JOURNAL OF NUCLEAR MEDICINE 5:417-427, 1964

# Parathyroid Scanning With Selenium[75] Labelled Methionine[1,2]

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In 1962 we evaluated the use of $Co^{57}$ $B_{12}$ concentration in the parathyroid gland of dogs as a possible method of visualizing the parathyroid gland *in vivo* with the photoscanner (1). An extension of this work to the human (2) demonstrated that although the $Co^{57}$ $B_{12}$ also concentrated in the human parathyroid gland similar to that found in the dog, the specific activity of the $Co^{57}$ $B_{12}$ preparation today is too low to make this a practical method at present for visualizing the human hyperfunctioning parathyroid adenoma.

When Potchen (3) demonstrated that tritiated methionine was concentrated in the rat parathyroid as demonstrated by autoradiography, we administered $Se^{75}$ methionine to two patients and demonstrated that at operation the parathyroid glands showed sufficient relative and absolute tissue concentration to make it theoretically possible to scan a hyperfunctioning parathyroid adenoma (4).

This communication presents our work to date on $Se^{75}$ methionine studies in humans and dogs in a continued effort to visualize the hyperfunctioning parathyroid adenoma preoperatively in the human.

### Humans

We have scanned three patients with hyperparathyroidism, two cases being associated with confirmed hyperfunctioning parathyroid adenomas. All patients have been hospitalized in a metabolic ward, placed on a low calcium, high protein diet and given 300 $\mu g$ of triiodothyronine a day for a minimum of five days before being given an intravenous injection of a calculated 250 $\mu c$ of $Se^{75}$ methionine.[3] In a 44 year old woman, L.C., the parathyroid adenoma was located in photoscans taken at 5 minutes, 1¾ hours, and 8 hours following injection (Fig. 1a)

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[2]Supported by the Nuclear Medicine Research Fund.

[3]Sethotope, Squibb Medatopes, New Brunswick, N.J.

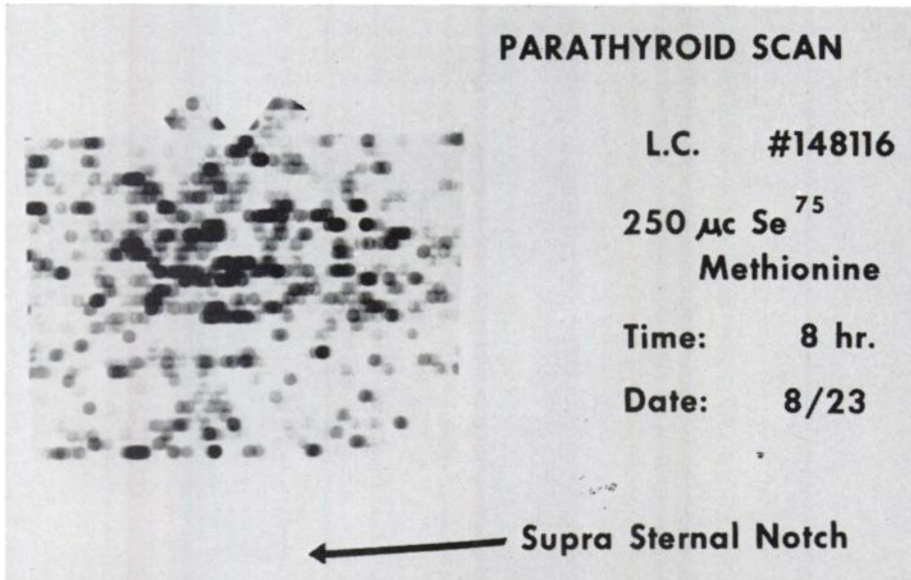



**Fig. 1a. Photograph of a photoscan taken at 8 hours after injection of 250 μc of $Se^{75}$ labelled methionine in L.C. An area of concentration of radioactivity is seen slightly to the right of the midline and just below the top of the thyroid cartilage. This diagnosis of the location was recorded on the chart preoperatively.**

as an area of increased concentration of radioactivity slightly to the right of the midline and just below the top of the thyroid cartilage. This diagnosis of location was recorded on the chart preoperatively. At surgery, 72 hours after injection, a 3 x 1 cm adenoma, weighing 3.3 grams was found deep behind the upper part of the right lobe of the thyroid gland as shown in Figure 1b. Figure 1c shows


