with cerebrovascular disease. As anticoagulants are ineffective and probably increase the risk of cerebral haemorrhage, it is suggested that vigorous hypotensive therapy might be employed more extensively in this situation.

The results of this trial show no evidence of a protective influence of anticoagulants against further strokes, so that in this particular context the problem of hazards and complications of treatment ceases to be relevant. However, as there are particular situations in which it may be desirable to use anticoagulant drugs in patients with cerebrovascular disease, the question remains one of some importance. In this particular series, as stated above, there were five fatal cerebrovascular accidents in the high-dosage group as against one in the low-dosage group. It is known that three of those in the high-dosage group were due to cerebral haemorrhage, but the exact pathological nature of the other three is unfortunately not known. While it is not possible to make a valid statistical assessment of the hazard of cerebral haemorrhage in patients with cerebrovascular disease who are treated with anticoagulants, there can be no doubt about its existence, and a small but appreciable incidence is to be found in most of the trials published. The trials most closely resembling the present one are those of the National Institutes of Health and the Veterans Administration in the United States, described together by Baker (1960). Among 133 treated patients, who were followed up on average for approximately 12 months, there were six fatal cases of cerebral haemorrhage; in addition there were four other fatal haemorrhages from other sites. It was felt that the treatment had provided no protection from recurrent cerebral infarction, although the number of patients experiencing transient ischaemic attacks and extracerebral thrombo-embolic episodes was thought to have been reduced. In their recent account of the surgical treatment of internal carotid stenosis Edwards and Gordon (1962) mentioned the deaths from cerebral haemorrhage of five patients who were on anticoagulant therapy. Such figures are fairly representative of the large number of clinical studies in which this complication has been encountered.

We would ourselves conclude that the use of anticoagulants in patients who have suffered a stroke is attended by a small but definite risk of cerebral haemorrhage; that this risk is not counterbalanced by adequate protection against the occurrence of further strokes; and that these drugs are therefore not to be recommended in chronic cerebrovascular disease except in the particular case of patients at risk of cerebral embolism or suffering from frequently recurring transient ischaemic attacks.

Summary

The final results of a controlled trial of long-term anticoagulant therapy in patients with cerebrovascular disease are presented. The trial has run over a period of four years and has included 66 treated patients and 65 controls with an average duration of treatment of approximately two and a half years. It has shown that, in patients of the type included, anticoagulant treatment fails to afford protection against recurrent cerebrovascular accidents and it adds further evidence of the risk of cerebral haemorrhage when patients with cerebrovascular disease are treated with anticoagulant drugs.

We are grateful to all the physicians and surgeons who referred patients to us and to the medical committees of the West Middlesex and North Middlesex Hospitals, where anticoagulant clinics were held; also to Professor J. N. Cumings and Dr. W. H. McMenemy, in whose laboratories prothrombin estimations were made. We are indebted to Evans Medical Limited for supply of tablets and to the Nuffield Foundation for generous financial support.

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USE OF RADIOACTIVE XENON FOR STUDIES OF REGIONAL LUNG FUNCTION*

A COMPARISON WITH OXYGEN-15

BY

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In lung disease and in heart disease there may be marked changes in the distribution of gas and blood in the lungs. These changes can be of diagnostic importance and can cause widespread change in bodily function. Often they can be detected by clinical examination with the help of radiography. But these methods alone are no substitute for more exact measurements, and they may be misleading and fail to detect gross changes in local blood or gas distribution. If the more complicated radiographic procedures (such as fluoroscopy, densitometry, tomography, and angiography) are used then these changes in distribution to different regions of the lungs can be detected more precisely, but the methods do not give a truly quantitative measure of local blood or gas flow.

The development of bronchospirrometry with the Carlens catheter allowed the comparative ventilation and blood flow to the two lungs to be measured. But—with the exception of using a triple-lumened catheter for isolating the right upper lobe (Mattson and Carlens, 1955)—no information about smaller units than a whole lung can be obtained, and unless the technique is in very skilled hands it is liable to error and can be distressing for the patient. By using a mass spectrometer for continuous gas analysis and with special sampling techniques during bronchoscopy, the ventilation to all the different lobes of the lung can be measured and some idea of their individual ventilation and blood-flow balance found (Hugh-Jones and West, 1960). But again

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this procedure requires skill, and bronchoscopy can be an uncomfortable procedure for some patients and cannot readily be repeated. It is, however, the only method available for measuring function in individual pulmonary lobes or segments, and is of value when lung surgery is contemplated.

