Lipid Metabolism in the Liver Studied In Vivo with Two Isomers of Labeled Fatty Acid Analogs

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The two radioiodinated fatty acid analogs 15-(para-^{131}I-phenyl-pentadecanoic acid (pPPA) and 15-(ortho-^{131}I-phenyl)-pentadecanoic acid (oPPA) are isomers with individually different routes in lipid metabolism but with near equal transport kinetics into tissue. **Methods:** Normal adult male Wistar rats (n = 79) and those with liver cell damage from adriamycin treatment (n = 84) received 1.48- 1.85 MBq ^{131}I-pPPA or ^{131}I-oPPA (specific activity, 33.3–46.3 GBq/μM) into the jugular vein. At 1, 2, 3, 5, 7, 10 and 20 min, livers of up to five animals per group were examined for total tracer uptake and tracer incorporation into various lipid fractions. **Results:** Uptake of both isomers into the total liver plateaued at about 2 min; the ratio oPPA/pPPA in normal liver averaged 2.63 and was significantly higher than the average ratio of 1.50 after adriamycin treatment. This fall in ratio was mainly due to an increase of pPPA uptake. Significant differences of the respective ratios were found in the plateau for the phospholipids (9.7 versus 3.0), cholesterol (2.4 versus 0.7) and triglycerides (2.0 versus 0.4). **Conclusion:** The dual-tracer technique with pPPA and oPPA promises to be clinically useful for the diagnosis of liver disease by imaging the ratios of tracer uptake in the total liver and by in vitro analysis of the uptake ratio in serum triglycerides.

Key Words: lipid metabolism; hepatic metabolism; labeled fatty acids

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The liver plays a central role for the body in substrate synthesis, storage, catabolism and detoxification. Thus, functional imaging of liver metabolism warrants particular interest. Various fatty acids containing a gamma emitting radionuclide have been proposed and tested (*1-3*); yet the measurements were beset by the difficulty in distinguishing between fates of the radionuclide and undegraded substrate in local perfusion, diffusion, transport and metabolism in the liver.

The fatty acid analog 15-(para-^{123}I-phenyl)-pentadecanoic acid (pPPA) was developed for myocardial imaging (*4,5*). With the synthesis of pPPA the isomer 15-(ortho-^{123}I-phenyl)-pentadecanoic acid (oPPA) is produced. In rat hearts, both pPPA and oPPA rapidly entered the free fatty-acid pool, after activation with coenzyme-A, but oPPA was only little incorporated into complex lipids and hardly at all entered into beta-oxidation; it quickly reentered into the circulation (*6–9*). On the other hand, pPPA behaved similarly to palmitic acid in its rate of entering beta-oxidation and its esterification into complex lipids (*6,9,10*); catabolites were rapidly excreted. Also in the normal and diseased human myocardium there were marked differences between the kinetics of pPPA and oPPA (*11–13*). These differences in metabolism led to a dualtracer approach in vivo that uncovered significant disturbances of myocardial lipid metabolism in at least two thirds of patients with dilated cardiomyopathy (*14*).

Use of the quotient of oPPA and pPPA, rather than their individual values from measurements of incorporation and turnover of each tracer alone, eliminates the contribution of tracer signals from the local organ-tissue perfusion and from tracer diffusion and transport from the circulating blood into the cells (*15*). The present study with dual-tracer analysis of oPPA and pPPA, both labeled with ^{131}I, assesses lipid metabolism in the liver of normal rats and of rats with liver cell damage from lipid peroxydation induced by doxorubicin (adriamycin) (*16,17*).

MATERIALS AND METHODS

The synthesis, radioactive labeling of both fatty acids with ^{131}I, their quality control and radiopharmaceutical preparation for intravenous injection were done according to the method of Machulla et al. (*5*). The specific activities of both pPPA and oPPA ranged between 33.3 to 46.3 GBq per μmole. The radiochemical purity of both tracers was assayed by high pressure liqid chromatography and always exceeded 98%.

The investigations were performed on 163 2-mo-old male Wistar rats weighing from 200 to 300 g. At the time of experiment, all animals had fasted for 24 hr and had been on fresh water only.