**Fig. 1b. Photograph of parathyroid adenoma in L.C. *in situ* with right lobe of thyroid retracted to left. The tumor is located in the area of radioactivity localized in the preoperative photoscan (see 1a).**

**Fig. 1c. Location of the parathyroid adenoma in L.C. shown diagrammatically after surgery.**

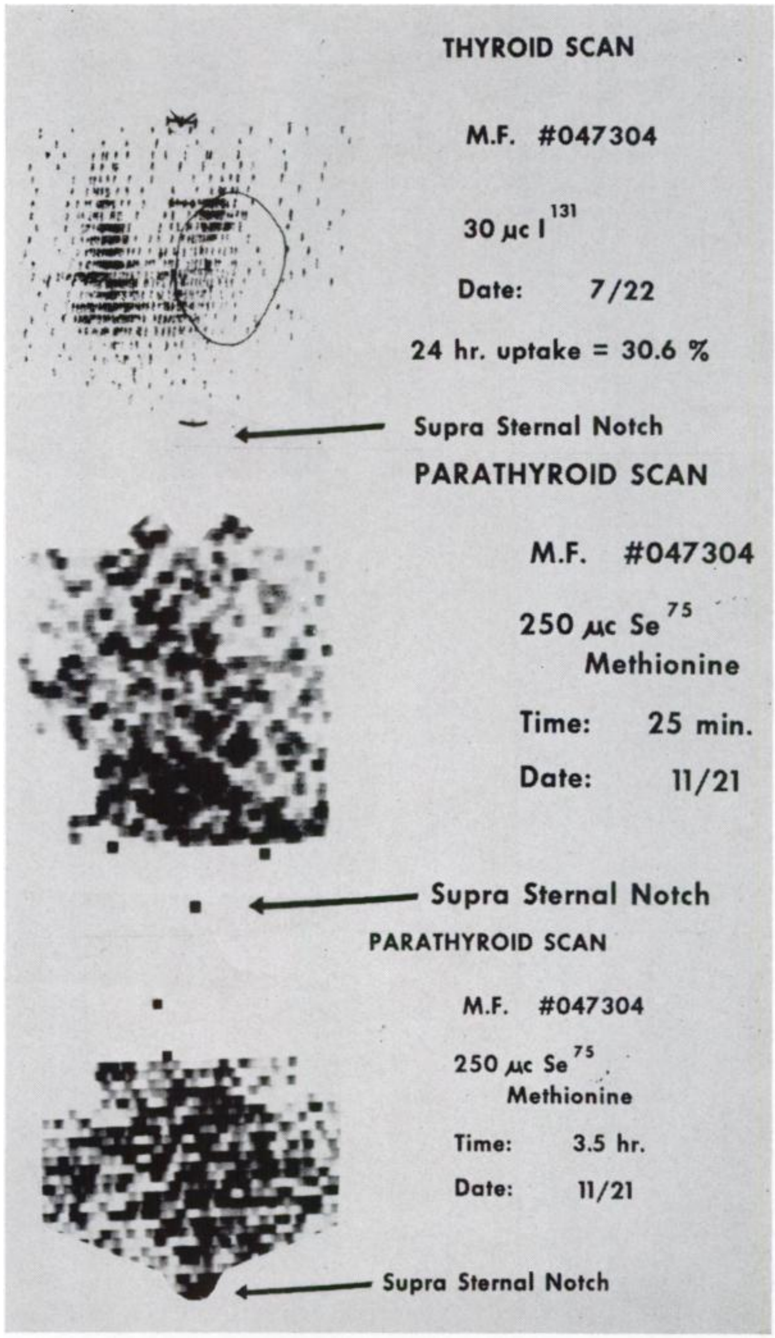



**Fig. 2a.** Thyroid adenoma in M.F. shown preoperatively in left lobe in $I^{131}$ thyroid scan.

**2b.** Suggestion of localized concentration of $Se^{75}$ radioactivity in M.F. in 25 minute scan at lower end of right lobe.

**2c.** Photograph of photoscan in M.F. at 3.5 hours shows no definite residual of this localized concentration of radioactivity.

diagrammatically the location of the excised parathyroid adenoma. The parathyroid gland could not be located on the scans at 24, 36, 48 hours.

A second patient, J.M., a 34 year old male, with clinically evident primary hyperparathyroidism had scans performed upon him at 15 minutes, 4 and 11 hours after injection. None of these scans showed convincing evidence of localized uptake of $Se^{75}$. A parathyroid adenoma weighing 1.1 gram was found and removed and tissues were sampled for radioactivity at surgery 24 hours after injection.