The use of radioactive gases has made the study of regional lung function much easier. Radioactive ^{133}Xe was the first gas to be used (Knipping *et al.*, 1957), but at that time it was used only to give approximate measurements of local ventilation and so was of limited value. For the past four years radioactive $^{15}\text{O}_2$ has been used at Hammersmith Hospital (Dyson *et al.*, 1960). This isotope, used itself or in the form of C^{15}O_2 , has proved of great value in studying lung physiology (West and Dollery, 1960, 1962) and also in studying the regional changes in lung function which occur both in lung disease (West *et al.*, 1961) and in heart disease such as mitral stenosis (Dollery and West, 1960) and congenital heart disease (Dollery *et al.*, 1961). The main disadvantage of $^{15}\text{O}_2$ is its very short half-life of two minutes, which means that patients have to be investigated in a room adjacent to the cyclotron.

Recently the use of ^{133}Xe has been developed (Ball *et al.*, 1962) so that both ventilation and blood flow can be compared in different regions of the lungs. Since ^{133}Xe is produced in a nuclear pile and has a half-life of five days it is generally available, unlike $^{15}\text{O}_2$. We have compared the usefulness of radioactive oxygen and xenon for the study of changes in regional ventilation and blood flow in various diseases, and give some examples here. We found xenon of particular value in studying patients who had poorly ventilated regions in their lungs, to be a substitute for $^{15}\text{O}_2$ for most clinical purposes, but not to be as versatile as $^{15}\text{O}_2$ for some research requirements.

Methods.—These were essentially the same as those described by Ball *et al.* (1962), but we have modified the counting procedure so as to obtain better-defined counting-fields, and have extended the information derived about local ventilation.

Handling the Isotope

Xenon-133 was delivered from the radiochemical centre every two weeks in an ampoule containing several hundred millicuries of ^{133}Xe under low pressure. The ampoule was of about 6-ml. volume and had at one end a tube with a break seal. The ampoule was connected to a glass tonometer of 100 ml. capacity which was shielded with lead. A mercury reservoir was connected to the lower tap of the tonometer and a mirror allowed the mercury level inside the lead shield to be seen through a slit. To decant the ^{133}Xe into the tonometer the whole system was pumped down to 0.1 mm. pressure, using a rotary oil pump connected to a side fitting with a tap. The seal was broken, using a rod already positioned in the connecting tube, and some of the ^{133}Xe passed out of the ampoule into the tonometer. The tonometer was closed and pure CO_2 introduced into the ampoule and its connexions through a side arm. The very low pressure in the tonometer was then used to draw the CO_2 and more xenon into the tonometer. This manoeuvre could be repeated several times until the system reached atmospheric pressure and about 90% of the ^{133}Xe was in the tonometer.

When required the mercury reservoir was used to expel aliquots of gas into a 5-ml. glass syringe fitted with

a tap. The amount of ^{133}Xe in the syringe was measured in a re-entrant ionization chamber. At other times the xenon was stored below atmospheric pressure to reduce the risk of a leak of highly radioactive gas. The final tonometer mixture contained 5–8 mc. of ^{133}Xe per ml. of CO_2 and retained a usable radioactivity for about two weeks.

Xenon was prepared for injection by filling a sterile 50-ml. Luer lock syringe with saline and injecting 1–2 ml. of the gas mixture through the nozzle to displace an equal volume of saline. The syringe was closed with a tap and was shaken until most of the CO_2 had dissolved, thus forcing the ^{133}Xe into solution, since its partial pressure in the contracted bubble is large relative to the water. This stock solution was dispensed into other syringes as needed.

Counting

Xenon-133 decays with the emission of x rays of 30 KeV and gamma-rays of 80 KeV energy, in contrast to the much more penetrating annihilation gamma-radiation of $^{15}\text{O}_2$, which has an energy of 510 KeV. The bias on amplifiers was set to cut out the 30 KeV x rays of ^{133}Xe and some of the scattered radiation so that the 80 KeV radiation was used for counting.

Two pairs of 1½-in. (3.8-cm.)-diameter by 1-in. (2.5-cm.)-thick crystal scintillation counters were used arranged in front of and behind each lung like the arrangement already described for $^{15}\text{O}_2$ (Dyson *et al.*, 1960). The signals from the photomultipliers were amplified, added together in pairs, fed through rate-meters and displayed on pen recorders. Each pen showed the counts contributed from a roughly cylindrical field stretching through one lung. Cylindrical lead collimators 6 in. (15 cm.) long by 1½ in. (3.8 cm.)

