A Fluorinated Glucose Analog, 2-fluoro-2-deoxy-D-glucose (F-18): Nontoxic Tracer for Rapid Tumor Detection

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Rapid uptake of F-18 FDG was observed in a variety of transplanted and spontaneous tumors in animals. The tumor uptake reached a peak by 30 min and remained relatively constant up to 60 min, with a very slow wash-out of F-18 activity from the tumor thereafter. Tumor-to-normal tissue and tumor-to-blood ratios ranged from 2.10–9.15 and 2.61–17.82, respectively, depending on the type of tumor. A scintiscan of a seminoma in a dog showed very high uptake in the viable part and lack of uptake in the necrotic mass. Toxicological studies in mice using 1000 times human tracer dose (HTD) per wk for 3 wk and in dogs using 50 times HTD per wk for 3 wk did not show any evidence of acute or chronic toxicity.

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Inhibition of metabolism by structural analogs of metabolites is one of the recent concepts of cancer chemotherapy (*1–3*). Increased metabolic demand of the cancer cell for glucose has also been well documented (*4–6*), and a study comparing several normal and malignant tissues has shown that the activity of hexokinase, an enzyme for glucose catabolism, was significantly higher in malignant tissues (*7*). Many glucose analogs have therefore been investigated as potential glucose antimetabolites to inhibit glycolysis, and thereby growth in the tumor cells (*3,5,8*). Of these, 2-deoxy-D-glucose (2-DG) has proved to be the most promising (*3,5,9–12*).

In 1972 Coe reported that the fluorinated sugar 2-deoxy-2-fluoro-D-glucose, a structural analog of glucose, caused significant inhibition of glycolysis in ascites tumor cells grown in vitro (*13*). Our preliminary studies with 2-[^{18}F]fluoro-2-deoxy-D-glucose (F-18 FDG), have shown some specificity of uptake in tumors (*14*). The present study was undertaken to investigate F-18 FDG further as a potential tumor-seeker both in transplanted and spontaneous tumors.

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2-deoxy-D-glucose (2-DG) in high doses (>100 mg/kg) is known to produce toxic effects both in animals and human beings (*3,15–18*), because of its inhibitory effects on glucose metabolism and consequent cerebral glucoprivation. Although the LD_{50} for 2-deoxy-2-fluoro-D-glucose in mice and rats has been reported to be approximately 600 mg/kg (*8*), we required a more detailed study preliminary to the use of F-18 FDG in humans. Therefore we also report the results of the toxicity evaluation of F-18 FDG in animals.

MATERIALS AND METHODS

Radiopharmaceuticals. 2-[^{18}F]fluoro-2-deoxy-D-glucose (F-18 FDG) was synthesized by the method described earlier (*19,20*). The specific activity varied according to the integrated cyclotron beam dose on the target, and ranged from 1–29.4 mCi/mg at end of synthesis. The radiochemical purity was over 95%, determined as described previously (*20*). Gallium-67 citrate was also used for comparative distribution studies in mice and dogs.

Animal experiments. Several tumor-host systems were studied.

1. Mice: spontaneous murine leukemia, HRS/J strain,* types (hr/+) and (hr/hr); spontaneous and transplanted adenocarcinoma, BNL strain,† and transplanted L-1210 leukemia, CDF_1 strain.‡

2. Rats: adenocarcinoma induced by diethylstilbestrol and x-rays; fibroadenoma and pitutary tumors, ACI strain.‖

3. Syrian hamsters: transplanted Greene melanoma of eye.

4. New Zealand rabbits: amelanotic melanoma of eye.

5. Dog: spontaneous seminoma in a mongrel.

F-18 FDG was dissolved in saline and appropriate doses were injected intravenously in all animals except in hamsters, where the intraperitoneal route was used for convenience. Animals were killed at 30, 60, and 120 min after injection. The organs were removed, blotted, weighed, and counted in a sodium iodide well counter, and the activity corrected for decay. Data were expressed as percentage injected dose per gram of organ or tissue. Ratios for tumor-to-blood and tumor-to-corresponding normal tissues were also obtained on a % dose/g basis.