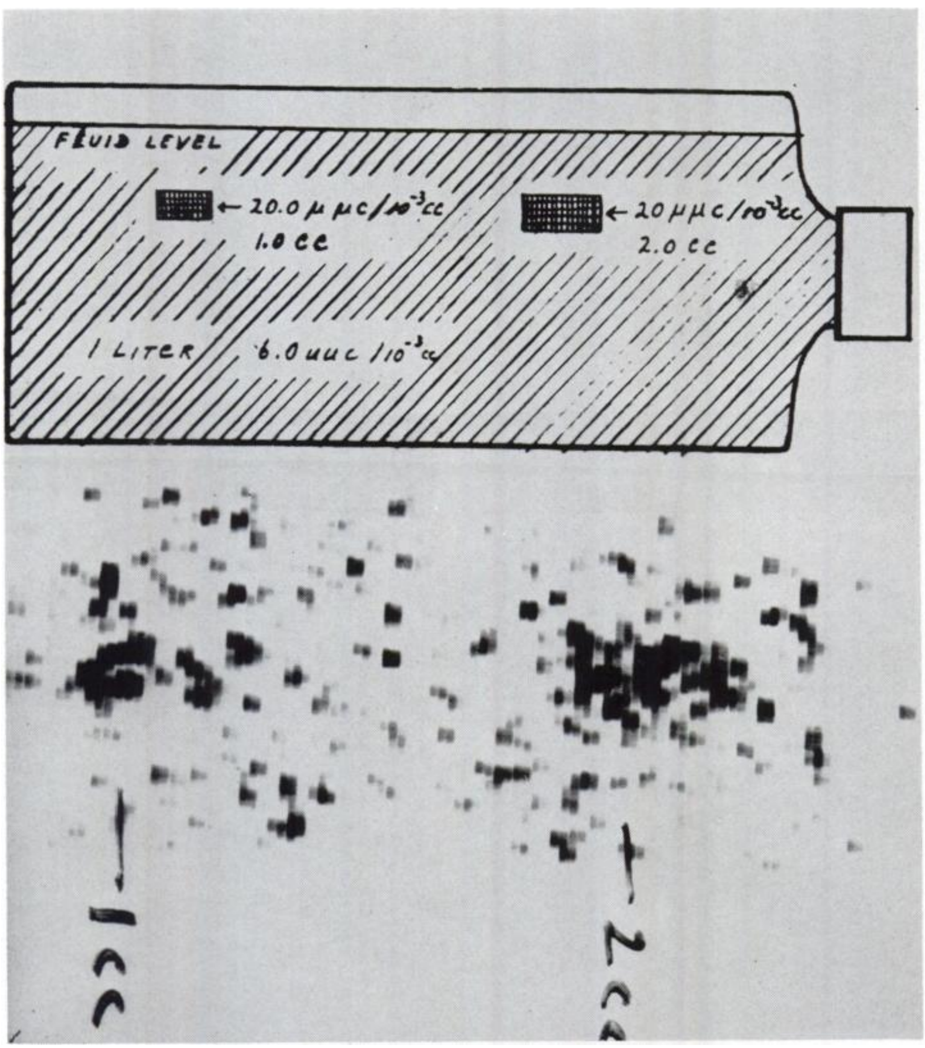



**Fig. 3a. Photograph of a phantom with two mock tumors in a background $Se^{75}$ radioactivity concentration of one-third the "tumor" concentration, simulating the relative radioactivity concentration found in tissue counting studies in patients L.C. and J.M.**

**3b. Scan of mock tumors shows in figure 3a. The mock tumors are easily detected with the photoscanner under the simulated conditions found in the human.**

TABLE I

RELATIVE TISSUE CONCENTRATION OF RADIOISOTOPE LABELLED COMPOUNDS ($\mu\mu c/mg$)

| | *L. C. (72 hours)* | *J. M. (24 hours)* |
|---|---|---|
| PARATHYROID | 18.4 | 11.6 |
| THYROID | 7.8 | 6.5 |
| MUSCLE | 12.9 | 3.1 |
| BLOOD | 5.7 | 5.0 |

A third patient, M.F., a 74 year old woman with clinically evident hyperparathyroidism and a thyroid adenoma in the lower part of the left lobe of the thyroid gland (Figure 2a) had parathyroid scans performed immediately after the $Se^{75}$ methionine injection, and at 25 minutes, 2 and 3½ hours after injection. The scans at 25 minutes and 2 hours showed a suggestion of localized uptake of $Se^{75}$