FIG. 1.—Isocount curves for ^{133}Xe plotted with a point source in a tank of oatmeal-sawdust mixture, density 0.3, with 3-cm. water-tanks on either end to represent the chest wall. Below, the plot with cylindrical collimators 6 in. (15 cm.) long and 1½ in. (3.8 cm.) diameter, and, above, with conical collimators 6 in. (15 cm.) long and 1½ in. (3.8 cm.) diameter at the crystal, tapering to ½ in. (1.3 cm.) diameter at the orifice (also used for $^{15}\text{O}_2$).

diameter collected 87% of counts from a cylinder of lung approximately 13 cm. in diameter between the counters. They gave high counts with poor spatial resolution. Conical lead collimators 6 in. (15 cm.) long by 1½ in. (3.8 cm.) diameter sloping in to ½ in. (1.3 cm.) diameter collected 87% of counts from a cylinder of lung approximately 9 cm. in diameter. This was the same field diameter usually employed for radioactive oxygen, and these collimators were used in most of the present series of investigations. The counting-fields with these two sets of collimators are shown in Fig. 1.

Procedure

Xenon was inhaled from a specially constructed lead-screened closed-circuit spirometer fitted with a motor-driven fan and an internal Geiger-Müller tube to monitor the level of radioactivity in the circuit. The apparatus was filled with oxygen and sufficient ^{133}Xe added to achieve a concentration of about 1.5 mc. per litre in the machine. The gas was inhaled first as a single normal breath, then as a deep breath, and then rebreathed until a steady level of radioactivity had been reached in the lungs. Counting rates of 1,000–3,000 counts a second were obtained using the conical collimators. At the end of this equilibration period the patient breathed room air and the rate of washout of ^{133}Xe from different regions was observed.

For regional blood-flow comparisons, 5–10 ml. of saline containing 0.3–1 mc. of dissolved ^{133}Xe was injected rapidly through a P.E.60 "polythene" catheter inserted percutaneously and passed into the axillary vein or superior vena cava. The injected ^{133}Xe appeared in the lung rapidly and the patient then held his breath until a steady level of radioactivity had been reached. Central injection through the polythene catheter ensured that all the xenon arrived in the lung within a few seconds, and even severely breathless patients were able to hold their breath for the short time needed. Injection directly into a forearm vein led to a very slow arrival in patients with cor pulmonale on the border of heart failure, and such patients were unable to hold their breath long enough for the xenon concentration in the lungs to reach a plateau. The rate of washout of the blood-borne xenon from the relevant lung regions

during normal air-breathing was also recorded as a measure of the ventilation of the perfused alveolae.

The arrangement of the closed-circuit spirometer and the counters is shown in Fig. 2.

Radiation Dose

The radiation dose for a two-minute period of re-breathing with a concentration of xenon of 1 mc./litre in the lungs is about 70 millirads to the lung, 18–22 millirads to fat, and 4–8 millirads to the gonads (Dollery *et al.*, 1962; Matthews *et al.*, 1962). For longer periods of re-breathing the doses are increased in proportion. The calibration assumes that xenon in the lungs is in equilibrium with arterial blood, that tissue uptake and washout depend on perfusion, and that the tissues are in equilibrium with venous blood. The total dose in a period of re-breathing and subsequent washout is independent of perfusion. The dose following injection of xenon dissolved in saline is very small. A procedure in a single patient usually comprised two periods of re-breathing and two injections. The total radiation dose to the lungs from this procedure would not exceed 300 millirads in a patient with a very slow washout and would be about half of this in a patient with normal ventilation. The radiation dose is therefore within acceptable limits and comparable with that from diagnostic radiological procedures.

Interpretation of Results with Radioactive Xenon

When there are gross differences in the function of two lung zones they can readily be seen on the traces from the pens. For most purposes a numerical estimate of comparative function is more convenient, and this can be derived from the curves in two ways. The following discussion will be by reference to the traces from a normal subject in Fig. 3. The essence of the first method is to use the counting rate at equilibrium in the two zones under study as an index of their relative alveolar volumes which take part in gas exchange. This index is valid if all the gas in the lungs and the spirometer contains the same concentration of ^{133}Xe . It is then a simple matter to divide the height of the deflection after a single normal breath (a) and the deflection after a deep breath (b) by the counting rate at equilibrium (c) to relate the ventilation on these breaths to the local effective lung volume (Fig. 3).

These values of a/c and b/c can be compared directly with a'/c' and b'/c' from the other lung under study. Similarly, with injected xenon the height of the deflections d and d' can be compared with one another by dividing by the lung volume c and c'. Then the relative blood flow per unit of lung volume in the two zones is d/c:d'/c' (Fig. 3). The comparison of the blood flow assumes that the ^{133}Xe is uniformly mixed in blood when it reaches the lung and that the "slug" of radioactivity arrives quickly. If the xenon is a long time arriving the difference of flow between a high-flow area and a low-flow area will be underestimated because relatively more will be carried away dissolved in the blood in the high-flow zone before arrival is complete.

