving characteristics of the instruments used to detect the isotope than by the radiation dose to patients.

Of the many radioactive gases that exist,  $^{133}\text{Xe}$  is the most promising for pulmonary-function studies today. The isotope has a half-life of 5.27 days, and its gamma ray of 81 kev is suitable for localization studies with the instruments now available. This is particularly true with our scintillation camera which has recently been installed with bi-alkali cathode photomultiplier tubes. The low work function for electron release in these photomultiplier tubes improves the resolution in studies using radioactive isotopes such as  $^{133}\text{Xe}$  which emit relatively low-energy gamma photons.

Because one obtains high counting rates with 5–10 mc of  $^{133}\text{Xe}$ , the "dead time" of the recording instruments must be maintained at an absolute minimum. Recent circuitry modifications have decreased the dead time of our scintillation camera to about 4  $\mu\text{sec}$  which appears to be about the shortest dead time possible for an instrument with this design. However, it is sufficiently good to let us obtain scintiphotograms of isotope distribution at about 1-sec intervals.

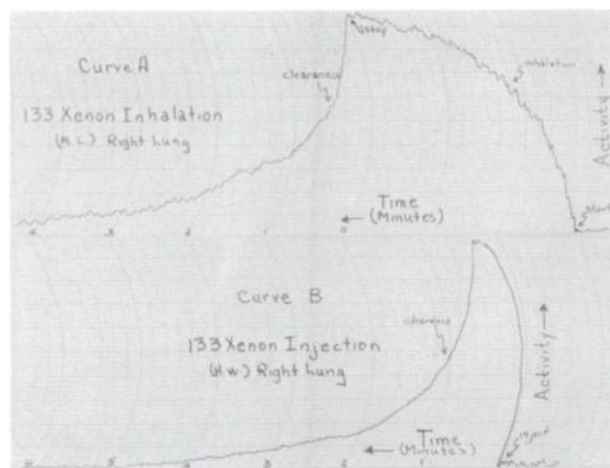


FIG. 3. Pulmonary uptake and clearance curves following inhalation or intravenous administration of  $^{133}\text{Xe}$ .

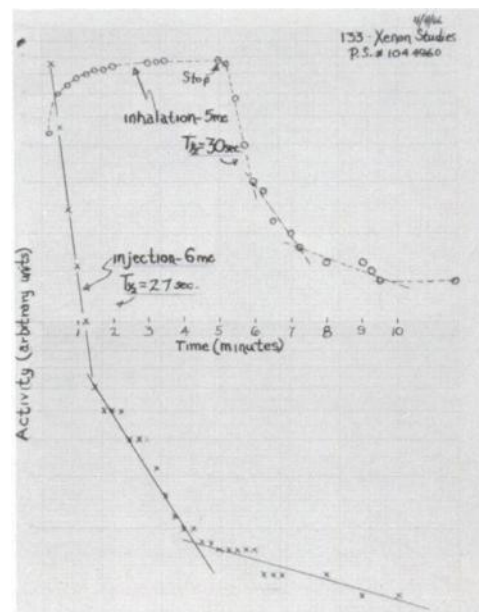


FIG. 4. Semilog plot for analyzing clearance times of xenon administered by intravenous injection or inhalation (normal subject).

A third modification made on our scintillation camera was the addition of a second ratemeter so that counts collected from half the crystal are fed to one ratemeter and recorder and those from the other half go to a second ratemeter and recorder.\* With this system data on xenon uptake and clearance can be obtained simultaneously with serial scintiphotograms of the radioactive xenon distribution in both hemilungs.

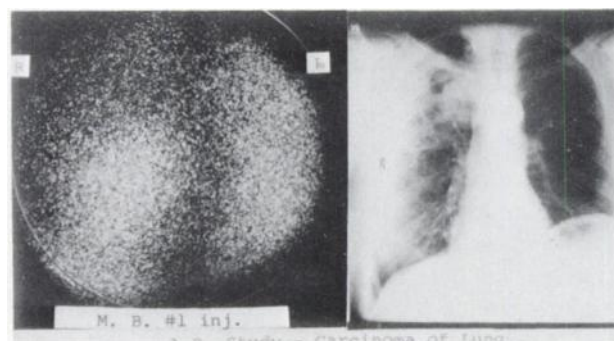
### RESULTS

Figure 3 shows typical patterns of xenon uptake and clearance from lungs of two patients taken at random. Curve A was obtained during administration of xenon by inhalation for 4 min. The subject then breathed room air and a xenon clearance was recorded. Curve B shows clearance of xenon from a normal lung after intravenous administration of 5 mc of xenon in saline.