Comparative distribution studies were performed in mice bearing either adenocarcinoma or L-1210 leukemia. F-18 FDG studies were carried out up to 120 min, since the 109-min half-life of F-18 did not permit long-term studies. Gallium-67 citrate studies were carried out up to 24 hr. Imaging was performed with F-18 FDG and Ga-67 citrate in a dog bearing a spontaneous seminoma. For F-18 FDG, a high-energy, parallel-hole collimator§ was used and 50,000 preset counts were collected over the tumor region. For Ga-67 citrate, a medium-energy collimator was used and 100K preset counts were collected over the same area as for F-18 FDG.

Sterile turpentine abscesses were produced in the thighs of New Zealand female rabbits. F-18 FDG (1.5 mCi) was injected i.v., and scintiphotos were obtained with conventional gamma camera up to 2 hr. The same animal was injected i.v. with Ga-67 citrate (0.5 mCi), and scintiphotos were taken at 2, 5, and 24 hr after injection.

Since F-18 FDG is a substrate for hexokinase, and the hexokinase level is known to increase in certain types of malignant transformation (*4,6*), determination of hexokinase activity in normal and tumor tissues was also performed as previously described (*21*).

Toxicity studies. These were performed following the guidelines recommended by FDA for any investigational new drug.¶ Six BNL-strain albino mice were injected intraperitoneally with FDG, 14.3 mg/kg, at weekly intervals for 3 wk (total of 3000 times the human tracer dose). They were given food and water *ad libitum*, and observed over the 3-wk period. A control group of mice were injected intraperitoneally with the same volume of sterile normal saline on the same schedule, and observed for 3 wk. Mice were monitored for any weight changes or morbidity. After 3 wk they were killed and their internal organs examined grossly and microscopically. Two adult female conditioned beagle dogs were injected intravenously with FDG, 0.72 mg/kg at weekly intervals for 3 wk (total of 150 times the human tracer dose), and a control dog received the same volume of sterile normal saline on the same schedule. Dogs were routinely examined (temperature, blood pressure, pulse, ausculation) for any clinical signs and symptoms of abnormalities for 3 wk. Blood and urine samples were obtained for analysis: before injection, and at 2 hr, 1 wk, and 2 wk after injection. Cerebrospinal fluid samples were also collected. The following analyses were performed.

1. Urine: physical and microscopic examination, electrolytes, creatinine, glucose, protein, urobilinogen, and osmolarity.

2. Blood: RBC, WBC, platelets, reticulocytes, differential, hemoglobin, hematocrit, erythrocyte sedimentation rate, prothrombin time, osmolarity, electrolytes, glucose, urea nitrogen, uric acid, creatinine, alkaline phosphatase, LDH, SGOT, SGPT, CPK, total protein, albumin, and total bilirubin.

3. Cerebrospinal fluid: glucose, protein, and chloride.

At the end of 3 wk, the dogs were killed with an overdose of i.v. pentobarbital and their internal organs were examined grossly and microscopically.

RESULTS

Tables 1-3 and Figs. 1 and 2 show the F-18 FDG uptakes (% dose/g) at 30 and 60 min after injection and ratios of uptake in tumor and corresponding normal tissues in various animals bearing tumors of different cell types. Tumor-to-blood and tumor-to-normal tissue ratios ranged from 2.61-17.82 and 2.10-9.15, respectively, in different host systems at 60 min after injection. Tumor-to-normal tissue ratios were similar at 30 and 60 min after injection, but tumor-to-blood ratio increased at 60 min. Accordingly, a 60-min study time was chosen for most of the experiments (Table 2). The specific activity of the injected dose of F-18 FDG (μg/animal) was different for different breeds of animals studied, but spearate studies in mice with varying loading doses showed that there was no loading-dose effect between dose levels of 0.04 and 0.40 mg/kg.