Before injection of the radiolabeled fatty acids, the control group (79 animals) had no preliminary treatment; the animals in the adriamycin (ADM) group (84 animals) were injected intraperitoneally with a cumulative dose of 15 mg ADM per kilogram body weight on four consecutive days (3 × 4 mg and 1 × 3 mg). This dose is known to induce liver damage mainly due to lipid peroxidation (*17–20*). Twenty-four hours after the last ADM injection, all animals were weighed and anesthetized by subcutaneous injection of nembutal (pentobarbital), 50 mg/kg body weight. Then the jugular vein was prepared and a dose of 1.48–1.85 MBq (40 to 50 μCi) of pPPA or oPPA was injected into the vein. The total radioactivity injected per animal was recorded and used later for data analysis. At 1, 2, 3, 5, 7, 10 and 20 min after injection, two to five animals of each of the four experimental groups were killed per time interval. The resected livers were immediately weighed, frozen in liquid nitrogen and stored until biochemical workup. Each animal was coded with a random number to avoid bias in the subsequent biochemical analyses.

The frozen livers (average weight 2–2.5 g) were biochemically analyzed according to the method of Folch et al. (*21*) yielding total lipids and lipid fractions (phospholipids, cholesterol, benzoic acid, free fatty acid and triglycerides).

The amounts of ^{131}I in the total liver, total lipid extract and chromatographically separated lipid fractions were measured with a gamma counter-probe-changer and the chromatograms were scanned for compounds with a linear analyzer. After all data were collected, the measurements on total body weight, liver weight and

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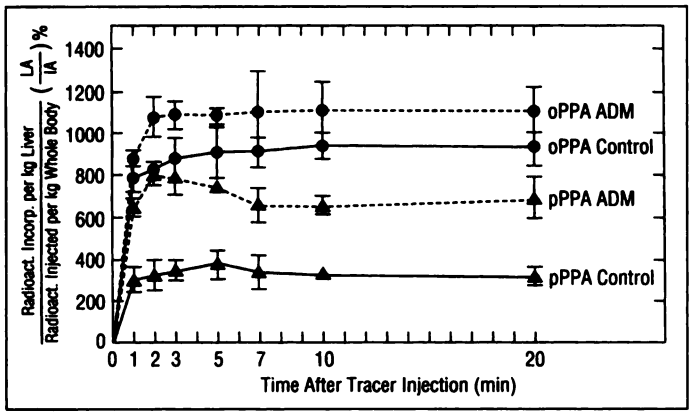

FIGURE 1. Radioactivity incorporated into whole liver, 1–20 min after intravenour injection of pPPA or oPPA in normal animals (control) and after treatment with adriamycin (ADM); the bars give ± s.d.

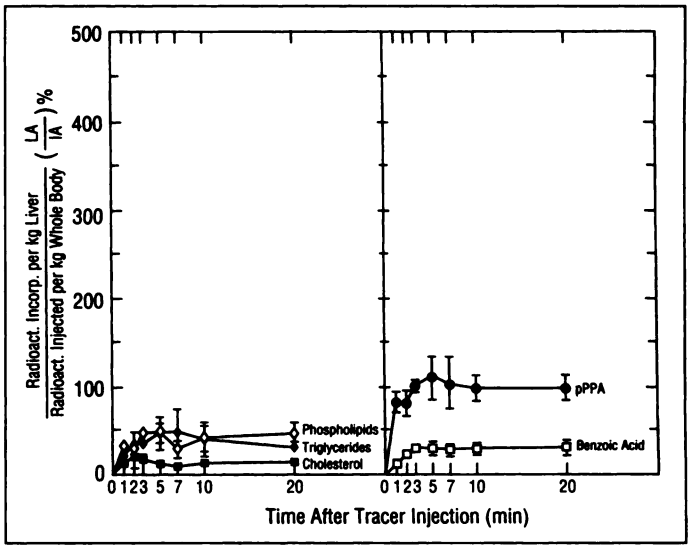

FIGURE 2. Radioactivity incorporated into isolated lipid fractions of the liver, 1–20 min after intravenous injection of pPPA in normal animals; the bars give ± s.d.

radioactivities of total liver of each animal were taken to calculate the total radioactivity incorporated per kilogram liver in the percent injected activity in the animal per kilogram body weight (abbreviated as LA/IA).

The measured radioactivities of the separated lipid fractions were quantitatively related to the radioactivity of the total lipid extract as a fraction of total liver radioactivity and expressed again for each animal in terms of quotients LA/IA as described elsewhere (*3,9*). This procedure facilitates the comparison of the results from animals with different body and liver weights.