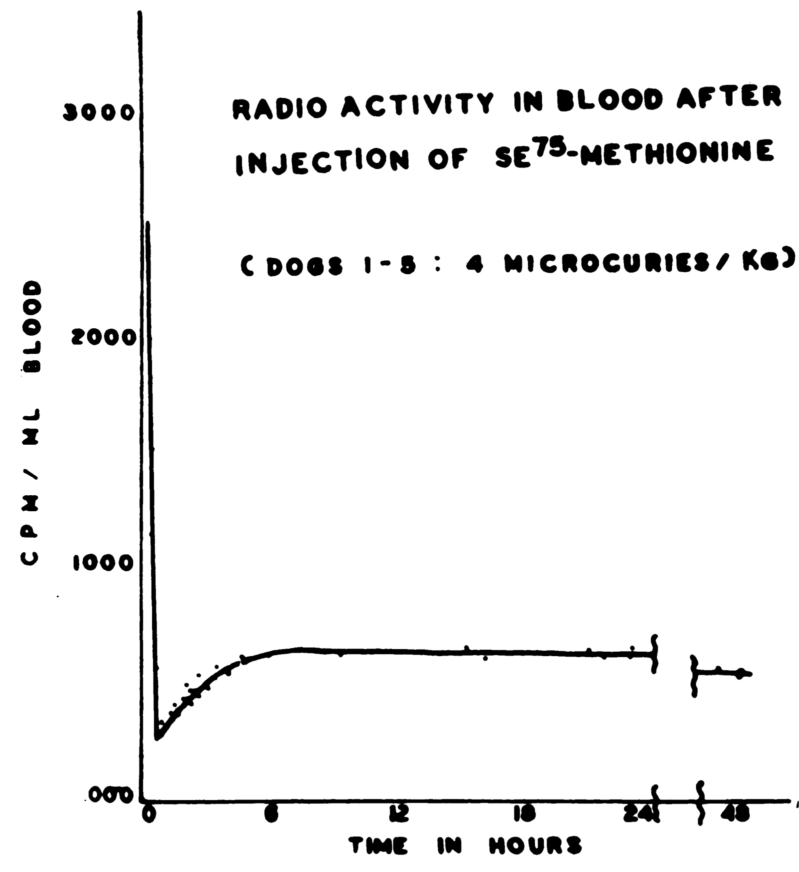



**Fig. 4a. Curves of radioactivity concentrations in the dog after intravenous injection of $Se^{75}$ labelled methionine. The blood curve is lowest at 30 minutes and rises to a plateau at 6 hours.**

at the lower end of the right lobe of the thryoid gland as shown in Figure 2b, but not in the later scan at 3½ hours as shown in Figure 2c.

Two of 4 parathyroid glands removed at operation 21 days after injection were described as showing nodular hyperplasia. These two glands were located; (a) behind the thyroid adenoma, 3 x 5 mm in diameter, as shown at operation in Figure 3d, and was mostly fat, and (b) from the "superior mediastinum," 3 x 5 x 7 mm in diameter. A third bit of parathyroid tissue, located where suggestive uptake of $Se^{75}$ was seen in the region of the lower end of the right lobe of the thyroid gland, was only 4 mm in size.

Table I is a presentation of the tissue counting data on the first two patients. It is evident that the concentration of $Se^{75}$ in parathyroid adenoma was as great as 3 times the concentration in muscle and blood and about 2 times the concentration in the thyroid gland.

A study of an experimental phantom demonstrated that this relative concentration was sufficient to detect a parathyroid adenoma. The phantom, as shown in Figure 3a, consisted of two mock tumors in a background $Se^{75}$ concentration of one-third the "tumor" concentration. The scan shown in Figure 3b easily detected these mock tumors. The relative concentration ratios of 2 or 3 to 1 found 24 and 72 hours after injection may well have been lower than the ratios which actually existed during the first hours after injection.

