Carbon-11-labeled Amino Acids for the Rectilinear and Positron Tomographic Imaging of the Human Pancreas

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Modification of the Bücherer-Strecker amino acid synthesis facilitated the production of* DL-[^{11}C]*tryptophan and* DL-[^{11}C]*valine for clinical trials in patients with proven or suspected pancreatic disease.

Examples of rectilinear scans and tomographic images of the pancreas are presented in this initial paper. Positron computed tomography was done with the ORTEC ECAT system. Rapid localization of these C-11-labeled amino acids and fast clearance from the plasma permit almost immediate examination following i.v. injection. Illustrative images include the normal pancreas, pancreatitis, and pancreatic carcinoma. The use of positron tomography with C-11-labeled* DL*-tryptophan and* DL*-valine appears to offer a new and promising diagnostic modality for the detection and study of pancreatic diseases.

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Since its introduction by Blau and Bender in 1962 (*1*), pancreatic imaging with [^{75}Se]selenomethionine (Se-75 MTh) has had only moderate success, and this nuclear-medical procedure is now used routinely at only a small number of medical centers (*2–7*). Currently it appears that only a normal pancreas image has clinical significance, since 95% of subjects having a normal scan have actually been free of pancreatic disease, whereas only 60% of patients having abnormal scans are suffering from pancreatic disease (*8,9*).

Recent advances in pancreatic imaging by transmission computerized tomography (*10–12*) and by ultrasonography (*13–16*) have been promising, but development of new radiopharmaceuticals for the diagnosis of pancreatic diseases has been slow. One of the major difficulties encountered with the use of Se-75 MTh and other unnatural labeled amino acids stems from their altered biochemical behavior compared with that of natural amino acids (*17*). For this reason C-11 ($T_{1/2}$ = 20.4 min) and N-13 ($T_{1/2}$ = 10.0 min) appear to be better choices for the labeling of amino acids for in vivo studies, since such materials will follow normal metabolic pathways. Also, since both radionuclides are positron emitters, positron tomography (*18,19*) can be used.

Our radiopharmaceutical group has developed methods for the C-11 labeling, at the carboxyl group, of DL-valine (*20*) and DL-tryptophan (*22*) in quantities large enough to permit clinical trials. In this paper we report our initial results in pancreatic imaging with these two amino acids using positron tomography as well as conventional rectilinear scanning.

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MATERIALS AND METHODS

Preparation of racemic C-11 valine and C-11 tryptophan. Both carboxyl-labeled amino acids were synthesized by our high-temperature, high-pressure modification of the Bücherer-Strecker technique (*21*). Production of C-11 and synthesis and purification of the radiopharmaceuticals were carried out at Oak Ridge National Laboratory's 86-in. cyclotron complex. Final radiopharmacy preparation—adjustment of pH to 7.0 ± 0.2, microfiltration (0.22 μ), pyrogen testing, and radioassay—was done at the Medical and Health Sciences Division of Oak Ridge Associated Universities. Because of the 20.4-min half-life of C-11, Limulus amebocyte lysate results were read after 15 min.

Clinical studies. The patients had proven or clinically suspected pancreatic disease and participated in these Phase I and II studies under informed consent*. A listing of the patient populations and the different studies is given in Table 1. In a total of 30 patients, 35 studies were done with 34 doses. In only two instances both C-11 valine and C-11 tryptophan were administered on separate occasions to the same patient. Rectilinear scans with both Se-75 MTh and C-11 valine were done in four patients. Although it would have been desirable to compare the efficacy of the three different radiopharmaceuticals in each patient, this was not practical because of problems with availability of cyclotron, positron tomograph, and sometimes the patient. The studies were all done on an outpatient basis.

We made no attempt, by preparatory medication, to enhance pancreatic uptake of the amino acids. Patients were merely encouraged after an 8-hr fast to drink a milk shake approximately 30 min before administration of the tracer.

C-11 valine and C-11 tryptophan were given by i.v. injections (5–10 ml of saline), and the doses did not exceed 714 μCi/kg for C-11 valine (range 13.5–45 mCi per study) or 429 μCi/kg for C-11 tryptophan (range 6.0–35 mCi). Initial C-11 tryptophan and C-11 valine doses were intentionally made high but varied somewhat because of the differences encountered in production efficiencies. Doses are now kept between 10 and 15 mCi, since this level has been found to provide adequate image qualities with a positron tomographic instrument.