Figure 4 gives a logarithmic analysis of data from curves such as those in Fig. 3. Each curve is made up of more than one clearance component as the distinct changes in slope indicate. The initial or fast components of each curve are quite similar, as is clear from the fact that the  $T_{1/2}$  clearance times are nearly the same (27 and 30 sec for injection and inhalation studies, respectively). As time progresses, more residual activity is recorded for the xenon-inhalation procedures than for the xenon-injection ones.

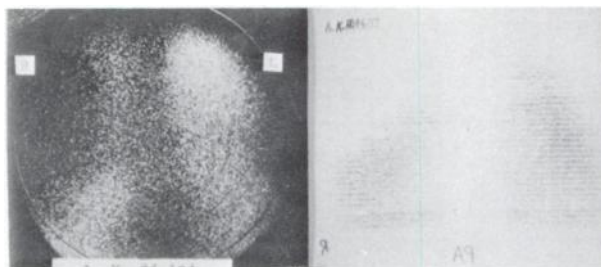
Figure 5 shows the initial scintiphotogram obtained after injecting 5 mc  $^{133}\text{Xe}$  to a patient (M.B.) with carcinoma of the lung. The chest x-ray reveals

\* Since this manuscript was written, a new console has been installed for the scintillation camera which permits quadrant field splitting so that data can be collected on upper and lower lung fields bilaterally. An analog-to-digital converter, 1,600-channel memory system and high-speed magnetic-tape unit are on order. This equipment will let us divide the lungs into as many as 1,600 segments for regional evaluation of pulmonary function. Computer analyses of these data are planned.



**FIG. 5.** Initial scintiphotogram of lung obtained after xenon injection is compared with chest x-ray of patient (M.B.) who has bronchogenic carcinoma.

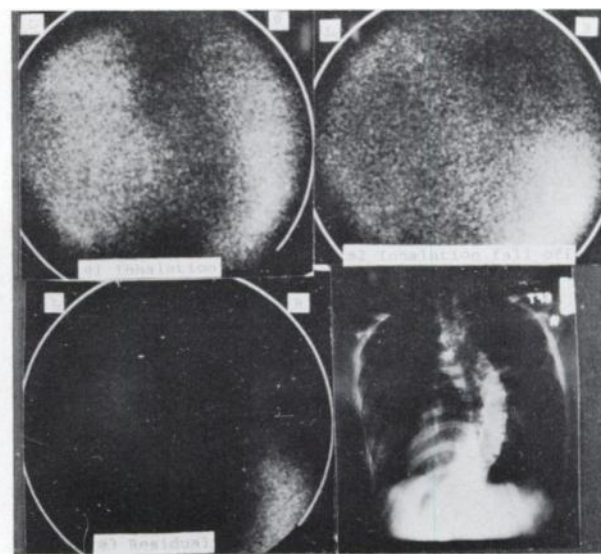
a consolidation in the right upper lung field which was biopsied during bronchoscopy and found to be a bronchogenic carcinoma. The scintiphotogram shows a decreased perfusion of the right upper lung field in the region of the tumor. The remainder of both lung fields visible on the scintiphotogram appears to be quite well perfused with blood.



**FIG. 6.**  $^{133}\text{Xe}$  and  $^{99m}\text{Tc}$  pulmonary scintiphotograms of patient (A.K.) with "farmer's lung."

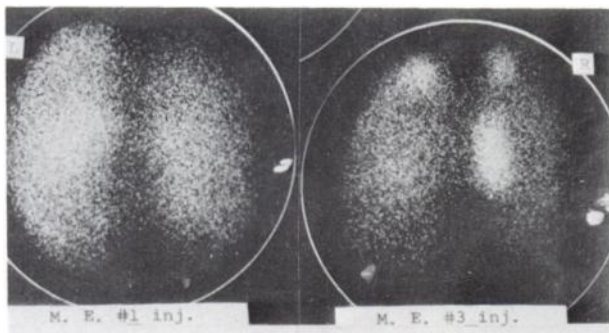
Figure 6 shows one scintiphotogram made after administering xenon in saline to a patient (A.K.) with a clinical diagnosis of "farmer's lung." The conventional scan in the figure was made after administering 3 mc  $^{99m}\text{Tc}$  labeled to macroaggregates of albumin. Both these studies show marked irregularity in the perfusion of the lung fields, particularly in the peripheral portion of the right lobe.