The blood curves of $Se^{75}$ concentration after injection in our dogs suggest that the optimal target to non-target ratio of $Se^{75}$ concentration would be found

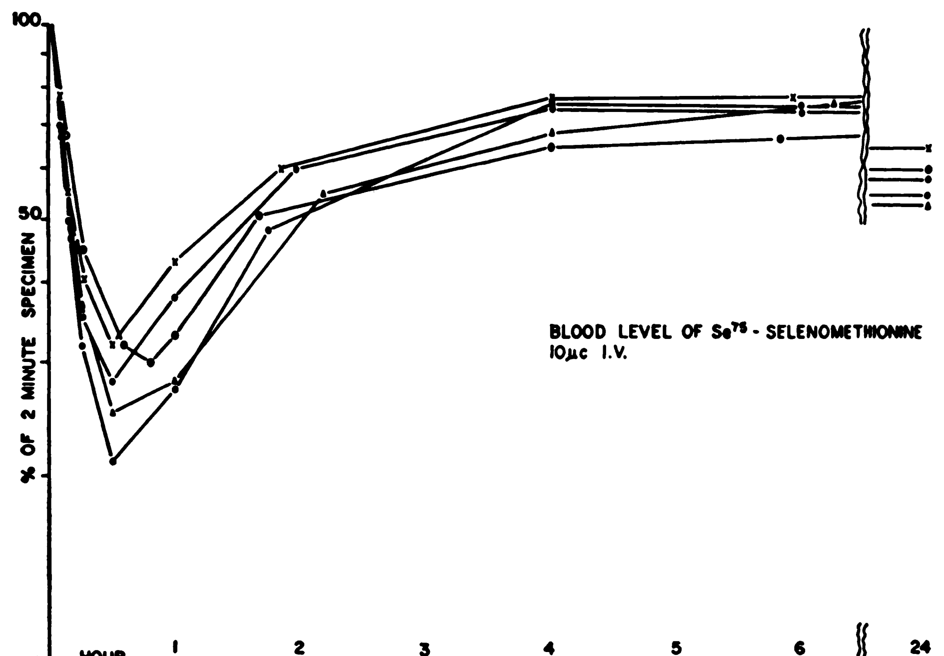



**Fig. 4b.** Almost identical curves as in (a), found in *humans* by Olendorf (J. Nucl. Med. *4*:231, 1963).

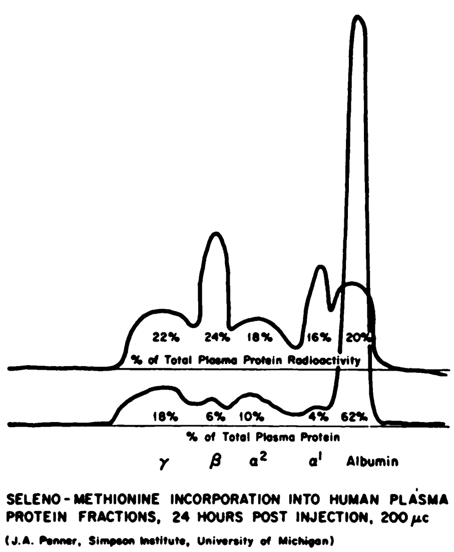
at two hours after injection as shown in Figure 4a. A similar blood curve was found in humans by Oldendorf (5), as shown in Figure 4b.

Furthermore our dog studies demonstrated that the concentration of $Se^{75}$ in normal parathyroid tissue was higher at 2 hours than at 24 and 48 hours after injection. Therefore, it is possible that this time of high concentration of $Se^{75}$ in parathyroid gland, when the blood concentration of $Se^{75}$ is the lowest, might also be found in the human.

Preliminary studies of urinary and fecal excretion of $Se^{75}$ during the first two weeks of injection of $Se^{75}$ methionine in two of these patients indicated that the 250 μc of $Se^{75}$ methionine used in these patients had a biologic half-life of 23 and 36 days. It is apparent that these estimates may need revision after completion of long-term studies which are being conducted. Based on the 23 day biologic half-life, (19.5 day effective half-life) 250 μc $Se^{75}$ methionine delivers a whole body dose of radiation of about 615 millirads[1], as shown by the following calculations.

The injected $Se^{75}$ methionine, after diminishing in concentration in the blood, reappears fairly uniformly distributed in the serum proteins as shown in the

[1]Hine, G. J. and Brownell, G. L.-Editors: Radiation Dosimetry, Academic Press Inc., N.Y., 1956, p. 862.



