PRELIMINARY NOTE

Beta-methyl[1-^{11}C]heptadecanoic Acid: A New Myocardial Metabolic Tracer for Positron Emission Tomography

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We have tagged heptadecanoic acid with C-11 at the carboxyl group and have inserted a methyl radical in the beta position to inhibit beta oxidation of the fatty acid; we have then explored the tracer's potential as an indicator of myocardial metabolism for use with the positron tomograph. In this preliminary evaluation, biodistribution studies were made in rats and dogs, and imaging of normal and infarcted dogs was performed. At 30 min the tissue distribution studies in rats and dogs showed, respectively, 1.9% and 8.3% uptake in the heart. Sequential images of the canine heart exhibited a remarkable uptake, peaking at 16–18 min and retaining the same level of activity over the one-hour study period. Images of the heart after LAD ligation showed an area of diminished uptake corresponding to the region of infarction. Thus this agent has the basic properties required for potential use in the assessment and quantitation of free fatty-acid metabolism in the heart in a manner similar to the measurement of glucose metabolism in the brain with 2-[^{18}F]fluoro-2-deoxy-D-glucose.

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The clinical prognosis of ischemic heart disease is related to the severity and location of the lesion and the quantity of residual viable myocardium. Since disease is usually accompanied by changes in the metabolic features of the tissue, the identification, differentiation, and quantitation of normal, ischemic, and acutely infarcted myocardium could be best achieved by the noninvasive application of a metabolic tracer or its analog.

Fatty acids have been estimated to provide 65% of the total energy requirement for heart muscle. Zieler (*1*) has shown that nonesterified fatty acids in plasma are taken up by the myocardium and by skeletal muscle, esterified to triglycerides, and incorporated into lipid granules. These fatty acids are released by hydrolysis of the triglycerides and are the major immediate substrate oxidized by the heart and skeletal muscle at rest and during exercise.

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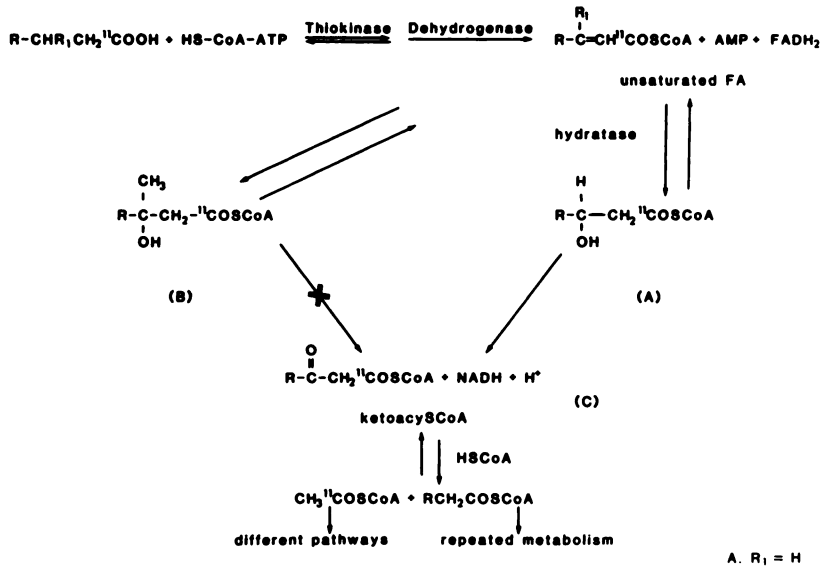
Fatty acids, labeled with C-11 or F-18 and used in conjunction with tomographic techniques, have been suggested for the study of regional myocardial metabolism (*2–10*). Goldstein et al. (*10*) demonstrated in rabbits that the rate of clearance of C-11 palmitate from the myocardium can serve as an index for whole-heart metabolism of fatty acids. They conclude that measurements of regional myocardial metabolism will be feasible when fast scanning systems are available.