Rectilinear scans. All rectilinear scans were made with a dual-head scanner equipped with 5-in. NaI detectors. Fine-focus, high-energy collimators, designed and constructed at ORAU, were used for positron detection in the single-photon mode. For pancreatic scanning with Se-75 MTh, medium-energy, medium-focus collimators were used, with a 100-keV window covering the 265 keV and 280 keV Se-75 gamma peaks. For the C-11 tracers, the window covered 440–620 keV. C-11 valine and C-11 tryptophan rectilinear scans were not corrected for decay.

All scans were started within 5 min after i.v. injection of the selected tracer. The patient's left side was elevated for a 15° tilt. Scan speed was chosen to give approximately 400 counts per cm^2 over the area of the pancreas. The scanning area extended from 5 cm above the tip of the xiphoid to the umbilicus, requiring a scanning time of approximately 10 min. Additional scans were made over a period of 45–60 min, giving a total of four to six images.

Although the positron tomograph can be used in the rectilinear scanning mode, the rectilinear scans in this study were not obtained with the ECAT since the short half-life of C-11 did not permit us to obtain both types of image with a single dose.

Positron tomographic images. These were made with a commercially available instrument†. The first plane was located 2 cm below the level of L-1, and subsequent planes were imaged with 18-mm increments in a cephalad direction. Each plane has a thickness of 21 mm, resulting in a 3-mm overlap for adjacent slices. Scan time was 200 sec per plane, with decay correction. In most patients imaging was started within 5 min after injection of the dose. Scans of the same four planes were usually repeated 20–25 min after injection. In a few patients a third set of scans of the same four planes was obtained after 40–45 min. Most scans were reconstructed

TABLE 1. PATIENT POPULATIONS USED IN C-11 AMINO ACID STUDIES

Radiopharmaceutical	Instrument	Diagnosis			
		Proven or suspected pancreatitis	Proven or suspected ca. of pancreas	Other pancreatic diseases*	Mesenteric lymphoma
C-11 DL-valine	Rectilinear	2	5	1	1
	ECAT	1	1	0	1
C-11 DL-tryptophan	Rectilinear	2	2	0	0
	ECAT	4	12	2	1

* One case with Zollinger-Ellison-syndrome and one with hypoglycemia.

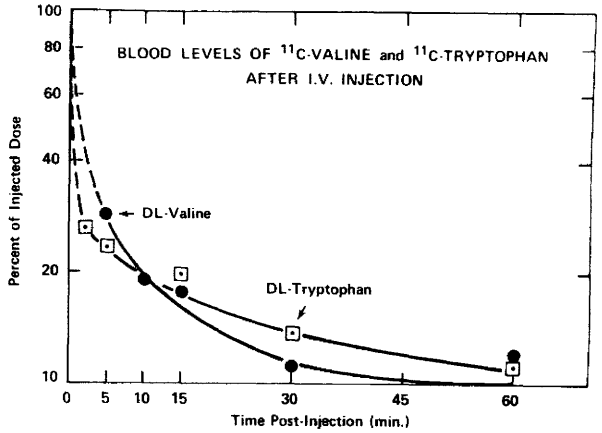

FIG. 1. Semilog blood-clearance curves for carboxyl-labeled C-11 DL-tryptophan and DL-valine. Rapid clearance of these amino acids from blood allows early scanning, compatible with short half-life of C-11.

with calculated attenuation correction because this produces a smoother image. Calculated attenuation correction was done by methods described previously (*23,24*). For measured attenuation correction, transmission data were collected over a 4-min period per plane using an annular source of Ge-68/Ga-68 of approximately 0.5-mCi activity.

Laboratory studies. Patients were monitored for any possible, although unexpected, toxic effects by running routine hematologic tests as well as plasma hemoglobin and urinanalysis. In addition, these patients were observed for changes in vital signs and subjective and objective evidence of systemic reactions or side effects.

The blood clearance of the tracers was determined by radioassay at 5, 15, 30, 60, and 120 min after injection. Subsequent to the imaging procedure, whole-body counts and radioassays of the urine were obtained for dosimetry purposes and to determine the mode of excretion.