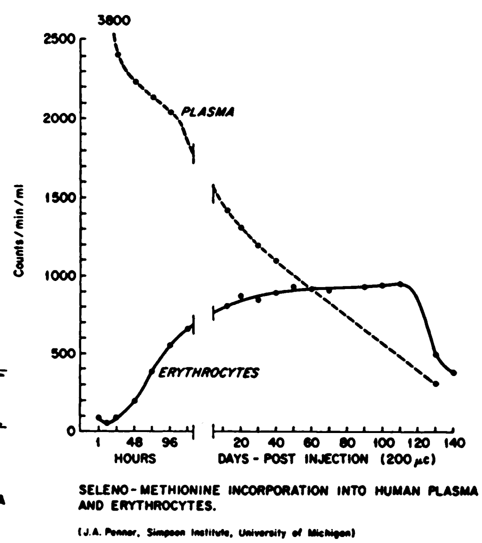




**Fig. 5.** $Se^{75}$ methionine distribution in human plasma protein fractions, 24 hours after injection of 200 μc of $Se^{75}$ methionine. The radioactivity is widely distributed throughout all plasma protein fractions. (Penner, J. A.: Selenomethionine incorporation into plasma proteins, Clin. Res. *12:*April, 1964).

**Fig. 6.** Appearance of $Se^{75}$ methionine in red blood cells and disappearance from red blood cells and plasma to 140 days after intravenous injection of 200 μc of $Se^{75}$ labelled methionine. The disappearance is fastest from the plasma. (Penner, J. A.: Clin. Res. *12:*April, 1964).

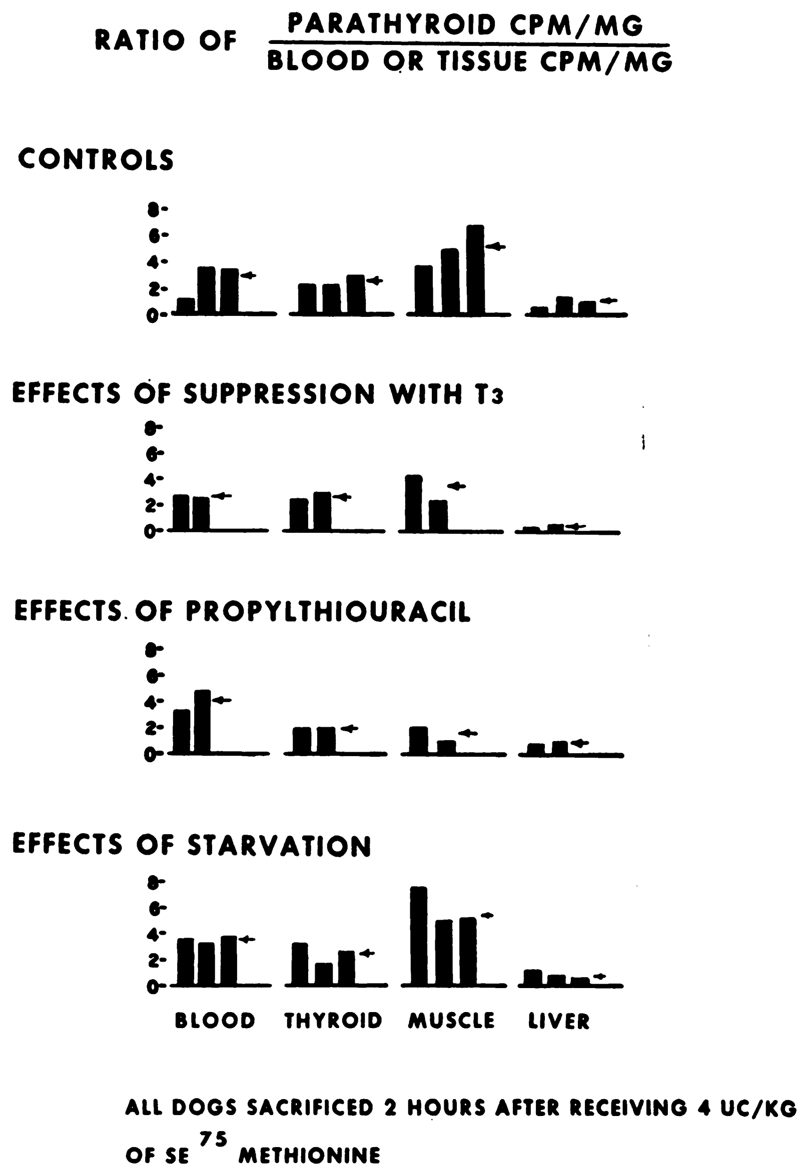



Fig. 7. Summary of dog experiments designed to evaluate the effect of thyroid suppression with triiodothyronine ($T^3$), propylthiouracil stimulation of the thyroid gland, and starvation, on the relative parathyroid concentration of $Se^{75}$ methionine as compared to the concentration of $Se^{75}$ in blood, thyroid, muscle and liver 2 hours after intravenous injection of $Se^{75}$ methionine. No effect is seen on uptake of these tissues relative to the parathyroid.