In studies with C-11 palmitic acid and other long straight-chain C-11-labeled fatty acids, there is always a fast washout of activity from the myocardium due to the beta-oxidation process, in which the fatty acids are degraded to the corresponding acetylSCoA or propionylSCoA (Scheme 1). Alpha and omega oxidation seem to make only a small contribution to fatty-acid metabolism (*11*).

A labeled fatty-acid analog that is partially metabolized and trapped in the myocardium is a potential agent for imaging and metabolic studies. This principle of metabolic trapping has been used to assess the energy



A. $R_1 = H$
B. $R_1 = CH_3$

SCHEME 1. Metabolic pathway for beta oxidation of fatty acid.

requirements of the brain in rats, cats, and primates with 2-deoxy-D-[^{14}C]glucose (*12,13*). 2-[^{18}F]fluoro-2-deoxy-glucose has been utilized by Reivich et al. (*14,15*), Phelps et al. (*16,17*), and our group (*18*) to measure the local glucose metabolic rate in the human brain, and by Phelps et al. to investigate glucose metabolism in the myocardium (*19*). A similar approach was used in adrenal imaging studies (*20,21*), although there was no quantification.

Accordingly, in the present study we have synthesized beta-methyl-[^{11}C]heptadecanoic acid [(C-11)-BMHDA], a fatty-acid analog designed to inhibit the beta-oxidation process by preventing the formation of the corresponding beta-ketoacylSCoA (Scheme 1B). The biodistribution of this agent was studied in rats and dogs. Its extraction and retention in the myocardium, as a function of time, were assessed and compared with those of [1-^{11}C]heptadecanoic acid [(C-11)HDA], a straight-chain fatty-acid substrate. Preliminary sequential images of normal and infarcted canine myocardia were made.

MATERIALS AND METHODS

Elemental analysis. Analysis for carbon, hydrogen, and bromine was performed commercially.*

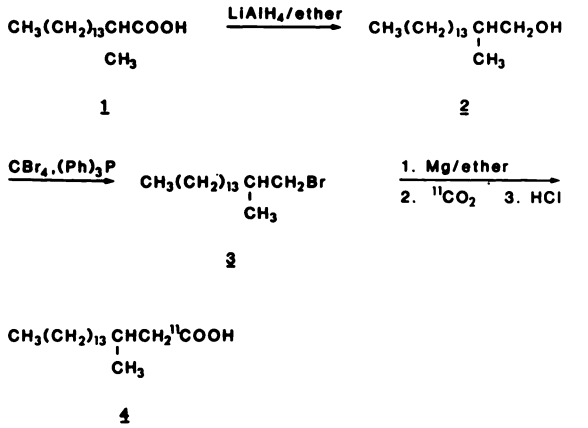
Spectroscopic analyses. Proton NMR† and electron-impact mass spectra‡ were obtained.

Chromatography. Thin-layer chromatography was done on silica gel F 254‖ in hexanes:ether:acetic acid, 70:30:1 (v/v/v). Chromatograms of radiolabeled compounds were scanned with a radiochromatogram scanner. Spots of compounds in propylene glycol solution were dried at room temperature for 10 min at 1 mm pressure before development. High-pressure liquid chromatography was carried out on a 5-μ octadecyl silane (ODS) 25-cm column with tetrahydrofuran:acetonitrile:water, 40:40:20, at a flow rate of 1 ml/min.§

Production of $^{11}CO_2$ (*22*). This was obtained by deuteron irradiation of boric oxide enriched with B-10. The radioactive gas was flushed from the target with helium and collected in a glass trap immersed in liquid nitrogen.

Synthesis of beta-methyl-[^{11}C]heptadecanoic acid (Scheme 2).

