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Use of ^{18}F labelled fluorocarbon-11 to investigate the fate of inhaled fluorocarbons in man and in the rat

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Williams, Faith M., Draffan, G. H., Dollery, C. T., Clark, J. C., Palmer, A. J., and Vernon, P. (1974). *Thorax*, 29, 99–103. Use of ^{18}F labelled fluorocarbon-11 to investigate the fate of inhaled fluorocarbons in man and in the rat. The distribution and elimination of ^{18}F labelled fluorocarbon-11 has been followed in a group of rats killed after air breathing following six minutes' exposure to ^{18}F fluorocarbon-11. Whole body and individual organ count rates were measured. In four volunteers the fate of ^{18}F labelled fluorocarbon-11 was followed by both whole body counting and gamma camera measurement of the activity in the lung and mouth region after inhalation from a specially loaded aerosol dispenser.

In the rat there was a high initial level in high blood flow organs and in the adrenals and fat: the level in blood and high blood flow organs fell rapidly. Elimination from fat was slow but the adrenal level had fallen within one hour. The fall in whole body count rate was similar to that in fat.

In man, the fall in lung concentration was consistent with rapid uptake into tissues followed by slow elimination; the whole body count rate curve also indicated slow elimination. There was no evidence of deposition of droplets of fluorocarbon in the mouth region after use of the aerosol.

The present investigation was undertaken as part of a series (Draffan, Dollery, Williams, and Clare, 1974) designed to evaluate the hazards that might arise from the fluorocarbon propellants used in pressurized aerosol products for the treatment of asthma. The aim was to determine the absorption, distribution, and elimination of fluorocarbons in man and rat.

The levels of fluorocarbons-11 and -12 (F-11, CCl_3F; F-12, CCl_2F_2) in arterial and venous blood and alveolar air have been measured in man following the use of an aerosol inhaler (Dollery *et al.*, 1970; Paterson, Sudlow, and Walker, 1971; Dollery *et al.*, 1974; Draffan *et al.*, 1974). Immediately after use of the inhaler the concentration of fluorocarbon in arterial blood rose to a peak and then fell again, initially rapidly and then more slowly. The slow phase probably reflected elimination of fluorocarbon concentrated in the tissues and fat deposits. Morgan, Black, Walsh, and Belcher (1972) investigated the retention of ^{38}Cl fluorocarbon after inhalation of the vapour, by counting the expired gas, and drew a similar conclusion.

These studies were made with cyclotron produced ^{18}F fluorocarbon-11. ^{18}F has a radiation (51 KeV) suitable for external detection and a half-life of 110 minutes. The count rate/time curves of the whole body and specific organs in rats exposed to ^{18}F fluorocarbon vapour were measured. In man, distribution and elimination were followed by whole body counting and use

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of a gamma camera after inhalation from a specially loaded aerosol dispenser, similar to that used by patients with asthma.

METHODS

PREPARATION OF FLUOROCARBON-11 LABELLED WITH ^{18}F (described in greater detail by Clark, Goulding, and Palmer (1973)) Fluorine-18 was prepared as silver fluoride by the cyclotron irradiation of a vessel filled with neon and lined with carrier silver fluoride. The nuclear reaction used was $^{20}Ne(d,\alpha)^{18}F$. After the irradiation with 15 MeV deuterons the neon was removed and CCl_4 was transferred into the target vessel which was then heated to 170°C when the following reaction proceeded:

$$CCl_4 + 2Ag^{18}F \xrightarrow{170°C} CCl_3\,^{18}F + AgCl\ Ag^{18}F$$

The target contents were removed after a reaction time of 30–40 minutes by vacuum distillation into a trap at −196°C. The contents of the trap were diluted with toluene to raise the boiling point of the mixture and thus simplify the subsequent handling of CCl_3F (boiling point 23°C at 760 mmHg). This mixture was then purified by radio-gas chromatography. Purified samples of fluorocarbon-11 were recovered at the chromatograph outlet by condensation at −196°C, the specific activity being typically 20 μCi/mg at the end of chemistry for a 10 μAhr irradiation.