Figure 7 contains three selected posterior-view scintiphotograms and a chest x-ray of a patient (C.D.) with a right scoliosis. The initial picture (No. 1), made during inhalation of xenon from the spirometer, shows reasonably uniform ventilation of both lung fields. The second scintiphotogram was



**FIG. 7.** Chest x-ray and three selected pulmonary scintiphotograms obtained after  $^{133}\text{Xe}$  inhalation on a patient (C.D.) with rotoscoliosis. Pictures are posterior views.





**FIG. 8.** Two lung scintiphotos on a patient with heart disease. Initial scintiphoto (left) was made immediately after  $^{133}\text{Xe}$  injection. Scintiphoto (right) was made about 10 sec later. Both are posterior views.

made immediately after disconnecting the spirometer from the patient and shows some delay in xenon clearance in the right lower lung field. This delay is even clearer in scintiphoto No. 3 which was made 2 min later.

Figure 8 shows two selected posterior-view scintiphotos of a patient with emphysema (M.E.). The initial scintiphoto (No. 1) was obtained immediately after intravenous injection of 5 mc of xenon. The other scintiphoto is the third in the series and was obtained about 40 sec after xenon injection. This picture shows that the xenon has cleared from the majority of the lung fields bilaterally except for three localized areas at the apices bilaterally and in the right midlung field. These findings suggest that there are localized areas which are well perfused but poorly ventilated, as one would expect in bullous emphysema.

In addition to the xenon studies, we recorded spiograms for the majority of our patients using a Godart Pulmotest. Direct recordings were made of tidal volume, respiratory rate, minute volume, vital capacity and its subdivisions, timed vital capacity, forced expiratory volume, maximum flow rates and maximum breathing capacity. These values, all recorded with patients in a sitting position, were made the same day as the  $^{133}\text{Xe}$  study. Before recording the spiogram, a single arterial blood sample was taken from all patients in a supine position to obtain arterial oxygen tension ( $\text{PaO}_2$ ).

Data from these studies and a xenon clearance on selected patients are summarized in Table 1. The first patient listed in the table (M.B.) is the one in Fig 3. All pulmonary-function tests on this patient were abnormal, particularly the forced expiratory volume and maximum breathing capacity which are about 50% of normal. Xenon clearance times are abnormally long, particularly on the right side where the half time of xenon clearance following inhalation was 56 sec—about twice normal.

The next three patients in Table 1 are those shown in Figs. 4–6. Patient A.K. with “farmer’s lung” has abnormally long xenon-clearance times after both inhalation and injection of xenon. Patient C.D. with a scoliosis shows moderate depression of pulmonary function by conventional tests. The xenon-clearance half time on the left side appears to be normal while on the right side there is an indication of a delay that correlates well with the persistence of xenon activity in the right lower lung field (Fig. 5). Pulmonary-function data and xenon-clearance measurements on patient M.E. with rheumatic heart disease are nearly normal.

The last three patients in Table 1 were diagnosed to have multiple A-V fistulae, cystic fibrosis and chronic bronchitis, respectively. All these patients—particularly the two with cystic fibrosis and chronic bronchitis—have some abnormalities in conventional pulmonary-function tests. In addition, the xenon-clearance values are abnormal in the patients, particularly the values obtained after xenon inhalation by the last two patients in Table 1.

#### DISCUSSION

There are two gas systems which are now used to evaluate pulmonary function. Each gas has different physical characteristics that give it certain advantages for certain tests. The noble gases, of which  $^{133}\text{Xe}$  is the most widely used, made up the first system. Because xenon does not diffuse readily into pulmonary tissue fluids, it is an excellent gas for measuring ventilatory function of the lungs. The second system—the oxygen system—is used in studies with oxygen, carbon monoxide and carbon dioxide. Oxygen in its molecular form is somewhat more soluble than xenon; however, it is the least soluble of the three gases in the oxygen system, and its peak activity in the lungs after a single inhalation is representative of pulmonary ventilation. Carbon dioxide is the most soluble of these gases and is used for measuring pulmonary blood flow because the gas diffuses very rapidly.

The pulmonary administration of these radioisotopes can be made by two routes: inhalation or intravenous injection. Both noble gases and radioisotopes from the oxygen system are administered by inhalation; noble gases in saline solution can also be administered by intravenous injection. We have used both administration routes in our studies with  $^{133}\text{Xe}$ .

We chose xenon for our studies because it is readily available. Its 5.27-day physical half-life and 81-keV gamma-ray photon make it more desirable than  $^{85}\text{Kr}$  which is also chemically inert but has a half-life longer than 10 years and emits a gamma photon in less than 1% of its disintegrations.