2-Methylhexadecanol (2). The compound was prepared by reduction of 2-methylhexadecanoic acid¶ (**1**) with lithium aluminum hydride in ether using standard procedures. Thin-layer chromatography of crude **2** showed very little starting material and **2** was used for synthesis of **3** without further purification. A small amount of **2** was characterized after crystallization from petroleum ether: (mp 42–43°C) mp 34–37°C (*23*). ^{1}H NMR ($CdCl_3$) δ 0.90 (d,2), 1.07–1.90 (m,31), 3.48 (d,2), electron-impact mass spectrum (m/e) 256.25



SCHEME 2. Synthesis of β-methyl-[1-^{11}C]heptadecanoic acid.

(0.06,M), 238.25 (5.86,M—H_2O), 210.19 (3.00, M—H_2O—CH_2=CH_2).

2-Methyl-1-bromohexadecane (3). A procedure similar to that of Hooz (*24*) for the preparation of alkyl bromides was followed. Triphenylphosphine** (7.3 g, 28 mmol) and 2-methylhexadecanol (3.68 g, 14 mmol) were dissolved in 80 ml benzene. A solution of carbon tetrabromide** (9.2 g, 28 mmol) in 20 ml benzene was added slowly and the mixture refluxed for 90 min. The reaction mixture was cooled and filtered, and the residue washed with 3 × 50-ml portions of petroleum ether. The solution was evaporated to dryness, the residue stirred with 100 ml petroleum ether, and left overnight in the freezer. The solution was filtered, the residue washed with 2 × 25 ml petroleum ether, and the combined solution evaporated to dryness. Thin-layer chromatography showed no starting material. The residue was distilled twice to yield 3.6 g (**3**) (81%): bp 131°C, 1.2 mm Hg ^1H NMR ($CdCl_3$) δ 0.95 (d,2), 1.20-2.10 (m,30), 3.33 (d,2), electron-impact mass spectrum (m/e) (M* refers to Br-81 isotope, M refers to Br-79), 320.19 (0.40, M*), 318.13 (0.44,M), 239.25 (14.50, M*-Br-81, M-Br-79).

Anal. calc. for $C_{17}H_{35}Br$: C = 63.93, H = 11.05, Br = 25.02. Found: C = 64.16, H = 10.67, Br = 25.03.

Beta-methyl [1-^{11}C]heptadecanoic acid (4). A solution of **3** (300 mg, 0.94 mmol) in 5 ml ether (dried over CaH_2 and redistilled just before use) was injected into 5 ml refluxed ether containing magnesium (27 mg, 1.1 mmol). Reflux was continued for 90 min under an argon atmosphere. The reaction mixture was cooled to room temperature and 1.5 ml of the solution was injected into the $^{11}CO_2$ trap and the solution shaken for 5 min. The radiochemical yield was 35-40%. The solution was transferred to a separatory funnel. The trap was then washed with 2 × 2 ml ether and the combined ether solutions were shaken with 0.3 ml 1 *N* HCl. The ether solution was washed with water (2 × 2 ml), dried (Na_2SO_4), and evaporated. The residue was dissolved in 4 ml propylene glycol and filtered through a 0.22-μ membrane filter. The radiochemical purity was confirmed by TLC (>99%, R_f of **4** and beta-methylheptadecanoic acid 0.25) and HPLC (>99%, retention time of **4** and beta-methylheptadecanoic acid 6.8 min).

Synthesis of beta-methylheptadecanoic acid. The remaining Grignard solution that was used for the preparation of **4** was purged with carbon dioxide for 10 min, transferred to a separatory funnel, and shaken with 5 ml 1*N* HCl followed by 2 × 5 ml H_2O. The ether was dried (Na_2SO_4) and the residue refluxed with methanolic HCl. The resulting methyl beta-methylheptadecanoate was purified by preparative TLC. The pure methyl ester was hydrolyzed and the resulting acid crystallized from acetone: mp 46-47°C mp 46-47°C (*25*). ^1H NMR ($CdCl_3$) δ 1.00 (d,3), 1.16-1.66 (m,30), 2.23-2.36 (t,2) 11.06 (S,1).