$T_p = 127$ *days* $\qquad \bar{E} = 0.011$ *Mev*

$T_b = 23$ *days* $\qquad T^{1\beta} = 1.84$ *r per mc hr at 1 cm*

$T\ eff = 19.5$ *days* $\qquad \bar{g} = 126$

$$D_{\gamma} + _{\beta} = CT\ eff\ (73.8\ \bar{E}_{\beta} + 3.46 \times 10^{-2}\ \bar{g}\ T^{1})$$

$$D_{\beta} + _{\gamma} = \left(\frac{250}{7 \times 104}\right) (19.5)\ [(73.8)\ (0.11) + (3.46 \times 10^{-2})\ (126)\ (1.84)]$$

$$= 69.6 \times 10^{-3}\ [8.83]\ rads$$

$$= 0.615\ rad/250\ \mu c\ Se^{75}\ Methionine$$

radio electrophoresis performed by Dr. John Penner (6) of the serum of a patient one day after injection, in Figure 5.

The $Se^{75}$ methionine is apparently incorporated both in the protein of the plasma and in the red blood cells but disappears more rapidly with time from the plasma as shown in Figure 6 from a patient followed by Dr. Penner for 140 days (7).

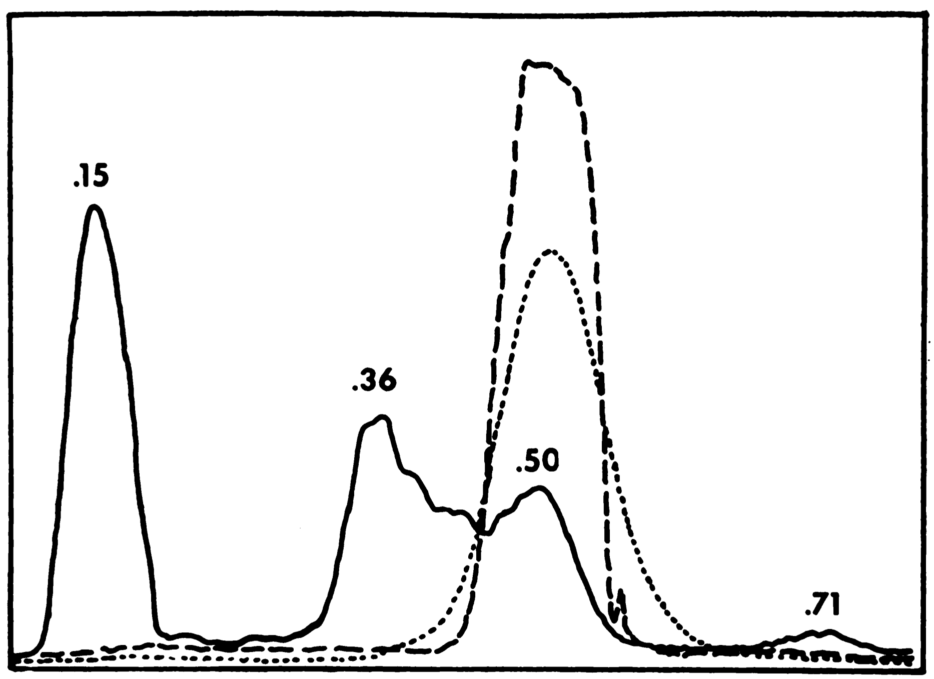



**Fig. 8. One dimensional ascending paper chromatographic analysis of $Se^{75}$ methionine in butanol acetic acid and water solvent. Ninhydrin staining reveals three collections of amino-acids other than methionine although all of the $Se^{75}$ radioactivity migrates at the same Rf as pure methionine (.50).**

*Dogs*

Since our humans had been given triiodothyronine to suppress protein synthesis in the thyroid gland, a high protein diet to load the larger protein pools, and a low calcium diet to stimulate parathyroid gland protein synthesis activity, we have started experiments in dogs to evaluate the importance of each of these possible factors. To date, we have studied 3 normal control dogs, 3 starved dogs, 4 dogs in triiodothyronine suppression and 2 dogs on propylthiouracil stimulation of the thyroid gland. All dogs were prepared under these various experimental conditions for a time period of 4 - 9 days, then given 4 μc of $Se^{75}$ methionine/kg of body weight and sacrificed 2 hours later for assay of absolute and relative tissue concentrations of $Se^{75}$ in a well-type scintillation counter. Figure 7 summarizes the results of these studies. No effect of any of these experimental methods used to increase the target to non-target ratio were effective.