To measure pulmonary perfusion, we inject 5–10 mc of xenon in saline into an antecubital vein. As the injection is made, the patient is instructed to inhale slowly to avoid a Val Salva maneuver. The peak counting rate obtained is proportional to pulmonary blood flow, and the subsequent exponential clearance is a measure of combined alveolar capillary diffusion and pulmonary ventilation. If xenon is available only as an air-gas mixture, it is possible to measure perfusion by observing the clearance curve after inhalation of a <sup>133</sup>Xe air mixture. For best results inhalation should be a single tidal volume containing 1–5 mc of xenon. In this case the exponential clearance one observes is a measure of alveolar capillary diffusion and arterial perfusion.

With the xenon system there is no adequate way to measure alveolar capillary diffusion directly. When xenon is administered by inhalation, the clearance is a measure of diffusion and perfusion. When it is administered by injection, the clearance is a measure of diffusion and ventilation. At no time is diffusion isolated independently for measurement. The best method of measuring pulmonary ventilation is to have the patient inhale a xenon-air mixture from a spirometer system for several minutes until an equilibrium state is reached. In such a system oxygen is added to replace the carbon dioxide that is continuously removed. The rebreathing technique lets one examine the "wash-in" of xenon into poorly ventilated areas of the lungs until equilibrium is reached (Fig. 3). After this procedure, the patient begins to breathe room air, and a "wash-out" curve of xenon is obtained. With a scintillation camera one can obtain serial scintiphotograms during these wash-in and wash-out phases to determine the regional ventilatory capacity of the lung. Xenon is particularly valuable for evaluating ventilatory prob-

lems when there are poorly ventilated spaces because the isotope has a low solubility, making rebreathing maneuvers possible. These rebreathing maneuvers let one study the time required for equilibrium to be reached. If equilibrium is delayed, there is good evidence of poor ventilation throughout the lungs as is the case in asthma, emphysema, bullous disease of the lung and bronchial stenosis.

Perfusion problems of the lung can be visualized clearly by conventional scanning techniques after administration of macroaggregates. However, because the administration of these "micro-emboli" is unphysiological, the use of radioactive xenon is preferable. A regional analysis of perfusion is important for evaluating possible pulmonary emboli and for studying patients with mitral stenosis in whom there may be a marked alteration in distribution of pulmonary blood flow, particularly when the patient is placed upright.

We have made pulmonary-function studies on 51 patients using either or both the inhalation and intravenous technique for <sup>133</sup>Xe administration. Clearance curves have been recorded for both techniques. Studies of normals show that the curves obtained after inhalation are quite similar to those obtained after xenon injection. Calculations show that clearance curves are normally made up of a fast component and one or more slower components. The slower components are more evident after xenon inhalation than after xenon injection. The slow clearance components probably relate to the prolonged clearance time of xenon from body tissues as well as to the small amount of xenon that is recirculated through the lungs. Occasionally we find that the initial half time clearance for inhalation is shorter than for injection and probably represents a tracing on patients who are hyperventilating. In

TABLE 1. PULMONARY-FUNCTION AND Xe-CLEARANCE DATA

Patient	Pulmonary pathology	PaO <sub>2</sub> (mmHg)	Conventional pulmonary-function tests (% of normal)			Half time for Xe clearance (sec)			
			VC*	FEV†	MVV‡	Right lung injection	Right lung inhalation	Left lung injection	Left lung inhalation
M. B.	Carcinoma right lung	55	89	51	48	35	56	26	35
A. K.	Farmer's lung	—	—	—	—	150	220	120	130
C. D.	Scoliosis	98	64	83	77	45	48	27	30
M. E.	Rheumatic heart disease	82	93	70	93	28	47	23	36
A. L.	Multiple A-V fistulae	78	118	63	58	42	42	35	36
R. H.	Cystic fibrosis	59	71	46	24	—	236	—	118
C. J.	Chronic bronchitis	50	33	69	37	82	140	92	275
	Normal (average)	90	100	100	100	28	28	28	28

\* Vital capacity (% of normal).

† Initial 1-sec forced expiratory volume (% of normal).

‡ Maximum voluntary ventilation (% of normal).

patients with normal pulmonary function we find that there is usually excellent correlation between the initial half-time clearance measurements (Table 1).

We have also used  $^{133}\text{Xe}$  to study patients with a variety of pulmonary disorders including scoliosis, asthma, emphysema, lung carcinoma, cystic fibrosis, hemosiderosis, farmer's lung and various forms of cardiac disease. Conventional pulmonary-function studies have also been performed on these patients. A detailed comparison of these data with those of xenon clearance is considered elsewhere (15). Preliminary correlative analyses of data have shown good agreement among these methods for evaluating pulmonary function.