Comparative distribution studies with Ga-67 citrate in mice with breast adenocarcinoma showed that F-18 FDG gave much higher tumor-to-blood ratios at 1 hr (15.96 compared with 0.27), although the ratios for tumor to normal tissue were similar (3.28 compared with 3.05, Table 4). With passage of time, however, both of these ratios increased for Ga-67, whereas with F-18 FDG they appeared to decrease after 60 min.

Figure 3 shows scintigrams with F-18 FDG (at 2 hr after injection) and Ga-67 citrate (at 24 hr) in a dog with seminoma. There was high uptake of F-18 FDG in the viable tumor tissues by 30 min after injection. There was excellent visualization of the tumor, due to low blood and

TABLE 1. UPTAKE OF F-18 FDG IN CNS TUMORS*

Tumors	Uptake (% dose/g)	Ratios (% dose/g) tumor/tissue	tumor/blood
Pituitary tumor (rat)	0.79 ± 0.05	3.23 ± 0.37	4.25 ± 0.33
Amelanotic melanoma (rabbit eye)	0.43 ± 0.07	3.10 ± 1.10	3.46 ± 0.73
Greene melanoma (hamster eye)	2.32 ± 0.20	4.64 ± 0.81	6.01 ± 0.89

* Time = 60 min. Each point represents mean ± s.d.. of 6–10 animals.

tissue backgrounds. However, the dog was catheterized to eliminate the urinary activity, since a considerable amount of F-18 FDG is excreted in the urine (*20*). There was comparable uptake of Ga-67 at 24 hr after injection, but there was also higher blood background and very high colonic activity.

Figure 4 shows scintigrams with Ga-67 citrate and F-18 FDG in a rabbit with an experimental sterile abscess. There was visualization of the abscess with Ga-67 at 2 hr but the background activity was rather high. There was very good delineation by 5 hr, and still better at 24 hr, due to decreased background activity. However, no localized uptake in the abscess was seen with F-18 FDG up to 2 hr.

Two phenotypes of mice (hr/hr and hr/+), bearing spontaneous leukemia with malignant infiltrations of spleen and liver, showed a nearly twofold increase in F-18 FDG-6-phosphate activity in those two organs compared with the corresponding normal control tissues (Table 5), indicating an increased hexokinase activity with malignant transformation.

The tracer dose of F-18 FDG, for brain or heart studies in man, is approximately 1 mg of F-18 FDG (0.014 mg/kg). Toxicity studies in mice given three doses of 14.3 mg/kg of FDG (3000 times human tracer dose) did not reveal any immediate or long-term effects as determined by routine observations, changes in body weight, and gross and histopathology of the internal organs. Toxicity studies in dogs injected with three doses of 0.72 mg/kg of FDG (150 times human dose) did not show any immediate or long-term effects. No significant abnormalities were detected in blood, urine, or CSF analyses, and no significant gross or microscopic abnormalities were detected in the heart, brain, spleen, liver, kidneys, lungs, ovaries, or intestines.**

TABLE 2. F-18 FDG LEUKEMIC ORGAN-TO-BLOOD RATIOS IN TRANSPLANTED L-1210 LEUKEMIA IN MICE

Organ*	Organ % dose/g† / Blood % dose/g 30 min	60 min
Liver	6.72 ± 1.10	10.86 ± 2.63
Spleen	8.06 ± 0.04	17.82 ± 0.88
Bone marrow	3.39 ± 0.03	7.65 ± 0.40

* Organs infiltrated with leukemic cells.
† Each point represents mean ± s.d. of 6–10 animals.