TABLE 2. ESTIMATED RADIATION DOSE TO REFERENCE MAN FROM INTRAVENOUS ADMINISTRATION OF CARBOXYL-LABELED C-11 DL-VALINE AND DL-TRYPTOPHAN

	Absorbed dose (rads/mCi)*	
	C-11 DL-valine	C-11 DL-tryptophan
Total body	0.009	0.011
Pancreas	0.150	0.140
Liver	0.027	0.034
Kidney	0.032	0.035

* Based on 30-min tissue distribution of C-14 carboxyl-labeled DL-valine and DL-tryptophan in the dog, assuming immediate uptake by the organs, followed by complete decay in situ.

The amount of C-11 exhaled as $^{11}CO_2$ in three patients who received C-11 tryptophan was measured by sweeping exhaled air through 1 kg of barium hydroxide-lime.

RESULTS

Observations for toxicity. A total of 22 doses of C-11 tryptophan and 12 of C-11 valine were given to 30 patients. No untoward reactions occurred. No changes were observed in any of the hematologic parameters or in urinalyses, and there was no evidence of pyrogenicity.

Blood clearance and whole-body retention. Figure 1 illustrates the rapid plasma clearance of these tracers. Fifteen minutes after injection, the vascular content of both agents had dropped to less than 20% of the administered dose. An average of 12% of the C-11 tryptophan dose, and 14% of the C-11 valine, was present in urine voided immediately after the imaging procedures (approximately 40–60 min after injection of the dose). Radioassay of expired air (monitored in the first three C-11 tryptophan patients) indicated that less than 0.3% of the administered C-11 activity had been expired (loss of radioactivity through decarboxylation). The sum of the whole-body retention and the urinary excretion indicated little if any loss of activity through decarboxylation with either C-11 valine or C-11 tryptophan. These results in humans are in contrast to results obtained in the rat, where definite decarboxylation was observed: for C-11 valine, 18.2% at 30 min and 34.1% at 2 hr; and for C-11 tryptophan, 3.5% at 30 min and 11.8% at 2 hr (*20,21*).

Radiation dosimetry. Dosimetry calculations for C-11 tryptophan and C-11 valine were carried out by the ORAU Radiopharmaceutical Internal Dosimetry Information Center, and were based on the assumption that all of the dose decayed within the patient. Table 2 shows the estimated tissue and total-body radiation dose in humans derived from the tissue distribution of C-14-labeled DL-valine and DL-tryptophan in dogs 30 min after injection. Deposition of a tracer was assumed to occur immediately after administration and at the 30-min concentration, and complete decay in situ was assumed. Whole-body radiation doses were based on the assumption of uniform tissue distribution and no excretion.

Examples of rectilinear scans. Rectilinear scans with Se-75 MTh, C-11 tryptophan, and C-11 valine in three patients with normal pancreas are shown in Fig. 2. Although there is good pancreatic uptake in each case, the distinction between pancreas and liver appears to be considerably better with C-11 tryptophan and C-11 valine than with Se-75 MTh.

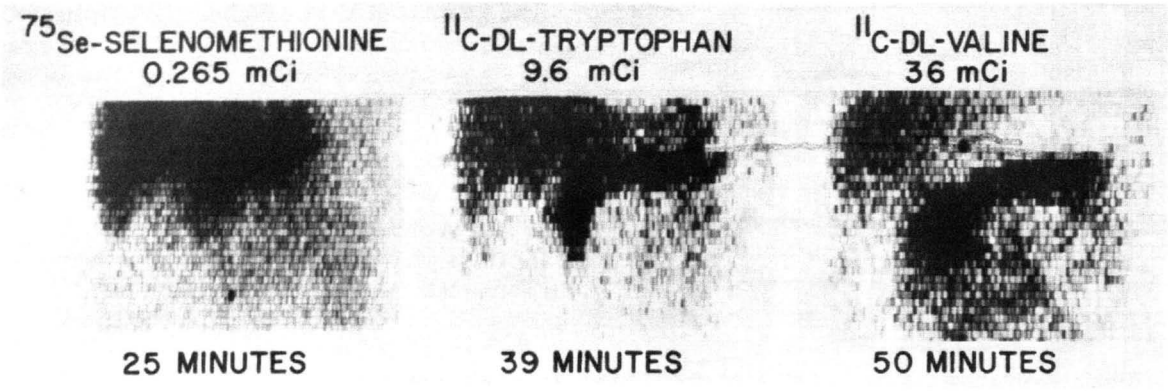

FIG. 2. Examples of normal pancreas images. Each scan is from a different patient. Patient with C-11 valine scan had a mesenteric lymphoma. C-11 valine below pancreas may be uptake in that neoplasm.