Synthesis of [1-^{11}C]heptadecanoic acid. Following the procedure for the preparation of **4**, 1-iodohexadecane (300 mg, 0.85 mmol), magnesium (25 mg, 1.03 mmol), and $^{11}CO_2$ were reacted to give [1-^{11}C]heptadecanoic acid. The radiochemical purity of the acid was ascertained by TLC (>99%). R_f of [1-^{11}C]heptadecanoic acid and heptadecanoic acid is 0.23. HPLC (>99% retention time 6.3 min).

Tissue distribution studies. CD Fischer rats (175-225 g) were anesthesized with ether and 0.2 ml (2-10 μCi) of the radiolabeled compound was injected through the femoral vein.They were killed by ether asphyxiation at 5, 15, 30, and 60 min after dose. The appropriate organs were excised and the radioactivity measured in a NaI(Tl) well scintillation counter.

Dogs. Four mongrel dogs were anesthesized with sodium pentabarbitol (0.55 cc/kg) and 0.8-3 mCi of beta-methyl-[^{11}C]heptadecanoic acid were injected through a femoral vein. After 1 min, serial blood samples were taken from a femoral-vein catheter to determine the blood clearance rate. A 3-ml aliquot was taken every minute for the first 5 min, every 5 min for the next fifteen, and every 10 min for the next hour. The blood samples were weighed, counted in a well scintillation counter, and the activity corrected for decay. In order to determine the time course of the distribution of the

TABLE 1. C-11 RADIOACTIVITY, AS % INJECTED DOSE/g TISSUE, FOLLOWING INTRAVENOUS INJECTION IN RATS OF β-METHYL-[1-^{11}C]HEPTADECANOIC ACID

Organ	5 min	15 min	30 min	60 min
Blood	0.41 ± 0.06*	0.19 ± 0.02	0.29 ± 0.05	0.28 ± 0.03
Heart	2.32 ± 0.32	2.16 ± 0.68	2.94 ± 0.70	2.70 ± 0.73
Lungs	1.43 ± 0.10	0.74 ± 0.08	0.50 ± 0.12	0.36 ± 0.05
Liver	1.64 ± 0.23	1.53 ± 0.29	2.69 ± 1.01	2.86 ± 0.41
Kidneys	0.80 ± 0.07	0.60 ± 0.04	0.84 ± 0.11	0.80 ± 0.05
Muscle	0.26 ± 0.06	0.19 ± 0.05	0.24 ± 0.03	0.20 ± 0.04

* Mean ± s.d. for 6 animals.

TABLE 2. C-11 RADIOACTIVITY, AS % INJECTED DOSE PER ORGAN, FOLLOWING INTRAVENOUS INJECTION IN RATS OF β-METHYL-[1-^{11}C]HEPTADECANOIC ACID

Organ	5 min	15 min	30 min	60 min
Blood	7.56 ± 0.93*	3.59 ± 0.55	4.43 ± 0.56	4.09 ± 0.66
Heart	1.64 ± 0.22	1.53 ± 0.46	1.91 ± 0.42	1.67 ± 0.45
Lungs	1.65 ± 0.20	0.88 ± 0.15	0.48 ± 0.19	0.32 ± 0.04
Liver	15.34 ± 2.76	13.95 ± 3.08	16.23 ± 3.56	16.00 ± 2.45
Kidneys	1.65 ± 0.16	1.22 ± 0.07	1.34 ± 0.17	1.28 ± 0.12
Muscle	26.50 ± 5.93	19.48 ± 4.79	21.21 ± 5.00	16.05 ± 3.92

* Mean ± s.d. for 6 animals.