DISCUSSION

This study showed that there was an early and high uptake of F-18 FDG in a variety of transplanted and spontaneous tumors in several animal hosts. The specific uptake of F-18 FDG in tumors may be related both to (a) enhanced transport, and (b) changes in the metabolism in tumor cells. It has been shown that during cellular transformation, enhancement of transport of 2-deoxy-D-[^{14}C]glucose occurs due to an increase in simple and facilitated diffusion of glucose as a result of an alteration in the plasma membrane's sugar-transport system (*20–22*). Also an early discovery in cancer biochemistry was made in carbohydrate metabolism by Warburg (*25*), who demonstrated that in undifferentiated, rapidly growing tumors, aerobic glycolysis is increased and respiration is decreased. In contrast, in well-differentiated, poorly growing tumors glycolysis is decreased or remains unchanged and respiration is increased (*20,24*). This imbalance in carbohydrate metabolism in cancer cells is due to ordered as well as random changes in carbohydrate enzyme behavior of cancer

TABLE 3. F-18 FDG ORGAN-TO-BLOOD RATIOS IN SPONTANEOUS MURINE LEUKEMIA*

Organ†	Organ % dose/g‡ / Blood % dose/g Phenotype: hr/+	hr/hr
Liver	4.20 ± 0.37	2.61 ± 0.08
Spleen	3.59 ± 0.96	4.26 ± 1.31
Thymus	5.15 ± 0.57	5.31 ± 1.27
Lymph node	6.22 ± 0.94	—

* Time = 60 min.
† Organ infiltrated with leukemic cells.
‡ Each point represents mean ± s.d. of 6–10 animals.

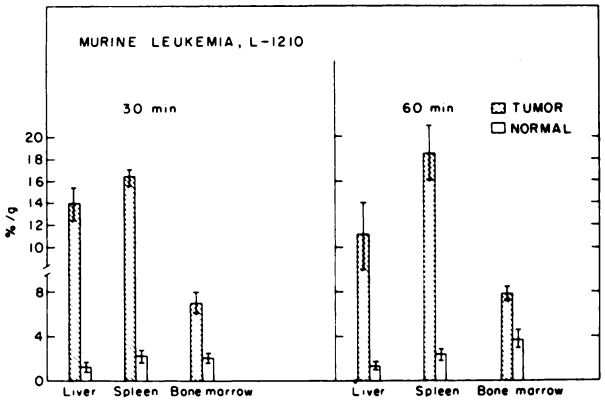

Fig. 1. Uptakes of F-18 FDG in organs indicated, at 30 and 60 min, in normal mice (clear bars) and when infiltrated with L-1210 leukemia (hatched bars).

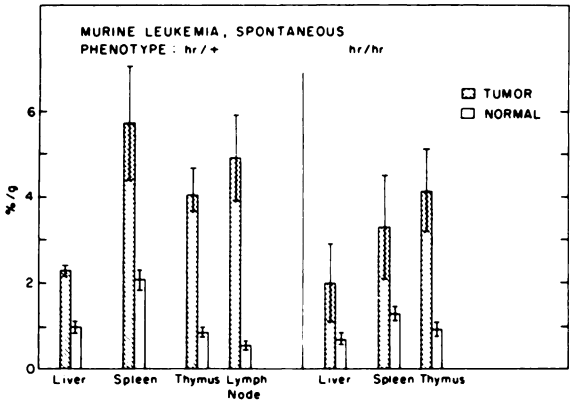

FIG. 2. Spontaneous leukemia in two mouse phenotypes: 60-min uptakes of F-18 FDG, comparing infiltrated organs (hatched) with normals (clear).

cells (*4*). The key enzymes of glucose catabolism (hexokinase, phosphofructokinase, pyruvate kinase) show a pattern of ordered alterations linked with growth rate of a particular tumor. For example, a rapidly growing tumor like the Novikoff hepatoma showed more glycolytic enzyme activity than slowly growing Morris hepatoma (*22,26*).