All results are given as mean values ± s.d. per experimental point in each of the four groups of animals. For the two control and two experimental groups at each time interval s.d. were compared using the F-test, and the significance of differences between means for each time interval and for the plateau phases of the respective time activity curves was ascertained by the parametric Student's t-test. Confidence intervals (95%) were obtained for the tracer ratios in the control and experimental groups, by using the range of one s.d. for each quantity in the ratios.

RESULTS

Time Course of pPPA and oPPA in Whole Normal Liver and after Adriamycin Treatment

After a steep rise over the first 2 min after tracer injection, the mean values of radioactivity plateaued in all four groups, until the end of measurement (Fig. 1). oPPA was incorporated into the whole normal liver more efficiently than pPPA by a mean factor of 2.63 (range 2.40–2.92).

ADM treatment caused a significant increase of pPPA by a mean factor of 2.21 (range 1.92–2.45) and to a lesser extent of oPPA by a mean factor of 1.22 (range 1.11–1.30). Accordingly, the mean ratio of uptake of oPPA to pPPA in the plateau region after ADM treatment fell to 1.50 (range 1.33–1.69), by a factor of 0.57 of the value in normal liver. The mean numerical values and numbers of animals per experimental point are listed in Table 1.

Time Course of Distribution of pPPA and oPPA in Lipids of Normal Liver and after Adriamycin Treatment

The time courses of radioactivity incorporated into the various lipid fractions of the four groups of animals are illustrated in Figures 2, 3, 4 and 5. All radioactivities initially increased steeply after tracer injections and reached a plateau beginning not later than about 10 min. Contrary to the radioactivity of free pPPA, that of free oPPA rapidly decreased from its maximum at 1 min and reached the plateau at about 10 min. For quantitation of tracer incorporation into the separated lipid fractions, the measurements in the plateau regions were selected.

Metabolism of pPPA in the Control Group

As shown in Figure 2, the highest amount of radioactivity in the plateau regions of the time-activity curves was recovered with free pPPA that rose to a mean value of LA/IA of 96%; it reached 43% for phospholipids, 36% for triglycerides and 12% for cholesterol. The catabolite benzoic acid increased to a mean value in plateau of 24%.

Metabolism of oPPA in the Control Group

Different from the pPPA control group most of the radioactivity of injected oPPA was recovered in the plateau region of phospholipids with a mean value of LA/IA of 418%, as seen in Figure 3. The triglyceride fraction rose correspondingly to 74%

TABLE 1
Numerical data for Figure 1 (Mean Values)

	Time (min)													
	1		2		3		5		7		10		20	
Group		no.		no.		no.		no.		no.		no.		no.
oPPA Control	786	3	820	3	882	3	907	3	903	3	941	2	917	3
pPPA Control	306	4	328	4	354	4	379	3	342	3	323	4	314	4
oPPA ADM	869	5	1070	5	1078	5	1080	5	1097	5	1100	5	1103	5
pPPA ADM	645	3	805	4	779	4	738	3	657	4	649	4	693	5

no. = number of investigated animals; ADM = adriamycin.

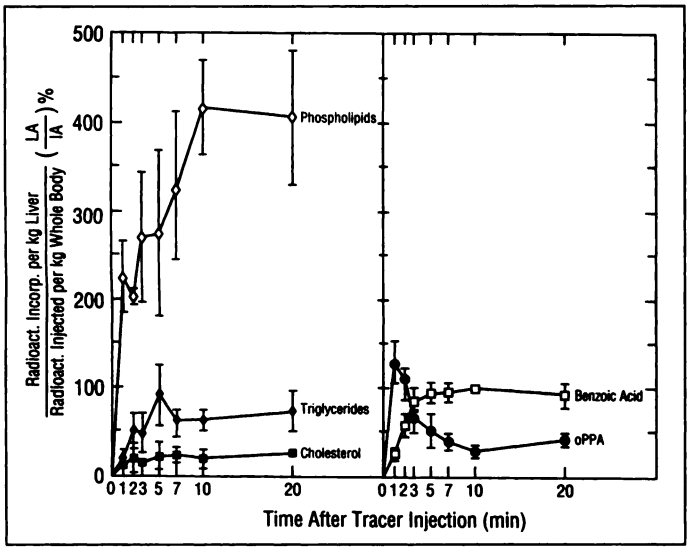

FIGURE 3. As in Figure 2 but after intravenous injection of oPPA in normal animals.