Fluorocarbon-11 was diluted with air for rebreathing by rats. For studies in human volunteers, it was mixed with stable fluorocarbon-12, CCl_2F_2, and transferred to an aerosol dispenser by vacuum distillation so that one pressure on the dispenser released 50 mg fluorocarbon containing 1 mCi ^{18}F.

DISTRIBUTION OF ^{18}F FLUOROCARBON-11 IN THE RAT Rats (100 g male Wistar under light nembutal anaesthesia) were exposed to an atmosphere of 0·3% v/v ^{18}F fluorocarbon-11 in air in a sealed 20 litre Perspex box fitted with a fan to maintain a uniform atmosphere. The animals were removed after a 6-minute exposure and killed by decapitation at 0, 15 or 60 minutes. (At 0 minutes the animals were killed under anaesthesia while still in the fluorocarbon atmosphere because of its rapid elimination from the blood on breathing air.) Blood and tissue were rapidly removed after death to sealed containers and counted in a NaI (Tl) well scintillation counter. The tissue levels of fluorocarbon-11 at each time were calculated. The whole body fluorocarbon content of a single rat was followed by observing its whole body ^{18}F activity using a 6×4 in NaI (Tl) detector. The rat was retained in a fixed geometry in a container which was ventilated to waste by means of a fan to prevent the accumulation of exhaled activity. From a phantom calibration of the whole body counter the whole body content of fluorocarbon-11 was calculated. In order to estimate the correction necessary due to surface adsorption on the skin and fur a dead rat was simultaneously exposed to the fluorocarbon vapour and the ^{18}F activity was estimated under similar geometric conditions. The skin contribution was less than 1%.

FATE OF ^{18}F FLUOROCARBON-11 IN MAN AFTER NORMAL ADMINISTRATION FROM AN AEROSOL DISPENSER This was investigated in four healthy male volunteers who were free of respiratory disease. The subject was seated and a gamma camera (Nuclear Enterprises Mark III) was placed against the body. On the other side of the subject at approximately 2 metres was a single 6×4 in NaI (Tl) detector used to count radiation from the whole body.

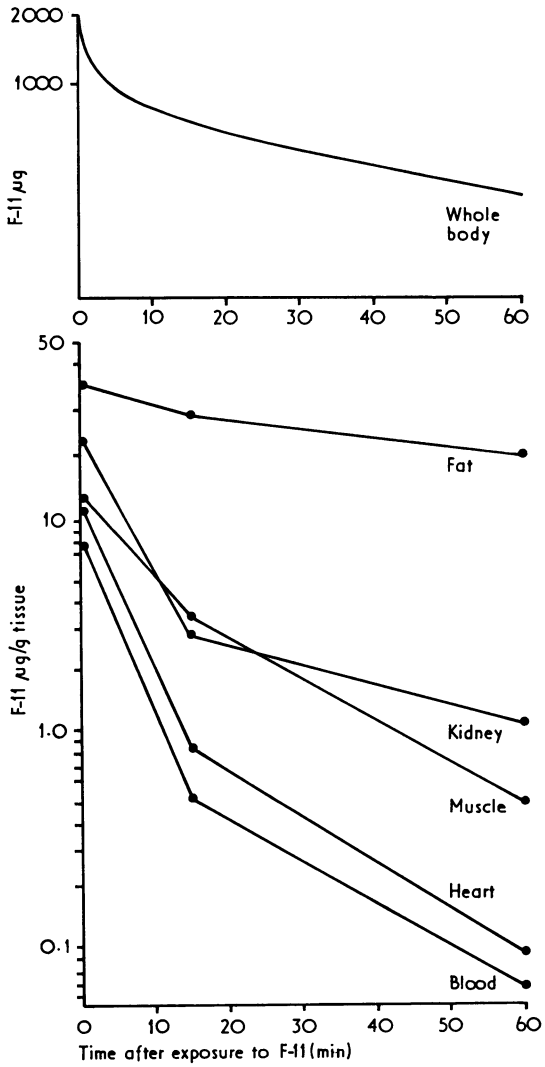

FIG. 1. *Decline of fluorocarbon-11 concentration from whole body and individual organs of rats in air, after breathing F-11, 0·3% vol/vol, for 6 minutes.*

Expired fluorocarbon was removed by enclosing the volunteer's head in a Perspex hood which was exhausted by a vacuum cleaner.