FIG. 2.—Arrangement of apparatus for using xenon. The subject is sitting in a chair with the pairs of counters arranged over the right and left lungs. The closed-circuit spirometer with a built-in monitor faces the chair.

The second method of comparing ventilation, using the washout time, is simpler in that, in a uniform field, it is unnecessary to reach complete equilibrium because an estimate of the lung volume in the field is not required. The slope of the washout of xenon with the patient breathing air is replotted on a semilogarithmic graph and the time for the radioactivity to fall to half is used for comparison. This method is useful in the study of very badly ventilated areas where it may be

FIG. 3.—Xenon traces from a young normal member of the staff. The left-sided counter (upper zone) is at the level of the sternal angle and the right-sided counter (lower zone) is 5 in. (12.5 cm.) lower down the chest. The height of the deflections for the normal breath and the deep breath (a and b) is less in the upper zone than in the lower (a' and b'). The counting rates at equilibrium, an index of alveolar volume in the field (c and c'), are similar in the two zones. After injection only about a quarter as much xenon arrived in the upper zones (d) as in the lower (d'). The dotted lines give the baseline and also the time intervals in minutes.

impossible to reach equilibrium except after an unacceptably long period of rebreathing. A mixed population of alveolae may be disclosed by a washout curve consisting of more than one exponential component. The washout after rebreathing is usually slower than after injection. One explanation of the faster washout after injection may be that the well-ventilated alveolae are better perfused than poorly ventilated alveolae. The washout curves are also influenced by xenon returning to the lung in the venous blood from the tissues. After rebreathing ^{133}Xe for several minutes the tissue concentration of xenon will be higher than after a single injection, and this also may contribute to the slow washout. This factor may be quite large in the later parts of the washout curves. A more detailed discussion of factors influencing the washout will be given in a later paper. The washout plots for the rebreathing period in Fig. 3 are shown in Fig. 4.

Results

1. Normal Subjects

Measurements were made in four young normal members of the hospital staff and in three of them comparisons with $^{15}\text{O}_2$ -labelled carbon dioxide were available (Table I). The agreement between the two methods is fairly close bearing in mind that changes in the upper-zone flow may occur after rest or excitement and that there was a time lapse of at least 15

TABLE I.—Ratio of Upper-zone to Lower-zone Blood Flows and Ventilation in Normal Subjects Studied with ^{133}Xe and C^{15}O_2

Subject	Ratio of Blood Flow/Unit Volume ^{133}Xe	Time of Half Washout (Secs.) after Rebreathing		Ratio of Blood Flow/Unit Volume C^{15}O_2
	Left Upper to Right Lower Zone	Left Upper Zone	Right Lower Zone	Left Upper to Right Lower Zone
1	0.28 : 1.0	34	29	—
2	0.29 : 1.0	24	24	0.3 : 1.0
3	0.20 : 1.0	47	35	0.32 : 1.0
4	0.50 : 1.0	40	37	0.8 : 1.0

minutes between the two sets of readings. The results agree with the previous report of West and Dollery (1960) showing that an upright normal man has a relatively low flow through the upper zones of the lungs. The xenon results also show that the time of half-washout is usually greater from the upper zones than the lower (Table I), thus demonstrating that the upper zones are slightly less well ventilated than the lower, although the ventilation difference is much less than the blood flow inequality. The results from one normal subject are shown in Fig. 3 and the washout curves from the two zones are shown in Fig. 4.

2. Heart Disease

Mitral Stenosis.—

Studies with $^{15}\text{O}_2$ -labelled carbon dioxide have shown that the blood flow may be much greater in the upper zone of the lung than the

FIG. 4.—A semilog plot of the rate of washout of xenon from the two zones of Fig. 3 while the subject was breathing room air. The time of half-washout was 47 seconds in the upper zone and 35 seconds in the lower zone.

lower in severe cases (Dollery and West, 1960), the reverse of the normal distribution. In the present investigation a series of six patients with mitral stenosis have been studied with both carbon dioxide and xenon. Five of these patients had severe mitral stenosis with pulmonary

TABLE II.—Ratio of Upper-zone to Lower-zone Blood Flow in Patients with Mitral Stenosis Studied with ^{133}Xe and C^{15}O_2

Patient	Blood Flow Ratio with C^{15}O_2	Blood Flow Ratio with ^{133}Xe
	Left Upper to Right Lower Zone	Left Upper to Right Lower Zone
1	1.0 : 0.02	1.0 : 0.2
2	1.0 : 0.67	1.0 : 0.76
3	1.0 : 0.4	1.0 : 0.4
4	1.0 : 0.55	1.0 : 0.8
5	1.0 : 0.6	1.0 : 0.78
6	0.31 : 1.0	0.46 : 1.0

hypertension, but one (No. 6) had mild mitral stenosis without any evidence of pulmonary hypertension. The results with both gases agree in showing that the blood flow was higher through the upper zones of the lungs in the patients with severe disease (Table II). The ^{133}Xe results from one of these patients (No. 1) are shown in Fig. 5.