Since the kidneys concentrate the C-11-labeled amino acids, a clear view of the head and/or tail of the pancreas was not always obtained.

Three examples of pancreatitis are presented in Fig. 3. In the Se-75 MTh and C-11 tryptophan scans, impaired pancreatic function is indicated by the poor tracer uptake. The pancreas of the patient who had the C-11 valine scan was diffusely enlarged but was able to concentrate the amino acid. This patient was recovering from an attack of acute pancreatitis.

Examples of positron tomographic sections. Normal positron tomograms of the pancreas, obtained after injection of C-11-labeled DL-tryptophan, are shown in Figs. 4 and 5. As shown in the 1-min image in Fig. 4, the amino acid's uptake by the pancreas and concentration in the kidneys was quite rapid. At the same time liver concentration was markedly lower. The 1-min image apparently shows the amino acid in the aorta. Renal activity was significantly cleared by 25 min, at which time the pancreas was well visualized in its entirety, without any defects.

Figure 5 shows another C-11 tryptophan scan of a normal pancreas 23 min after injection. This patient had a malignant melanoma of the choroid of the left eye and suspected hepatic and pancreatic metastases. The pancreas in this scan is considered normal. There is still residual activity in the kidneys. As can be seen, the image obtained using calculated attenuation correction is smoother than the image reconstructed by measured attenuation correction.

Figure 6 is a tomogram of a patient with chronic recurring pancreatitis. Here, 20 min following the injection of 24.1 mCi of C-11 tryptophan, the pancreas appears to be swollen, but the uptake of the tracer indicates sufficient function. The mottled uptake in the liver is interpreted as parenchymal liver disease.

Figure 7 shows a patient with carcinoma of the pancreas. This scan was started 4 min after the injection of C-11 tryptophan. There is complete loss of pancreatic structure, and tracer uptake occurs in a rather large intra-abdominal mass known to be pancreatic carcinoma. Inhomogeneous concentra-

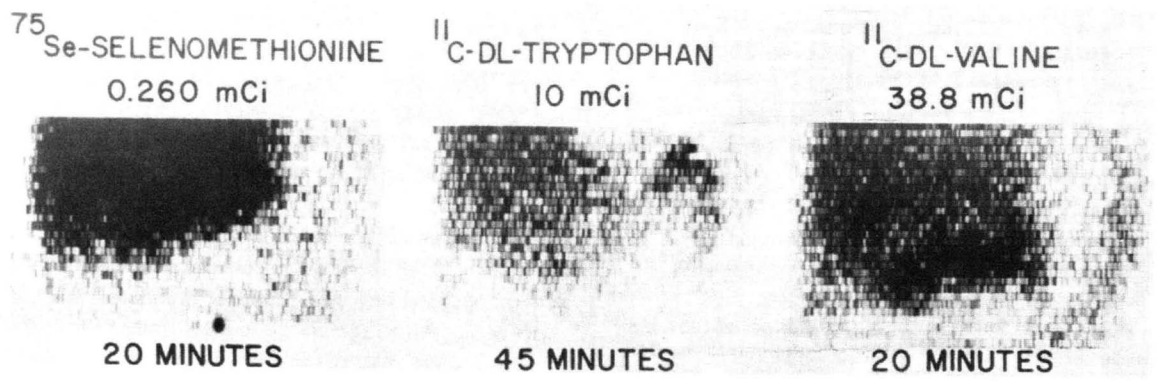

FIG. 3. Examples of pancreatitis. Each scan is from a different patient. Inadequate pancreatic function is documented by poor uptake of Se-75 Mth and C-11 tryptophan. The C-11 valine scan was made during recovery from acute pancreatitis.

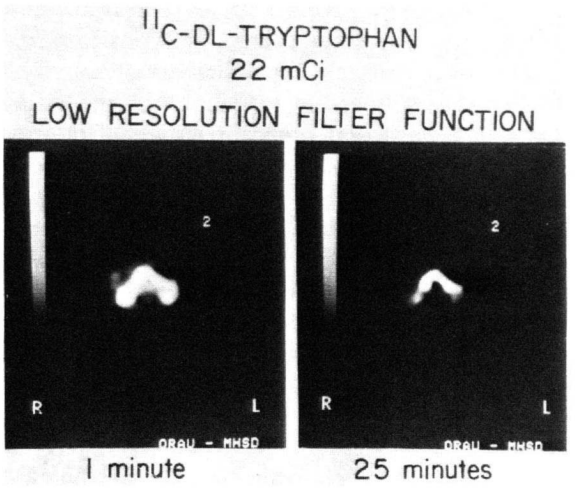

FIG. 4. Normal pancreas of patient with back pain and family history of pancreatic carcinoma and diabetes. Note changing image as clearing of tracer from large vessels and kidneys occurs between 1 and 25 min. Images reconstructed with low-resolution filter function usually give smoother outlines of pancreas.