It has been shown that 2-deoxy-D-glucose (2-DG) can be phosphorylated by hexokinase, and a trace of the phosphorylated product can be oxidized to gluconic acid (*23*), but the vast majority of the transported sugar remains as 2-deoxy-D-glucose phosphate (*23,24*). Weber (*4*) demonstrated that the level of hexokinase is increased two to three times in human hepatoma compared with normal liver tissue (2.06×10^{-7} μmol/hr/cell against 0.78×10^{-7}). Similarly, Monakhov et al. found a modification of hexokinase properties as a result of malignant transformation (7). We also observed that F-18 FDG-6-phosphate concentration was about twice as high in murine leukemia tissues as in corresponding normal tissues, indicating an increase in the hexokinase activity in those tissues (Table 5).

The tumor concentration of F-18 FDG reached a peak by 30 min after injection and remained relatively constant up to 60 min. After that, F-18 FDG concentration appeared to wash out slowly from the tumors (3.83 %/g against 2.27 %/g, $p < 0.005$–0.001, Table 4). It appears that transport of F-18 FDG within the tumor cells is rapid and is complete within 30 min. Thereafter any further accumulation of F-18 FDG within the cells ceases, and the poorly permeable, essentially trapped product ^{18}F-FDG-6-phosphate is very slowly metabolized to products to which the cell membranes are relatively more permeable. A slow washout of the activity from the tumor cells results. Renner (*23*) also reported a similar observation with C-14 DG and suggested that since the tumor cells contain an excess of hexokinase, 2-DG is phosphorylated as rapidly as it enters the cells and, without being extensively metabolized, is thereby trapped within the cells, allowing for an extended net uptake at the maximum rate. However, high concentrations of 2-DG-6-phosphate within the cells are known to inhibit further transport and utilization of glucose, due to a rapid and almost complete depletion of cellular ATP for the hexose-catalyzed phosphorylation of glucose, and also due to competitive inhibition of phosphohexokinase isomerase by DG-6-P (*27,28*).

Although the tumor uptake of F-18 FDG was high in various tumor models studied, the uptake (% dose/g) differed in different tumor models (Tables 1–3, Figs. 1 and 2). This variation could be due to (a) different growth rates (degree of differentiation) of various tumors, since metabolic makeup and demands of various malignancies are known to differ, paralleling differences in their growth rates and differentiation (*20,26,29,30*). For example, L-1210 is a very rapidly growing tumor,

TABLE 4. UPTAKES OF F-18 FDG AND Ga-67 IN MICE WITH ADENOCARCINOMA*

Ratios	F-18 FDG		Ga-67		
	1 hr	2 hr	1 hr	6 hr	24 hr
Tumor/blood	15.96 ± 4.26	8.11 ± 2.02	0.27 ± 0.06	0.48 ± 0.11	2.03 ± 0.22
Tumor/tissue	3.28 ± 0.79	2.83 ± 0.80	3.05 ± 0.23	3.38 ± 0.99	8.64 ± 0.93
Tumor uptake (% dose/g)	3.83 ± 1.17	2.27 ± 0.50	4.67 ± 1.35	4.40 ± 1.01	5.01 ± 1.02

* Each point represents mean ± s.d. of 10 animals.

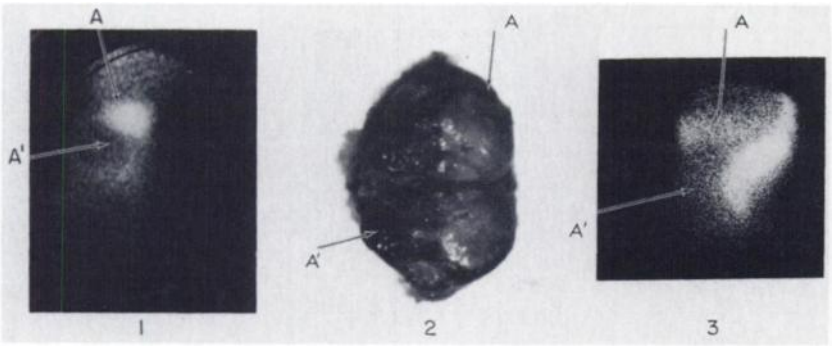

FIG. 3. In vivo scintigrams with F-18 FDG at 2 hr (1) and gallium-67 at 24 hr (3) in a dog with spontaneous seminoma. Excised tumor in center. A = visible tumor; A′ = necrotic. Note colonic activity with Ga-67.