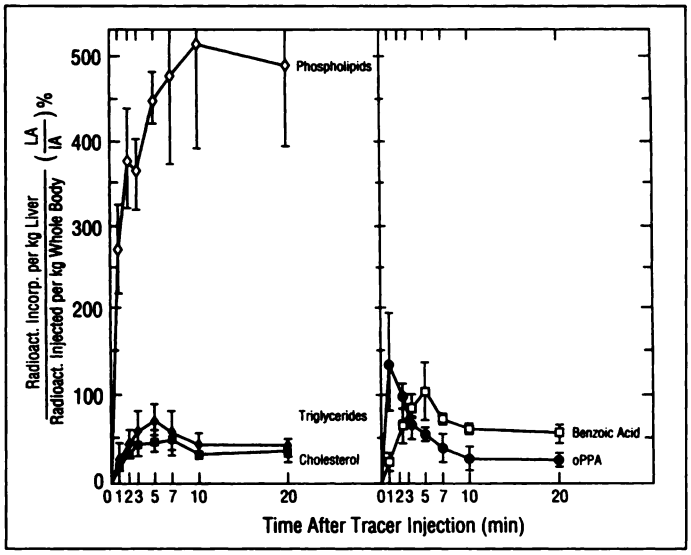

FIGURE 5. As in Figure 2 but after intravenous injection of oPPA after adriamycin treatment.

and the cholesterol to 29%. Again contrary to the findings with pPPA, the benzoic acid increased to a mean value of plateau of 98% and free oPPA rapidly fell to 41%.

Metabolism of pPPA after Treatment with Adriamycin

Figure 4 indicates that ADM treatment caused the radioactivity from pPPA to increase predominantly in the phospholipid fraction to a mean LA/IA value of 171%, about four times the corresponding value in the normal liver. The triglyceride fraction reached a mean of 99%, about 2.8 times control. The radioactivity in cholesterol rose to a mean of 44%, about 3.7 times control. No significant changes from control were seen for free pPPA and benzoic acid.

Metabolism of oPPA after Treatment with Adriamycin

ADM treatment induced the radioactivity in the phospholipids to rise by a mean factor of 1.2 above the value in normal liver to the mean LA/IA value of 505%, as shown in Figure 5. The triglyceride fraction reached a mean of 41%, by a factor of 0.55 of control. The cholesterol attained a corresponding value of 33% not significantly different from the control. Free oPPA fell to a mean of 26%, by a factor of about 0.6 of control, and the benzoic acid had correspondingly 59%, a factor of about 0.6 of control.

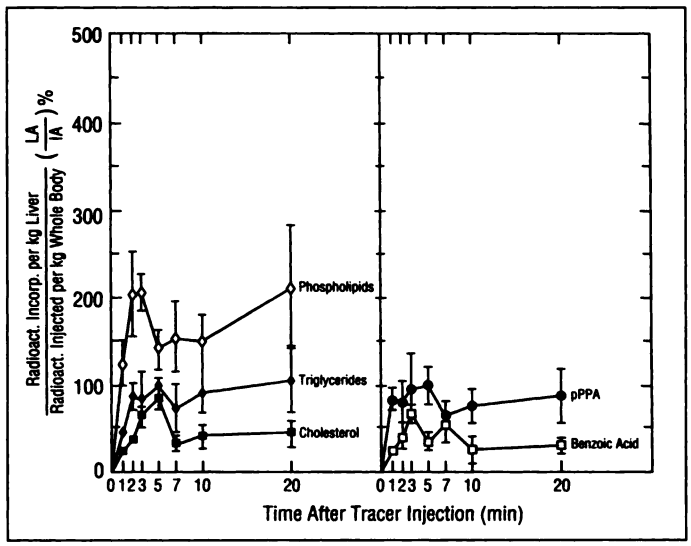

FIGURE 4. As in Figure 2 but after intravenous injection of pPPA after adriamycin treatment.