Lastly, our preliminary studies lead us to believe that two sources of variability in results at attempts to photoscan the parathyroid glands at present are:

1. Impurities of the $Se^{75}$ methionine which may lead to limitation of maximum rate of uptake of $Se^{75}$ methionine before sufficient radioactivity for detection has been accumulated by the parathyroid gland.
2. Uptake of $Se^{75}$ methionine by the bond marrow of the cervical spine and the sternum.

Figure 8 summarizes the paper chromatographic analysis of $Se^{75}$ methionine. Using a butanol, acetic acid and water (6:1.5:2.5) solvent system and ascending chromotography $Se^{75}$ methionine (solid line) chromotography showed nin-hydrin staining at four different Rfs. The radioactivity (dotted line) was localized at the peak having an Rf of .50, corresponding with the Rf peak of pure nonradioactive 1-methionine (dotted line). Other major peaks were at .70 and .36 and .15. Densitometric scanning indicated that these other peaks constituted more than 4 times the quantity of amino acid in the methionine area.

Close inspection of some scans on L.C. and J.M., as shown in Figures 9a and b, shown that the cervical concentration of radioactivity is usually in mid-

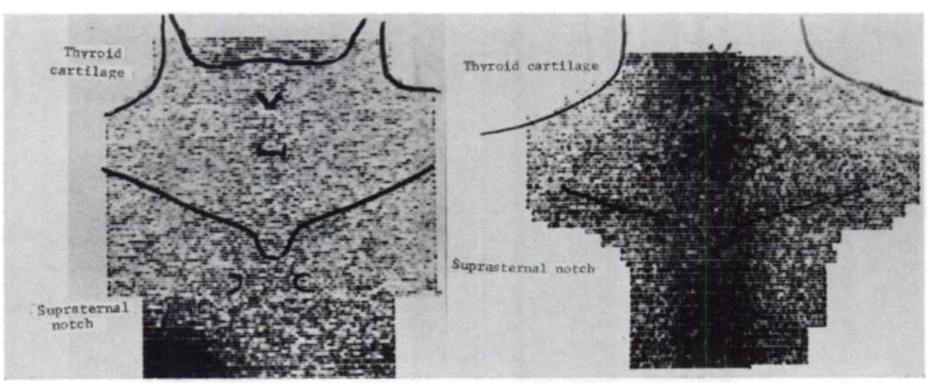



**Fig. 9. Selenomethionine scans on L.C. (a) and J.M. (b) showing apparent high concentration of radioactivity in bone marrow of cervical spine and sternum.**

line and may be somewhat spotty at different time intervals after injection. The concentration increases sharply at the suprasternal notch and matches the sternum in width. A suggestion of concentration is seen in the proximal end of the clavicles. This distribution of increased radioactivity concentration is compatible with localization in bone marrow. This impression of concentration of $Se^{75}$ labelled methonine in bone marrow was confirmed in patient J.B. by Dr. Penner (7) by bone marrow aspiration one hour after injection of 100 microcuries of selenomethionine. The bone marrow showed a count of 3,563 counts per minute per milliliter while peripheral blood obtained simultaneously showed 140 counts per minute per milliliter. The composition of the marrow was approximately 6 per cent white blood cells, 8 per cent fat, 40 per cent plasma and 36% red blood cells. The fat and white cell layer had the highest concentration of radioactivity. Thus, the marrow activity was found to be approximately 30 times that of the peripheral blood.

## SUMMARY AND CONCLUSIONS

$Se^{75}$ methionine relative concentration in parathyroid gland is theoretically sufficient at present to draw a picture of a parathyroid adenoma and may well have been done successfully. The present preparation is undependably impure at present, however, and the uptake in the marrow of the cervical spine and sternum make the technique difficult to interpret. It should be possible to obtain pure $Se^{75}$ labelled methionine in the future. $Se^{75}$ methionine parathyroid photoscanning may then become a practical procedure in detecting a fair sized parathyroid adenoma.

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