Cardiac Shunts.— $^{15}\text{O}_2$ -labelled carbon dioxide has been of particular value in the detection of left-to-right cardiac shunts (Dollery *et al.*, 1961). The C^{15}O_2 is very diffusible and soluble, and so it passes rapidly into the pulmonary capillary blood and some of the radioactive blood soon returns to the counting-field through the shunt. A rapid downstroke, indicating a high pulmonary

FIG. 5.—Traces from the left upper zone (sternal angle) and the right lower zone (5 in. (12.5 cm.) below the sternal angle) in a patient with severe mitral-valve disease. The rebreathing and washout traces are normal, showing that there was no ventilation abnormality. Little of the injected xenon arrived in the lower zone but five times as much went into the upper zone. The dotted lines show time in 2-second intervals and are also the baseline.

FIG. 6.—Carbon-dioxide clearance curves from the upper and lower zones of the lungs of a patient with a large ventricular septal defect without pulmonary hypertension. The rapid downstroke soon after inspiration, with a hump on the descending trace, shows a high pulmonary blood flow with a large left-to-right shunt. The carbon-dioxide results indicated a partition of flow between the upper and lower zones of 0.64:1 and xenon gave a value of 0.8:1 when adjusted for a volume difference in the two zones.

blood flow, followed by an upward hump on the curve caused by blood-borne radioactivity re-entering the counting-field is diagnostic of a shunt. Xenon, being relatively insoluble, does not enter the blood rapidly in this way and so it gives no information about the presence of a left-to-right cardiac shunt, although with arterial

sampling it could be used like ^{85}Kr or ^3H to measure right-to-left shunts (Fritts *et al.*, 1959; Long *et al.*, 1960; Lassen *et al.*, 1961). Xenon can still be used in a patient with a left-to-right shunt to compare the relative flow through the upper and lower zones. When the total pulmonary blood flow is high, as it is with a patient who has a large left-to-right shunt, the normal difference

FIG. 7.—Chest radiograph of a patient with a large bulla at the right lower zone.

FIG. 9.—Chest radiograph from a patient with emphysema, showing transradiant areas at both lower zones.

FIG. 8.—At the top are xenon traces from both lower zones of the patient whose x-ray picture is shown in Fig. 7. Over the cystic area there is a very slow wash-in of xenon and, while breathing air, a very slow washout. The traces below show that on a single breath of carbon dioxide labelled with ^{18}O , very little gas entered the cyst.

of blood flow between the upper and lower zones becomes less. But there are many other factors besides a left-to-right shunt which may cause this flow pattern. An example of $C^{15}O_2$ and xenon results from a patient with a ventricular septal defect is shown in Fig. 6.

3. Lung Disease

As oxygen and carbon dioxide are soluble gases they can be used satisfactorily for ventilation measurements only after a rapid single breath. The rate of fall of radioactivity during breath-holding is used as a measure of blood flow. As little gas may enter a badly ventilated area during a rapid single breath this limits the usefulness of $^{15}O_2$ in the study of such areas. Xenon-133 is particularly useful for the investigation of the function of poorly ventilated areas because its relatively low solubility (Conn, 1961) allows it to be rebreathed. The same is true of the circulation through poorly ventilated areas. If little oxygen or CO_2 enters a region then a satisfactory clearance curve cannot be obtained and no conclusion about the local blood flow is possible. Injected xenon will be carried by the blood flow to all the perfused air spaces, and, furthermore, the speed of washout from the lung with the patient breathing air gives valuable information about the ventilation of the alveolae to which the blood was distributed. This may not be the same as the ventilation of all the alveolae within the field of the counters. Xenon studies have been carried out on 35 patients with pulmonary disease and the results cannot readily be summarized. Four examples make the main points arising from these results, especially the information to be gained by these studies which is not apparent from radiography.