Changes of Ratios oPPA to pPPA in Lipids after Treatment with Adriamycin

Table 2 summarizes the changes in the ratios of incorporation of radioactivity from oPPA and pPPA into the various lipid fractions in the plateau region of the time-activity curves after ADM treatment. The mean ratios oPPA to pPPA generally fell from the value in normal liver after adriamycin treatment: for phospholipids significantly from 9.7 to 3.0, for triglycerides significantly from 2.0 to 0.4; for cholesterol significantly from 2.4 to 0.7. No significant change was observed regarding benzoic acid and the free fatty acids. On average the ratio oPPA to pPPA in the entire lipid fraction became reduced by ADM treatment by a factor of 0.35 of control.

DISCUSSION

Tracer Incorporation into the Total Liver

The two isomers had similar kinetics of uptake both in the normal liver and after adriamycin treatment. Within about 2 min the amount of radioactivity in the total liver in each group of animals attained a level that remained practically unaltered as a plateau over the time of observation of 20 min. The mean ratio of uptakes of oPPA and pPPA in the total normal liver in the plateau region was 2.63 in the controls but changed significantly to 1.50 after adriamycin treatment.

This is partly different from the values obtained in mice by Shreeve et al. (*3*). They also reported an initial higher rate of incorporation for oPPA than for pPPA at 5 min after tracer injections in normal animals, but the time courses in the normal animals varied, in that there was subsequently a continuous loss of oPPA tracer up to 30 min of observation, whereas after pPPA injection an initial loss was followed by a plateau of tracer beginning at about 20 min. After chronic ethanol feeding, the rate of loss of oPPA in these livers decreased significantly. The reason for the discrepancy between the kinetic data in mouse and rat may be species specific.

Also, differences in experimental procedures may be invoked. Shreeve et al. (*3*) used mouse serum as carrier for the two labeled fatty acid analogs, whereas in the present study human serum albumin (2.5%) was employed. Different carriers may generally cause alterations in the kinetics of fatty acid uptake in the tissue, as was demonstrated by Beckurts et al. (*6*)

TABLE 2
Quotients of Mean Values and Confidence Intervals of Radioactivity Incorporated into Isolated Lipids in Plateau Region of Time-Activity Curves after Intravenous Injection of oPPA versus pPPA in Control (contr.) Animals and after Adriamycin (ADM) Treatment

Quotients	Fractions				
	Phospholipids	Cholesterol	Benzoic acid	Fatty acid	Triglycerides
oPPA-contr.	9.7	2.4	4.0	0.4	2.0
pPPA-contr.	(5.9–18.2)	(1.4–4.2)	(2.9–5.6)	(0.3–0.6)	(1.2–3.9)
oPPA-ADM	3.0	0.7	1.9	0.3	0.4
pPPA-ADM	(1.9–4.6)	(0.5–1.3)	(1.1–5.5)	(0.2–0.6)	(0.2–0.8)

and Grossmann et al. (*8*). Yet, the turnover of tracer bound to tissue is not likely affected by the initial carrier substrate.

Tracer Incorporation into Various Lipid Fractions

In the normal liver, lipid metabolism is assumed to be at a metabolically steady-state situation and not to be disturbed by the two tracers. Therefore, the significant discrepancy in the recovery of radioactivities from oPPA and pPPA in the various lipid fractions (Figs. 2–5) indicates that in the normal liver specific enzymes prefer oPPA over pPPA for the synthesis of phospholipids, triglycerides and cholesterol, and also for beta-oxidation as indicated by the benzoic acid fraction. This discrepancy points to a metabolic bifurcation in an early step of lipid synthesis separating the pathways of the two labeled isomers. This step could well be an acyl-transferase reaction.

The pattern of distribution of oPPA and pPPA among the lipids appear to be species specific; thus, in mouse liver pPPA was preferentially incorporated into triglycerides overall other fractions, and the recoveries were lower when oPPA was injected (*3*). Also, in human liver, uptake of pPPA surpasses that of oPPA (*22*).

Additionally, organ-specific patterns of incorporation exist. Thus, pPPA was found in the rat myocardium to be readily esterified into complex lipids and accepted into the beta-oxidation pathway; in contrast, oPPA hardly entered complex lipids and beta-oxidation (*6–9*). Also, in the human myocardium, oPPA was rejected from beta-oxidation (*9,11,13*). Yet, oPPA was rapidly lost from the rat myocardium by retrograde transport/diffusion into the peripheral circulation (*6–9*), whereas in the human myocardium oPPA was retained in the cytosol (*9,11,13*). The reasons for these variations in the metabolism of oPPA and pPPA in different species and organs of a given species are not known.