The vital capacity is an indication of the pulmonary volume and should relate to the peak  $^{133}\text{Xe}$  concentration prior to the fast component of the  $^{133}\text{Xe}$  washout curve. The vital capacity is therefore an indication of the amount of restrictive lung disease. The forced expiratory volume per sec (FEV, 1 sec) and maximum voluntary ventilation (MVV) indicate the degree of obstructive lung disease because to a large degree they measure resistance to air flow (expiratory). These two values should relate closely to the half time of  $^{133}\text{Xe}$  clearance. Decreases in arterial oxygen tension should relate to a lower-than-normal total-lung  $^{133}\text{Xe}$  content after the patient breathes to equilibrium in a closed system compared with total-lung  $^{133}\text{Xe}$  after injection of an intravenous bolus of  $^{133}\text{Xe}$ .

#### ACKNOWLEDGMENT

The authors acknowledge with thanks the technical assistance of Stephen Bostrom. This work was supported by grants from the Public Health Service (NB-03364, 5R01-HE09204 and 1-T01-CA05190) and the Minnesota Division of the American Cancer Society.

#### REFERENCES

1. TAPLIN, G. V., JOHNSON, D. E., DORE, E. K. AND KAPLAN, H. S.: Suspensions of radioalbumin aggregates for

photoscanning liver, spleen, lung, and other organs. *J. Nucl. Med.* 5:259, 1964.

2. WAGNER, H. N., SABISTON, C. D., MCAFEE, J. G., TOW, D. AND STERN, H. S.: Diagnosis of massive pulmonary embolism in man by radioisotope scanning. *New England J. Med.* 271:377, 1964.

3. QUINN, J. L., III, AND WHITLEY, J. E.: Lung scintiscanning. *Radiology* 83:937, 1964.

4. LOKEN, M. K., TELANDER, G. T. AND SALMON, R. J.: Technetium 99m compounds for visualization of body organs. *JAMA* 194:152, 1965.

5. LOKEN, M. K. AND BUGBY, R. D.: Visualization of the lung by methods of scintiphography. *Am. J. Roentgenol., Rad. Ther. and Nucl. Med.* 97:850, 1966.

6. KNIPPING, H. W., BOLT, W., VALENTIN, H., VENRATH, H., AND ENDLER, P.: Regionale Funktionsanalyse in der Kreislaufund Lungen Klinik mit Hilfe der Isotopenthorakographie und der selektiven Angiographie der Lungengefasse. *Munch. Med. Wschr.* 99:1, 1957.

7. DOLLERY, C. T. AND WEST, J. B.: Regional uptake of radioactive oxygen, carbon monoxide and carbon dioxide in the lungs of patients with mitral stenosis. *Circulation Res.* 8:765, 1960.

8. DYSON, N. A., HUGH-JONES, P., NEWBERRY, G. R., SINCLAIR, J. D. AND WEST, J. B.: Studies of regional lung function using radioactive oxygen. *Brit. Med. J.* 1:231, 1960.

9. WEST, J. B. AND DOLLERY, C. T.: Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive  $\text{CO}_2$ . *J. Appl. Physiol.* 15:405, 1961.

10. BALL, W. C., STEWART, P. B., NEWSHAM, L. G. S. AND BATES, D. V.: Regional pulmonary function studied with xenon-133. *J. Clin. Invest.* 41:519, 1962.

11. MALLETT, B. L. AND VEALL, N.: The measurement of regional cerebral clearance rates in man using xenon-133 inhalation and extracranial recording. *Clin. Sci.* 29:179, 1965.

12. MCHENRY, L. C.: Cerebral blood flow. *New England J. Med.* 274:82, 1966.

13. LOKEN, M. K. AND WESTGATE, H. D.: Evaluation of pulmonary function using 133-xenon and the scintillation camera. *Am. J. Roentgenol., Rad. Ther. and Nuclear Med.* 100:835, 1967.

14. LASSEN, N. A.: Assessment of tissue radiation dose in clinical use of inert gases with examples of absorbed doses from 3-H, 85-Kr, 133-Xe. *Minerva Nucl.* 8:211, 1964.

15. WESTGATE, H. AND LOKEN, M. K.: Comparison of conventional tests and 133-xenon clearance techniques for evaluation of pulmonary function. *Amer. Rev. Resp. Diseases*. Submitted for publication.