After the volunteer had inhaled one puff from the canister, he held his breath for five seconds, during which time the canister was removed from the room and the vacuum cleaner was switched on. The whole body counter was switched on before the study and the gamma camera immediately after the canister had left the room. Volunteers were seated with back to camera, with either lungs or neck region in the field of view, or with side to the camera and neck region in the field. The volunteer remained stationary in the hood for two minutes during which time the gamma camera was in operation. After this time the volunteer relaxed within the hood but maintained a constant position, and whole body measurements were continued for 20 minutes. Frequent background measurements were made with the volunteer removed to check that no expired radioactivity remained in the hood.

Data from the gamma camera were digitalized and recorded on magnetic tape and subsequently processed on a CDC 6600 computer (Vernon and Glass, 1971). On the processed gamma camera pictures, areas were delineated and the activity/time curves were obtained for each area. The areas delineated were in the lung and mouth regions.

Data from the whole body NaI (Tl) detector measured in counts per one second interval were stored in a multichannel analyser and corrected for background and decay. From a water phantom calibration the whole body content of fluorocarbon-11 could be determined.

RESULTS

FATE OF ^{18}F FLUOROCARBON-11 IN THE RAT The levels of fluorocarbon-11 were measured in whole blood, heart muscle, psoas muscle, liver, kidney, spleen, lung, brain, adrenal, and fat. The levels of fluorocarbon in tissues at 0, 15, and 60 minutes after 6 minutes' rebreathing fluorocarbon (0·3% v/v) are shown in Figure 1. The rate of elimination of fluorocarbon from the heart and blood was similar, with a constant ratio of 1·8 to 1. Fluorocarbon-11 was also rapidly eliminated from the other high blood flow organs, kidney, liver, spleen, lung, and brain. The level in fat was greater than in other tissues. The slow elimination of fluorocarbon from the fat was similar to the fall in whole body count rate (Fig. 2). It is of interest that a high concentration of fluorocarbon-11 was present in the adrenal at 0 and 15 minutes but this had declined by 60 minutes.