Large Lung Bulla.—This patient, a man aged 54, had a large lung bulla at the base of the right lung (Fig. 7). Surgical removal was being considered and the function of both the bullous area and the other apparently normal area was studied. The traces shown in Fig. 8 are from the two lower zones. They show that on rebreathing very little xenon entered the right lower zone with the bulla in it, but what did persisted for a very long time after the patient began to breathe air. This finding is consistent with the presence of an exceedingly poorly ventilated area at the right lower zone. Thus the bulla had a very small ventilation just sufficient to keep it "pumped up." The $C^{15}O_2$ traces showed that virtually no gas entered the bullous area on a single breath, so that the small ventilation there was not detected. Injected ^{133}Xe showed

FIG. 11.—Traces with ^{15}O -labelled carbon dioxide recorded from the same regions as the xenon traces of Fig. 10. Little $C^{15}O_2$ entered the lower zone (lower trace recorded a $\times 3$ sensitivity) and the clearance rate was slow, apparently showing a low blood flow. Probably little of the inhaled $C^{15}O_2$ came into contact with the blood that was perfusing very badly ventilated alveolae which the gas did not penetrate on the single breath.

FIG. 10.—The rebreathing traces show that the wash-in and washout of xenon in the right lower zone was much slower than from the left upper zone. After injection a surprising amount of xenon entered the lower zone, but this was only very slowly washed out by normal breathing, showing that the blood was flowing to very badly ventilated alveolae. The dotted lines show time in 2-second intervals.

that there was virtually no blood flow through the bullous area. The other lung regions were fairly normal, apart from a somewhat prolonged washout time.

FIG. 12.—Chest radiograph from a very breathless patient with emphysema shows no regional abnormality.

Bullous Emphysema.—This patient, a man of 39, was extremely breathless on slight exertion. The chest radiograph (Fig. 9) showed that the lung at both bases was transradiant. The counters were positioned over the transradiant area at the right lower zone and over the more normal area at the left upper zone. The right lower zone proved to be very poorly ventilated compared with the left upper zone (Fig. 10). Yet the xenon injection showed that the blood flow through the upper zone was only a little more than that through the badly ventilated lower zone. The washout of injected xenon

FIG. 14.—Semilog plot of the washout curves from the four lung zones.

FIG. 13.—The xenon rebreathing traces from the two upper zones and the two lower zones recorded using the same level of radioactivity in the circuit, so they can be compared directly with one another. Only the left upper zone is normally ventilated with a time of half-washout of 27 seconds. All the other regions have a slow washout showing poor ventilation.

from the right lower zone was very slow, showing that the blood flow through that area was to very badly ventilated alveolae. The xenon results can be contrasted with measurements made with $C^{15}O_2$ in the same region (Fig. 11). Blood passing through such badly ventilated alveolae would be unable to participate in normal gas exchange because of the low ventilation perfusion ratio.

Primary Emphysema.—The patient, a woman aged 48, was breathless on the slightest exertion but had no history of severe bronchitis. She had at times been thought to be hysterical because the chest radiograph (Fig. 12) showed little abnormality. The ^{133}Xe traces from the two upper and lower zones (Fig. 13) showed that only the left upper zone had a normal ventilation (half-washout 23 seconds); all the other zones had very poor ventilation with prolonged washout times (Fig. 14).

Unilateral Transradiant Lung.—The patient, a man of 51, had been breathless since childhood, and earlier studies had demonstrated restricted ventilation and blood flow in the right lung, which was transradiant. Recently he had become considerably more breathless, and for

FIG. 15.—Chest radiograph of a patient who had been breathless on exertion since childhood with a rapid deterioration in exercise capacity in the previous two years. The right lung is abnormally transradiant.

this reason he was studied with ^{133}Xe . In the upper zones the blood flow was reduced on the transradiant side and the washout of xenon both after rebreathing and after injection was slow. At the lower zones both sides were found, unexpectedly, to have poor ventilation and a low blood flow. Thus only the left upper zone was functioning normally. The recent rapid deterioration of the patient's exercise capacity was probably related to the recent development of emphysema at the left lower zone also, a change visible only with difficulty on the radiograph.

A finding of striking regional abnormalities of ventilation without any evidence of them on the chest radiograph occurred in a number of other patients.

Discussion

The use of radioactive xenon is a step forward in the application of isotopes to the study of the lung and the pulmonary circulation.

FIG. 16.—Above, the traces from the upper zones show a fairly normal ventilation on the left side but a prolonged washout indicating poor ventilation of the transradiant side. Twice as much of the injected xenon went to the normal side as to the transradiant side. Below, the traces from the lower zones show, unexpectedly, that ventilation is poor on both the transradiant side and the apparently normal side. A similar amount of xenon entered both sides after injection and was only slowly washed out by the ventilation.