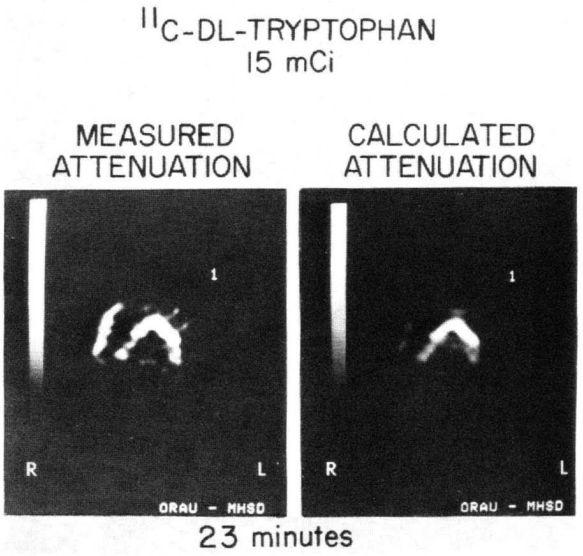

FIG. 5. Normal pancreas. Note smoother image obtained with calculated attenuation correction.

tion of the radiopharmaceutical is seen in the liver. Renal uptake is seen in each of the four planes.

Determination of pancreas-to-liver ratio. The strength of emission computerized tomography lies in its potential for quantitative physiologic in vivo studies of organ or tumor function. In Fig. 8 we demonstrate a simple method with the ECAT scanner to estimate the pancreas-to-liver ratio for C-11 tryptophan. In this study of a normal pancreas, vertical and horizontal histograms were displayed for selected activity profiles. The horizontal activity distribution profile through one slice of liver and pancreas shows a pancreas-to-liver concentration ratio of 5 to 1. For four patients with normal pancreas we have estimated the pancreas-to-liver ratio for C-11 tryptophan to be between 4:1 to 6:1 by using the histogram and region-of-interest method for different regions of the pancreas. In determining these ratios, assurance was obtained that pancreas and liver were clearly present in slices adjacent to the region of interest.

DISCUSSION

Despite the limited number of cases studied, we feel we have demonstrated the general usefulness of C-11 DL-valine and C-11 DL-tryptophan for visualizing the pancreas, and can make several tentative conclusions. Both C-11-labeled amino acids appear to have a greater pancreatic specificity than Se-75 MTh. It is generally agreed that C-11, N-13, and O-15 are ideal markers for biologic tracer studies, which would explain some of the improvement of the images obtained with C-11-labeled amino acids. It is our impression that C-11 tryptophan generally gives better pancreatic images than C-11 valine, although only two patients were examined with both amino acids and the ECAT scanner. This would correspond with C-14 animal-tissue distribution data which for a number of different species indicated higher pancreas-to-tissue concentration ratios for DL-tryptophan than for DL-valine (*20,21*).

All patients in this study having a normally functioning pancreas showed prompt pancreatic concentration of the C-11-labeled amino acids in both the rectilinear scans and the positron tomograms. The normal C-11 valine pancreas scan in Fig. 2

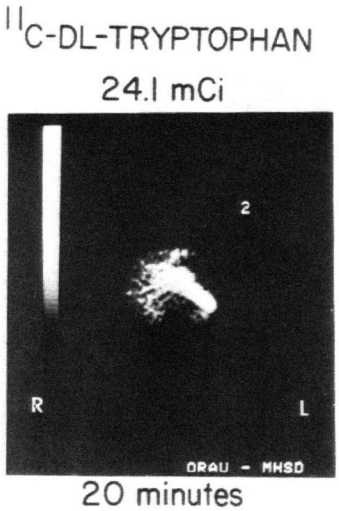

FIG. 6. Chronic recurring pancreatitis and parenchymal liver disease in chronic alcoholic patient.