Effect of Adriamycin Treatment on Tracer Incorporation into Lipid Fractions

The increased uptake of pPPA into the liver over that of oPPA after adriamycin treatment (Fig. 1) is due to the preferentially increased incorporation of pPPA over oPPA into the phospholipids, triglycerides and cholesterol. No significant changes in radioactivity from pPPA were seen for the benzoic acid and free fatty acid fractions after adriamycin treatment. This finding implies an adriamycin- induced stimulation of lipid synthesis with no recognizable alteration in the rate of fatty acid degradation by beta-oxidation. This is in agreement with an adriamycin induced damage of mitochondria (*23*).

An increased net-rate of transport/diffusion of free fatty acid into the hepatocytes after adriamycin treatment is a possible factor in the adriamycin-induced incorporation of pPPA into the various lipid fractions. There could also be a reduction of retrograde transport of pPPA from the free fatty acid pool into the blood circulation.

Contrary to the kinetics of pPPA after adriamycin treatment, oPPA incorporation into the phospholipids and cholesterol was only slightly increased, and it was reduced into the triglycerides and benzoic acid to about one half of that found in the normal liver. Obviously, stimulated lipid synthesis after adriamycin treatment was not readily apparent with oPPA being the tracer.

CONCLUSION

The findings reported in this article justify investigations of the ratio of uptakes of oPPA and pPPA into the total human liver by functional imaging. The pPPA and oPPA may be labeled with the same radioisotope of iodine for administering the two sequentially with a time interval perhaps of 30 min. With the help of a subsequent image substraction technique, data on uptakes of both substrates into the total liver or defined liver regions of interest are generated, as previously described (*14*). This procedure has the advantage of avoiding the need for corrections of attenuation of the emitted gamma radiation in the examined body, which would pose a considerable problem in case the two isomers were labeled with two different radioisotopes of iodine, such as ^{123}I and ^{131}I, with the different energies of their emitted gamma radiations.

Of the lipids circulating in the peripheral blood triglycerides originate in the liver. The ratio of incorporation of radioactivity from oPPA and pPPA into the triglycerides of the rat liver changed significantly by an average factor of 5 from 2.0 in normal animals to only 0.4 after adriamycin treatment. Thus, after intravenous injection of trace amounts of oPPA and pPPA that are labeled with two different radioisotopes, for example with ^{123}I and ^{131}I, the ratio of activities in the isolated serum triglycerides may mirror the state of lipid metabolism in the liver and be diagnostically relevant.

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FIRST IMPRESSIONS

Breast Prosthesis

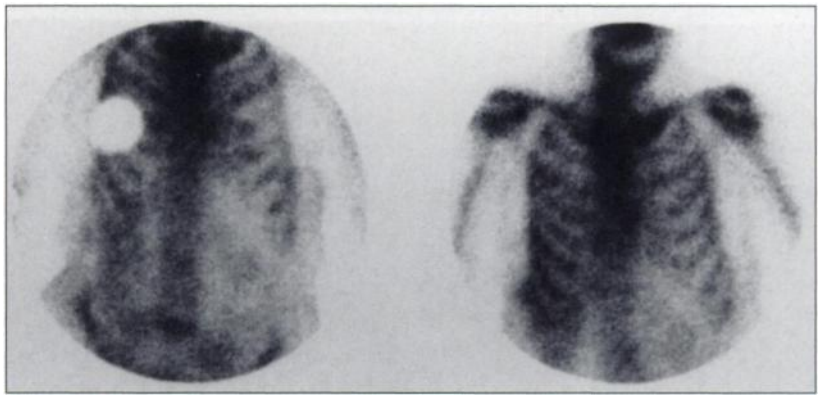

Figure 1.

PURPOSE

A patient with a history of breast carcinoma was referred for a bone scan for evaluation of bone metastases. A cold spot, mimicking the appearance of a photomultiplier tube defect, was observed in the right anterior chest of a patient with a breast prosthesis. An image (Fig. 1) obtained after the breast prothesis was removed revealed no abnormalities.

TRACER

Technetium-99m-MDP (20 mCi)

ROUTE OF ADMINISTRATION

Intravenous injection

TIME AFTER INJECTION

Three hours

INSTRUMENTATION

Large field of view gamma camera (General Electric)

CONTRIBUTORS

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