Xenon has two substantial advantages. The first is its general availability and the second its low solubility. Although the apparatus required for the use of xenon is expensive (about £8,000), it is immensely cheaper than the construction of a particle accelerator capable of making radioactive oxygen in quantity. Thus, if xenon proves useful in the clinical evaluation of patients there is no reason why it should not come into use at the larger thoracic centres.

A comparison of the results obtained with xenon and $^{15}\text{O}_2$ -labelled gases in normal subjects and in patients shows that the results of the two methods agree quite well. When information is required about the topographical distribution of lung function regarding both ventilation and blood flow either method will yield it satisfactorily. A disadvantage of xenon is the low energy of the radiation (80 and 30 KeV) which it emits. This means that shielding by the chest wall is of greater importance than it is with $^{15}\text{O}_2$, which emits much more energetic gamma rays (510 KeV). However, for most clinical purposes the counting-field for xenon is sufficiently uniform and well collimated. The collimation possible with xenon cannot compare with the small cylinders of lung that can be studied by using the positron annihilation radiation of $^{15}\text{O}_2$ with coincidence counting, but such small areas are not usually of clinical importance.

The low solubility of xenon is its greatest additional advantage to a centre like ours, which also has facilities for using radioactive oxygen. The low solubility of the gas enables a much closer study of the function of badly ventilated regions of the lung because it will enter them when it is rebreathed for several minutes. The speed of washout from poorly ventilated areas has proved the most useful measure of their ventilatory function. The washout curves may also give valuable indications of a mixed population of alveolae within a single counting-field when the semilogarithmic plot of the washout is curved or changes slope. The injection method of studying the partition of flow is also of particular value for studying the behaviour of badly ventilated regions, for these may be difficult to evaluate at all with inhaled gases such as $^{15}\text{O}_2$ or C^{15}O_2 . A comparison of the washout curves after rebreathing with those after injection may enable conclusions to be drawn about the balance of ventilation and blood flow within a given area although the washout curves are modified by xenon recirculating in the blood.

The whole procedure with xenon is much lengthier than when using $^{15}\text{O}_2$, particularly in patients with poor ventilation who may have very prolonged washout times. A further disadvantage is the need to do repeated venepunctures or to intubate a vein. This disadvantage has largely been overcome by inserting a polythene tube into an arm vein and passing it into the superior vena cava before the procedure begins, so that injections can be given at any time without causing the patient any discomfort.

A number of interesting points emerge from the results. The low flow in the upper zones of upright normal subjects has been confirmed by a different method, so has the high flow through the upper zones of patients with severe mitral stenosis. It is noteworthy that a normal subject may have an upper/lower zone flow partition of say 1:4 and a patient with severe mitral stenosis may have a ratio of 5:1 and yet both have a similar ventilation in the upper and lower zones.

This suggests that substantial changes in blood flow may have little influence on ventilation.

The different solubilities of radioactive xenon and carbon dioxide mean that the former is useless for detecting left-to-right cardiac shunts. Xenon might be useful for the study of intrapulmonary right-to-left shunts, but radioactive ^{83}Kr (which emits only non-penetrating electrons) is equally suitable, as the counting has to be done on samples of arterial blood and not by surface counting.

The xenon studies of patients with lung disease emphasized some findings which emerged with $^{15}\text{O}_2$ (West *et al.*, 1961) but also gave some new information.

One important conclusion to be drawn from using any radioactive-gas technique is that the absence of a regional abnormality on the chest radiograph does not mean that lung function is uniform. Radioactive-gas studies provide the easiest method of studying regional changes of ventilation and blood flow. In emphysematous patients they are of great importance in studies related to possible surgery. But they give only topographical and not anatomical information, so that they are complementary to and in no way supplant the studies of lobar function at bronchoscopy. The latter give precise information about the distribution of the tidal volume to the different lobes and give much more information about the regional mechanical changes in the lungs (McGrath and Hugh-Jones, in press; Hugh-Jones *et al.*, 1962), which are usually the main indication for surgery in emphysema. The radioactive-gas studies are a most useful "screening" procedure before bronchoscopic studies are decided on.

Injected xenon is a specially useful method of showing whether poorly ventilated areas are still perfused with blood. It can be striking to see the gas swiftly carried into an area of lung by the blood and then only very slowly removed by the ventilation. Such regions are of importance because the blood flowing through them cannot participate in normal gas exchange. We have noted that diseased areas at the lung base are more likely to retain a good blood flow than similar areas in the upper zones. Presumably this reflects a retention of part of the normally high blood flow in the lower zones of the lung.