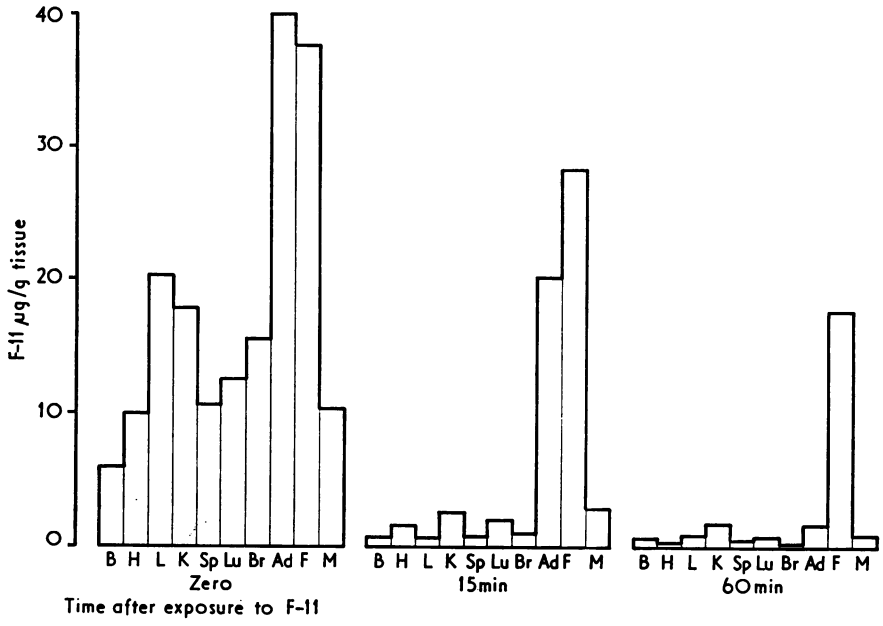

FIG. 2. *Histogram showing the decline in individual organs in the same group of rats as in Figure* 1.
B=blood, H=heart, L=liver, K=kidney, S=spleen, Lu=lung, Br=brain, Ad=adrenal, F=fat, M=skeletal muscle.

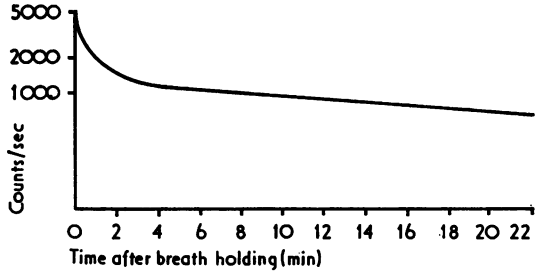

FIG. 3. *Decline of whole body count rate in one volunteer after a dose of* 1 *mCi* ^{18}F *fluorocarbon-11 from an aerosol dispenser.*

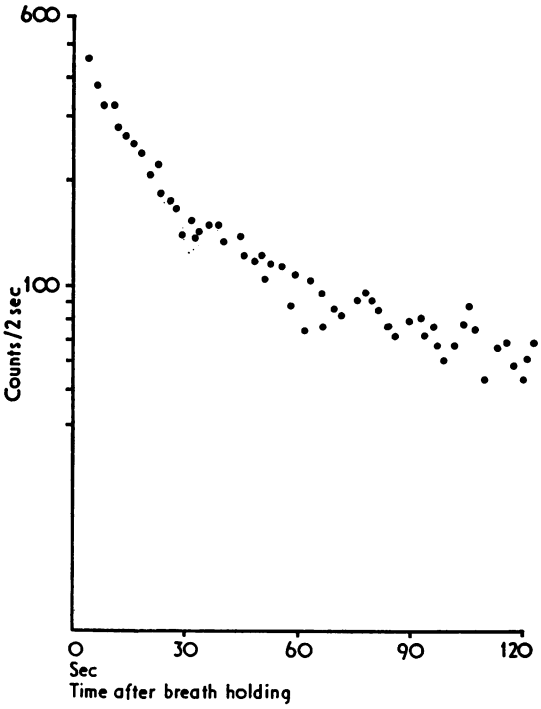

FIG. 4. *Decline in count rate of right lung of a volunteer after a dose of* 1 *mCi* ^{18}F *fluorocarbon-11 from an aerosol dispenser.*

FATE OF ^{18}F FLUOROCARBON-11 IN MAN The fall in whole body count rate following a single dose of ^{18}F fluorocarbon-11 was similar in all three volunteers monitored. Figure 3 shows a typical whole body count rate/time curve followed for 20 minutes. For the first two minutes the count rate decreased rapidly. The half-life of the final phase ranged from 12 to 20 minutes in the volunteers.

Figure 4 shows the fall in count rate of the upper part of the right lung with time in one volunteer. The curve can be separated into two phases with half-lives of 13·7 seconds and 87 seconds. A similar profile was observed for the fall in count rate of an area of the lung for a second volunteer.

The mouth and pharynx were examined in one individual to look for evidence of local deposition of liquid fluorocarbon-11. There was no evidence of an initial peak of radioactivity in this region (Fig. 5), suggesting that such local deposition did not occur.