TABLE 3. DISTRIBUTION OF C-11 RADIOACTIVITY IN DOG TISSUES THIRTY MINUTES AFTER INTRAVENOUS INJECTION OF β-METHYL-[1-^{11}C]HEPTADECANOIC ACID

Organ	% Injected dose/gram		% Injected dose/organ	
	Dog 1*	Dog 2*	Dog 1	Dog 2
Blood	0.003	0.004	7.635	3.210
Left ventricle	0.042	0.174	5.56	6.16
Right ventricle	0.029	0.102	2.16	2.43
Left atrium	0.019	0.077	0.04	0.09
Right atrium	0.015	0.068	0.04	0.12
Lungs	0.006	0.009	1.658	1.028
Liver	0.006	0.071	5.793	4.478
Muscle	0.002	0.004	31.776	27.613
Fat	0.001	0.002	4.492	4.439
Whole heart	—	—	7.80†	8.80†

* Dog 1 = 35 kg; dog 2 = 11 kg.
† Average dose for whole heart ± s.d. = 8.3 ± 0.5.

beta-methyl-[^{11}C]heptadecanoic acid in the heart and liver, two-dimensional images of the dogs were made with the positron camera. Before imaging, the dog was placed between the camera heads, a phantom filled with an aqueous solution of Ga-68 was placed beneath the animal, and transmission images were made. Sequential images were collected for 1 min each at the following times: 3 min, 8 min, 13 min, 28 min, 48 min, and 60 min. These images were corrected for decay and for photon attenuation.

RESULTS AND DISCUSSION

Biodistribution studies. Tables 1 and 2 contain the rat data, in percent injected dose per gram and percent dose per organ, respectively. At 5 min the dose/gram heart is 2.3% and at 1 hr 2.7%, with no remarkable change in the intermediate times. These results indicate that the beta-methyl-[^{11}C]heptadecanoic acid is extracted by the heart muscle, and the activity is retained in the heart. As expected, the muscle activity behaves similarly. The blood activity was 0.41% dose/gram at 5 min and decreased to 0.28% injected dose/gram at 60 min, with a heart-to-blood ratio of about 10:1. The lung activity at all times is lower than in the heart, with a heart-to-lung ratio of 7.5:1 at 60 min. The liver activity changes from 1.64% dose/g at 5 min to 2.86% dose/g at 60 min. The

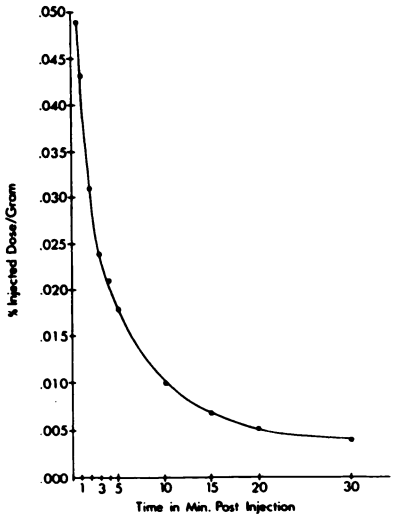


FIG. 1. Time course of radioactivity in blood of dog after i.v. injection of β-methyl-[1-^{11}C]heptadecanoic acid.

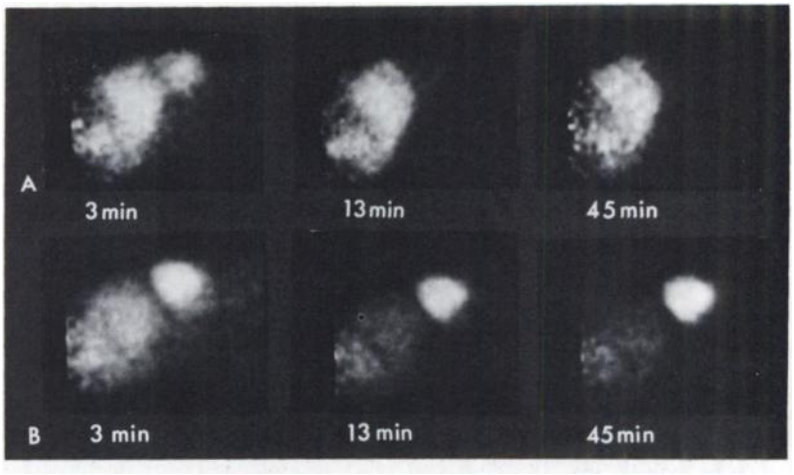


FIG. 2. Sequential images of dogs at 3, 13, and 45 min after i.v. injection of (C-11)HDA (A) and (C-11)BMHDA (B).

heart-to-liver ratio is 1.41 at 5 min and 0.94 at 60 min.