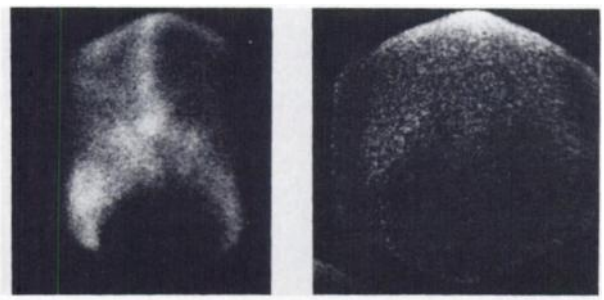

FIG. 4. Scintiphotos (conventional camera) of rabbit with sterile turpentine abscess in right thigh. Left: abscess shows clearly with Ga-67 citrate, but not (right) with F-18 FDG.

and showed the highest concentration (18.35% dose/g). On the other hand, pituitary tumors, which are relatively slow growing showed low F-18 FDG uptake (0.79% dose/g). Or (b) the blood supply (ECF space) of the tumor may also play a role in the delivery, and therefore uptake, of F-18 FDG in the tumors, although blood flow alone is not the limiting factor for F-18 FDG uptake in the cells (*31*). For example, the amelanotic melanoma transplanted into the posterior chamber had very little uptake (0.43% dose/g), and the posterior chamber of the eye is known to have very little blood supply. The scintigraphy of the spontaneous seminoma in a dog showed very high uptake of F-18 FGD in the viable tumor tissues, although the necrotic part failed to show any radioactivity (Fig. 3). Or (c) different hexokinase properties as a function of tumor type (*7*) might also play a role in varying the demand for the substrate F-18 FDG, thereby varying in the uptake of F-18 FDG in different tumors.

There are a number of advantages in using F-18 FDG as a tumor-detecting agent in comparison with the commonly used Ga-67 citrate. Previous studies (*20,21*) have indicated that the only significant organ uptakes of F-18 FDG are in brain and heart, and uptake there is rapid. Therefore, the background activity is low at an early time for administration, permitting study within 2 hr following injection of radioactivity. With Ga-67 citrate it is necessary to wait 1 to 3 days, and even then the background activity, especially in the abdomen, is rather high. Preliminary studies of turpentine-induced sterile abscesses showed lack of uptake of F-18 FDG, up to a study period of 2 hr. Therefore, F-18 FDG will be a useful agent in differential diagnosis of tumors from inflammatory lesions, which the tumor-seeking agent Ga-67 citrate fails to differentiate. Studies are in progress to correlate F-18 FDG concentration in tumors at different stages of growth cycle and also to evaluate the regression of tumors after chemotherapy using F-18 FDG concentration as a probe to monitor such effects.

FOOTNOTES

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¶ Guideline: Manufacturing and controls for IND's and NDA's. Clinical testing: Symposis of the new drug regulations. FDA papers. FDA/US HEW(FDA) 72-3013 1971.

** Detailed data available in IND No. 13483. Data on toxicity will be available from the authors on request.

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TABLE 5. CONCENTRATION OF F-18 FDG-6-PHOSPHATE IN NORMAL AND LEUKEMIC LIVER AND SPLEEN IN TWO PHENOTYPES OF MICE*

	% F-18 FDG-6-P/g of Tissue			
	Liver		Spleen	
Phenotype	control	tumor	control	tumor
hr/+	30.35–35.75	31.94–78.71	47.75–52.93	83.53–91.44
hr/hr	23.03–26.78	33.22–57.17	36.45–50.45	63.65–89.41

* Time = 60 min. Data represent concentration range for two separate experiments with two samples per experiment.

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