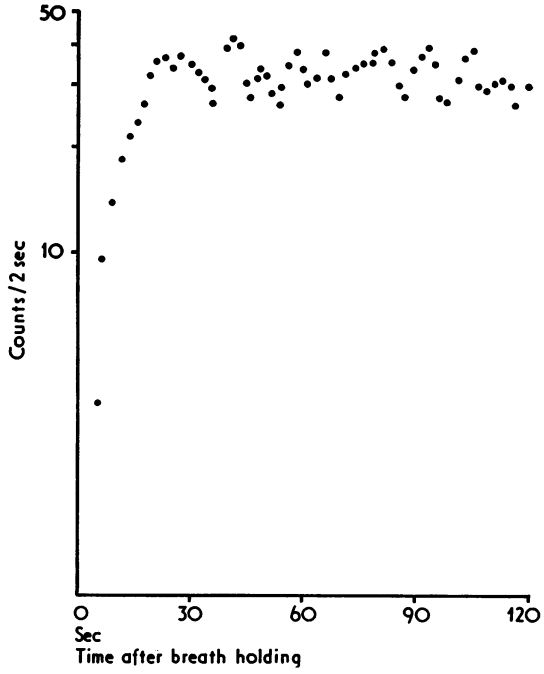

FIG. 5. *Activity/time curve for the mouth and pharynx region of a volunteer after a dose of* 1 *mCi* ^{18}F *fluorocarbon-11 from an aerosol dispenser.*

DISCUSSION

Fluorocarbon-11 has a high lipid solubility (olive oil/air partition=27) and volatility (BP 23° at 760 mmHg). It would be expected to leave the blood rapidly and concentrate in the tissues, especially in fat, and to be excreted slowly in the gaseous form via the lungs.

The results in the rat demonstrated a high initial concentration in high blood flow tissues, the adrenal gland, and fat. The concentration in the blood and high blood flow tissues fell rapidly once the animals were breathing air. The adrenal fluoro-

carbon concentration fell more slowly but had reached a low value by 60 minutes. Elimination from fat was very slow and had not reached half the initial value by one hour. The slow rate of elimination from fat must reflect a high tissue: blood partition coefficient and a low blood flow per unit mass of tissue. The blood: heart muscle ratio, 1:1·8, agrees well with that found *in vitro* using dog heart muscle (Dollery *et al.*, 1974). Cox, King, and Parke (1972) found that 97% of a single dose of fluorocarbon-11 given to a rat was expired unchanged within six hours, indicating that the radioactivity measured in our studies represents unchanged fluorocarbon.

The whole body count rate in man initially fell quickly. The final phase in our studies ($t\frac{1}{2}$ range 12 to 20 minutes) was shorter than that observed by Morgan *et al.* (1972), who measured expired ^{38}Cl fluorocarbon-11 ($t\frac{1}{2}$ approximately 100 minutes).

The profile of fluorocarbon elimination from the lung indicated an initial transfer of the dose to the blood stream and uptake by tissues and later pulmonary excretion of fluorocarbon released from the tissues and fat. The time course of elimination from the lung observed using the gamma camera was similar to the elimination from alveolar gas measured by mass spectrometry (Draffan *et al.*, 1974). The absence of an early peak and initial fall in count rate in the mouth region suggests that fluorocarbon-11 was not deposited in the mouth as droplets. If droplets had formed one would expect to see a rapid fall in count rate with the first breath as the droplets were volatilized and washed directly out of the mouth.

The main factor influencing the elimination of fluorocarbon-11 from the body is concentration in fat depots. The slow release of fluorocarbon from fat into blood should not prove any hazard to the heart of man. The high concentration in the adrenal gland must also reflect its lipid content. Perfluro-n-hexane (C_6F_{12}) can bind to microsomes and *in vitro* can act as an inhibitor of oxidation (Ullrich and Diehl, 1971). Fluorocarbon-11 (CCl_3F) will probably act in a similar manner. However, it is improbable that a high concentration would persist for long enough in man, after normal use of an aerosol inhaler, significantly to inhibit the formation of adrenal steroids.

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