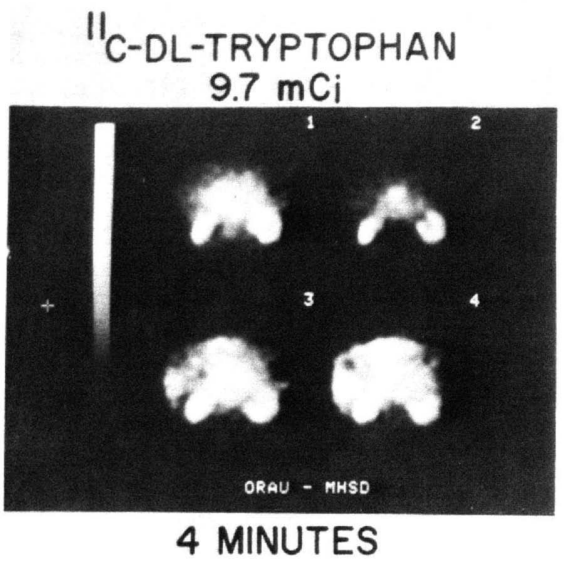

FIG. 7. Four consecutive planes through upper abdomen in patient with adenocarcinoma of pancreas. The four planes are not normalized to each other.

appears to show uptake of the amino acid in a large mesenteric lymphoma. In another case with intra-abdominal non-Hodgkin's lymphoma, C-11 tryptophan appeared to concentrate in the tumor. This indicates that some neoplastic tissues may have a high turnover rate for valine and tryptophan, and thus the C-11 agents may be useful tumor-localizing agents in certain cases.

As is pointed out above, early scans with the C-11-labeled amino acids usually show intense concentration of activity in the kidneys, which often makes scan interpretation with rectilinear scanning difficult, requiring serial scans. With positron tomography, of course, the concentration of activity in adjacent organs does not interfere with the visualization of a particular organ or region of interest.

Interpretation of positron tomographic images relies on the same criteria applied to scanning with Se-75 MTh. Adequate and prompt homogeneous concentration of a positron-emitting agent in the pancreas (i.e., C-11 amino acids) tends to rule out pancreatic disease; on the other hand, nonvisualization or poor uptake would be compatible with pancreatitis and segmental defects. Partial or nonvisualization could indicate a neoplastic or cystic process. It is of interest, however, that the C-11 tryptophan scan in two patients with carcinoma of the pancreas (one example is given in Fig. 7) showed increased activity in a large intra-abdominal mass replacing the pancreas.

The results of this preliminary study indicate that positron tomography using C-11-labeled amino acids offers a new and promising diagnostic method for detection and study of pancreatic diseases. The new technique may supplement anatomic imaging with ultrasonography and transmission computerized tomography.

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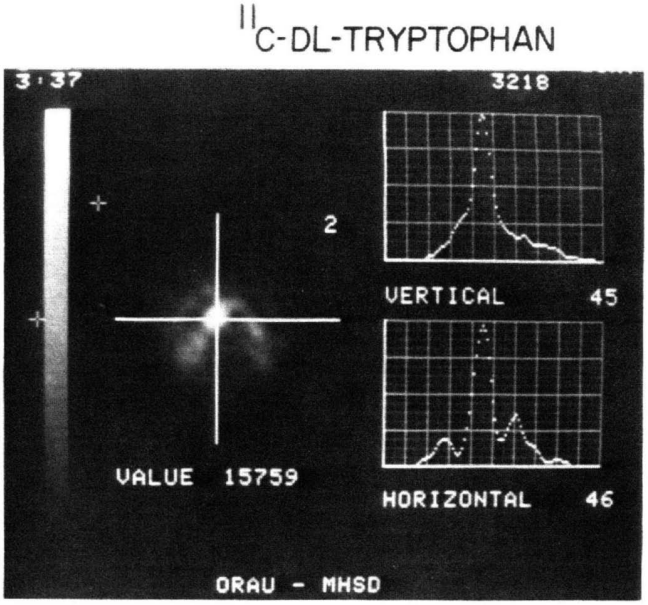

FIG. 8. Activity distribution curves along preselected lines through the image. Horizontal concentration profile indicates pancreas-to-liver ratio of 5:1.

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FOOTNOTES

* This study was done with the approval of the ORAU/ORNL Committee on Human Studies and under FDA INDs 12,457 and 12,967.

† EG&G ORTEC, Inc., Oak Ridge, TN.

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