The biodistribution at 30 min in two dogs is presented in Table 3. Uptake in different areas of the myocardium and average uptake for the whole heart have been calculated. The latter is 8.3 ± 0.5% dose/organ; the highest regional uptake, as expected, is in the left ventricle (5.8% dose/whole ventricle average). The blood activity in the dogs at 30 min is 0.003 and 0.004 % dose/g. Figure 1 shows that there are three components in the clearance of (C-11)BMHDA from the dogs' blood, essentially two fast components with half-times of 0.6 ± 0.14 min and 5.7 ± 0.6 min, which are similar to those of 2-[^{18}F]fluoro-2-deoxy-glucose, and a third slower component (*26*). The activity in the liver decreased with time, suggesting a pattern of clearance different from that in rats.

Imaging studies. For the imaging studies, (C-11)-BMHDA and (C-11) HDA (the tagged, straight-chain heptadecanoic acid) were both injected sequentially in the same dogs. Figure 2 is a comparison of the heart and liver images of the (C-11)HDA and (C-11)BMHDA in a dog at 3, 13, and 48 min. Figure 2A, with (C-11)HDA, shows clearly the fast washout of the tracer due to rapid beta oxidation. Figure 2B, with (C-11)BMHDA, shows a remarkable uptake and retention in the myocardium, with heart-to-liver ratios of 1.2:1 at 3 min and 2.7:1 at 60 min (Fig. 3). These ratios were calculated from average counts per pixel. The clearance from the liver is clearly seen in Fig. 2B. The activity in the myocardium stays constant during the whole experiment (60 min).

Figure 4 presents the heart activity per pixel plot for the (C-11)HDA and (C-11)BMHDA as a function of time. The fast washout of the activity of (C-11)HDA from the heart muscle is obvious when compared with the rapid accumulation (max. at 16–18 min) and retention of [1-^{11}C]BMHDA, which retains the same level of activity during three half-lives of the nuclide.

Imaging studies of a canine heart, following (C-11)-BMHDA injection at 1 hr after LAD ligation, show the remarkable uptake in areas of the normal heart and the decreased uptake in the apex, where the infarct was located (Fig. 5). The time-activity plots for the heart, the area of infarct, and the liver for this dog indicate a retention of the activity in the myocardium for 60 mins. The liver activity cleared slowly, the heart-to-liver ratio changed from 1.06 at 3 min to 1.79 at 60 min.

The normal heart utilizes fatty acids mainly by beta oxidation, as is reviewed briefly in Scheme 1 (*27*). At the third step a beta-ketoacylSCoA (C) derivative is produced. The introduction of a methyl group at the beta

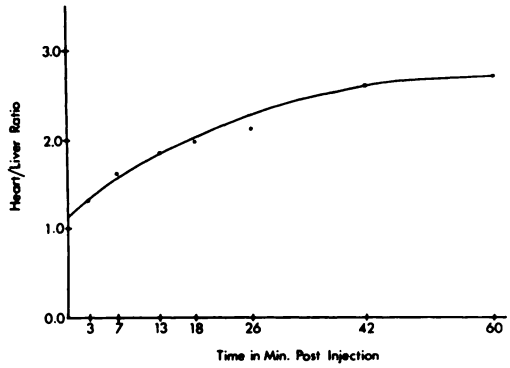


FIG. 3. Heart-to-liver ratio in dogs as a function of time after i.v. injection of (C-11)BMHDA.