Although $^{15}\text{O}_2$ is more versatile for research purposes because it can be used to label oxygen itself or to label carbon monoxide or carbon dioxide, the use of xenon promises to be of considerable clinical value and the techniques required to use it are not difficult. Xenon-133, which can be cheaply produced in a nuclear pile and distributed before it decays, may prove generally useful for studies of regional lung function.

Summary

The usefulness of two radioactive gases, ^{133}Xe and $^{15}\text{O}_2$, has been compared in studies of regional ventilation and blood flow in the lung. The technique of their use was fundamentally different. Radioactive oxygen was taken as a rapid single breath and the blood flow deduced from the clearance slope during breath-holding. Radioactive xenon, which is relatively insoluble, was rebreathed from a closed-circuit spirometer and the ventilation of different regions was characterized by the time of washout from them when the patient resumed breathing air. During the rebreathing period xenon entered both well and badly ventilated areas of the lung and so gave more information about the badly

ventilated areas than oxygen which was taken as a single breath. Comparisons of blood flow were made by injecting intravenously xenon dissolved in saline and observing the amounts evolved into different regions of the lungs.

Xenon proved of particular value in studies of poorly ventilated regions of the lung because less information was available about their function from studies with radioactive oxygen. For most other purposes the two methods gave similar results, although xenon was useless for detecting left-to-right shunts, for which carbon dioxide labelled with $^{15}\text{O}_2$ is of particular value. Furthermore, C^{15}O_2 can be used to compare flow rate and changes in it but xenon can only be used to determine the relative flow through two areas. Normal subjects had a low blood flow through the upper zones of their lungs and, in contrast, patients with severe mitral stenosis had a high upper-zone blood flow with a very limited flow in the lower zones. Both methods sometimes revealed striking regional ventilation abnormalities which were not apparent on chest radiographs.

The main practical advantage of xenon lies in its longer half-life (5.4 days) against the very short one (two minutes) of $^{15}\text{O}_2$. Although $^{15}\text{O}_2$ is more versatile for research purposes its short half-life makes its general use impracticable. Xenon-133 is generally available and could be widely applied in thoracic centres for evaluation of patients before lung surgery and for physiological and clinical investigation of patients with regional disease of the lungs.

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"CONOVID-E" AS AN ORAL CONTRACEPTIVE

BY

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In August, 1960, a clinical trial of "conovid-E" (2.5 mg. norethynodrel with 0.1 mg. ethinylloestradiol-3-methyl ether) was begun at the Slough and District Family Planning Clinic, under the auspices of the Council for the Investigation of Fertility Control. The object was to ascertain the efficiency of this small dose of norethynodrel in conjunction with 0.1 mg. of ethinylloestradiol-3-methyl ether. After publication of the results of the Birmingham oral contraceptive trial (Mears, 1962), a comparison could be made of the incidence of side-effects produced by the 2.5-mg. dosage with those given by conovid (5 mg. norethynodrel with 0.075 mg. ethinylloestradiol-3-methyl ether).

When the first 200 patients were reviewed in December, 1961, 162 were still taking part in the trial. The reasons given by the patients for leaving the trial are shown in Table I.

TABLE I.—Reasons for Leaving Trial

Dissociated from Oral Contraceptive	Indeterminate	Associated with Oral Contraceptive
Left the area .. 5	"Changed mind" 7	"Felt ill" .. 7
To become pregnant 3	Developed a cervical erosion 1	Nausea in 1st cycle .. 4
Transferred to separate post-partum trial .. 2	Developed a cervical polyp .. 1	Short cycles .. 2
Entered hospital for vaginal repair 1	Entered hospital for cautery of erosion .. 1	Heavy periods .. 1
Under hormone treatment elsewhere .. 1		Pregnant, owing to intermittent dosage .. 2
Total .. 12	Total .. 10	Total .. 16

TABLE II

Cycles	1	2	3	4	5	6	7, 8, 9	10, 11, 12	12+
No. of women-months ..	183	175	154	121	116	84	162	77	42

The results now given are based on 1,114 woman-months, made up as shown in Table II. The greatest number of cycles completed by any one patient during the time of review is 18.

Selection of Patients

Volunteers were married women, under 40 years on entry to the trial, with at least one living child. The youngest patient was aged 18. Lactating women were not accepted. In every case the written consent of the husband was obtained before the wife was accepted into the trial.

Of the volunteers, 47.5% had not sought contraceptive advice at a family planning clinic before. Either they had not wished to limit their families previously or, more probably, they rejected the idea of conventional mechanical methods. Some, though not wanting to have another child, had either disliked or been casual with mechanical methods, and consequently had a high failure rate.