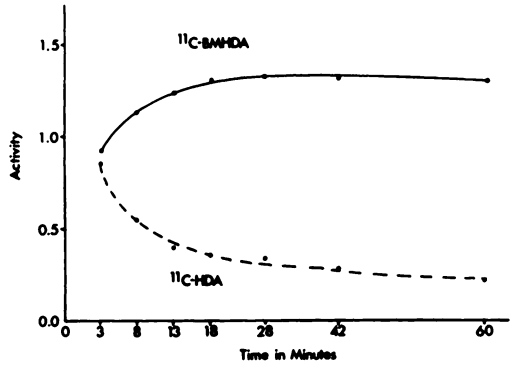


FIG. 4. Time course of heart activity in dogs after injection of (C-11)BMHDA and (C-11)HDA.

FIG. 5. Sequential images of infarcted dog heart at 3, 13, and 45 min after i.v. injection of (C-11)BMHDA.

position of the molecule prevents this step from occurring. We believe that (C-11)BMHDA is metabolized up to the hydroxylation step (B). Product (C) could not be produced because the presence of the methyl group results in an inhibition of the metabolic process. (C-11)HDA exhibits the normal pattern of metabolism with a fast washout of the myocardial activity, whereas (C-11)BMHDA is trapped in step (B) and no further washout of activity caused by the production of (C) or other metabolites is possible. We emphasize that the molecule is labeled on position one (the carboxylic group) for both fatty acids. The loss of the label on position one occurs in the first step of the beta-oxidation degradation of the straight-chain fatty acid as [^{11}C]-acetylSCoA. Our preliminary results suggest that (C-11)BMHDA is trapped in the myocardium as a result of the beta-oxidative degradation process, and therefore might be used for studies of myocardial fatty-acid metabolism. It could also be a basis for the design of a series of free fatty-acid agents to be used for the assessment of myocardial metabolism of the healthy and diseased heart, as is done with 2-^{18}FDG in the brain.

FOOTNOTES

* Galbraith Laboratories, Knoxville, TN.

† Varian T-60 spectrometer with $(CH_3)_4Si$ as internal standard.

‡ Finnigan MAT 212 double focusing mass spectrometer fitted with combination EI/CI ion source. The mass spectra required in this work were provided by the facility supported by NIH grant RR00317, Principal Investigator Professor K. Bieman, Biotechnology Resources Branch, Div. of Research Resources, Massachusetts Institute of Technology.

‖ Analtech, Inc.

§ Laboratory Data Control.

¶ K & K, Plainview, NY.

** Alfa, Andover, MA.

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ERRATA

The title of an article appearing in the February 1982 issue was accidentally placed in the table of contents for the January issue. As a result of this inclusion, the next three articles have been listed as beginning on incorrect pages. The corrections are as follows:

RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

A NEW FORMULATION OF Tc-99m MINIMICROAGGREGATED ALBUMIN FOR MARROW IMAGING: COMPARISON WITH OTHER COLLOIDS, In-111 AND Fe-59
John G. McAfee, Gopal Subramanian, Tamio Aburano, F. Deaver Thomas, P. Fernandes, G. Gagne, B. Lyons, and C. Zapf-Longo 21

PRODUCTION OF L-[l-^{11}C]VALINE BY HPLC RESOLUTION
Lee C. Washburn, Tan Tan Sun, Billy L. Byrd, and Alvin P. Callahan 29

INSTRUMENTATION

PERFORMANCE OF THE ROTATING SLANT-HOLE COLLIMATOR FOR THE DETECTION OF MYOCARDIAL PERFUSION ABNORMALITIES
Osman Ratib, Eberhard Henze, Edward Hoffman, Michael Phelps, and Heinrich R. Schelbert 34

The INVESTIGATIVE NUCLEAR MEDICINE section should be removed. The article by Merrick et al. appears in the February issue of JNM (pp 126-130).

The issue cited in the footnote found on p 1103 of the December 1981 issue of *JNM* (O'Mara et al., "Components of Professional Competence of Nuclear Medicine Physicians") is incorrect. The footnote should read:

* A revision of the components published in *The Journal of Nuclear Medicine*, Vol. 12, December, 1971.