JOURNAL OF NUCLEAR MEDICINE 7:88-98, 1966

A Comparison of Iodine-125 and Iodine-131 as Tracers in the Diagnosis of Thyroid Disease. I. Physical Aspects[1,3]

M. Ben Porath[2], A. Hochman and J. Gross

Jerusalem, Israel

Myers and Vanderleeden (1) first pointed out that the physical properties of ^{125}I provided certain advantages over the commonly used ^{131}I as a diagnostic tracer both *in vivo* and *in vitro*. In this work we have tried to evaluate to what extent ^{125}I may replace ^{131}I in clinical tests of thyroid function such as: thyroid uptake, urinary iodine excretion, PBI conversion ratio and *in vivo* scanning of the thyroid or its metastases.

As a first step in this evaluation, studies were carried out *in vitro* to determine the extent of error due to absorption of ^{125}I radiation by the body fluids in which it was to be measured. Subsequently, the absorption effects in *in vivo* counting were examined after devising appropriate phantoms.

EXPERIMENTS ON THE ABSORPTION OF ^{125}I RADIATION BY URINE AND PLASMA

Bakhle *et al* (2) pointed out that the composition and density of substances containing ^{125}I may be important factors in the determination of the radioactivity, because of the low energy of the ^{125}I photons. The extent of these effects in urine and plasma samples was determined by a comparison with aqueous standards. The urine samples were counted in polyethylene containers, in which they were collected. To estimate the difference in absorption, 5 μC ^{125}I were diluted in water to one liter and an equal quantity in one liter of nonradioactive urine. The same test was performed with 5 μC iodine-131. The ^{125}I samples were counted at the 25 KeV base line with a 12 KeV window (25-37 KeV range). The ^{131}I samples were counted at 350 KeV base with a 40 KeV window.

[1]This work was supported in part by a contract to J. G. from the International Atomic Energy Agency—and by grants from the Jack Schenkar Memorial Club, Covington, Kentucky, and the Rose Soibel Fimoff Memorial Club, Chicago, Illinois.

[2]Present address: Medical Physics Section, Radioisotope Service, Hines VA Hospital, Hines, Ill.

[3]The Medical Physics Section, the Department of Oncology, and The Department of Experimental Medicine and Cancer Research, The Hebrew University Hadassah Medical School, Jerusalem, Israel.

Similar comparisons were performed among water, urine and plasma samples in plastic test tubes. Volumes of 2 ml were counted within a 1¾″ × 2″ well counter at identical spectrometer settings.

Plasma samples of various densities were prepared by dissolving dried human plasma, at various concentrations, in distilled water. Four samples of each concentration were counted. The urine with density of 1.31 was prepared by evaporating a sample of urine with density of 1.18 to one third its original volume, using heat.

The results (Table I) indicate that, for *in vitro* studies, no complication occurs in the counting procedures when ^{125}I is used instead of ^{131}I for thyroid function studies. In cases of greater differences in densities, any difficulty might be overcome by the absolute disintegration determination method, as described by Elridge and Crowther (3).

PHANTOM TEST

Uptakes: The possible absorption of the soft x-rays in tissue that may occur in *in vivo* tests was studied next. For *neck* studies a lucite cylinder five inches in diameter was used as a neck phantom (Fig. 1). Holes of various diameters were drilled 0.5 cm from the cylinder face (envelope). Ten μC of ^{125}I were diluted to various volumes in plastic containers of several diameters, but of constant 43 mm height. The phantom was fixed to the collimated probe (Nuclear Chicago DS5-I with 1″ × 1″ crystal) at 20 cm distance. The field of view of the collimator at this distance is shown in Fig. 2 for point sources of ^{125}I and iodine-131. The containers were placed successively in the phantom, and counted individually. The results were normalized to the 31.0 mm diameter bottle containing 32.5 ml. This volume approximates that of the normal thyroid. The diameters and volumes of the various vials and the normalized counts are given in Table II, and plotted in Figure 3.

The results show that for thyroids ranging in weight from 20 to 55 gm there will be a maximum error of uptake of ± 10 percent when compared to the 32.5 ml standard as described above. For thyroids of 15-75 gm the error will increase to ± 20% under the same conditions. Under actual conditions the variation in size of the unselected thyroids did not introduce an error significantly greater than the overall variation of the measurements, as explained more fully in the following paper.

Scanning: The advantages of ^{125}I for scanning the thyroid, have been indicated by several workers (4,5,6,7). For our studies, we used a lucite phantom in the form of a 20 × 20 × 20 cm cube (Fig. 4). This cube can be disassembled into one-cm-high sections of 10 × 15 cm, 5 × 10 cm, 1 × 5 cm, 0.5 × 10 cm, 1 × 1 cm, and 0.5 × 1 cm. In 100 one cm cubes, holes of 0.5 cm in diameter, and 0.5 cm in depth were drilled. These cubes served as *point sources* which could be distributed anywhere in the phantom.

Point-Source Resolution: A single point source was placed one cm below the phantom surface. Profile scans were done on sources containing 25 μC of ^{125}I or 25 μC of iodine-131. The scanner used was a FH96 Frieseke-Hoepfner scintiscanner with a 31-hole collimator having focal distance of 11 cm. Scanning

TABLE I

COMPARISON OF THE EFFECT OF THE ABSORPTION OF ^{125}I AND ^{131}I RADIATION IN SAMPLES OF WATER, PLASMA AND URINE ON THE SAMPLE COUNT RATE

Sample	*Density* (*Gr. cm*$^{-3}$)	*Volume* *ml*	*Radioactivity* *μC*	*Average cpm* ^{125}I	*Average cpm* ^{131}I	*Cpm relative to* H_2O ^{125}I	*Cpm relative to* H_2O ^{131}I	*Detector*
H_2O	1.00	2.0	2×10^{-3}	1967	659	1.00	1.00	1¾″ x 2″
Venous plasma	1.20	2.0	2×10^{-3}	1994	664	1.01	1.01	Well type
Dissolved dried plasma	0.92	2.0	2×10^{-3}	1989	670	1.01	1.02	Scintillation
Dissolved dried plasma	1.28	2.0	2×10^{-3}	2004	650	1.02	0.99	Detector
Dissolved dried plasma	1.34	2.0	2×10^{-3}	1958	665	1.00	1.01	
Urine	1.18	2.0	2×10^{-3}	2010	657	1.02	1.00	
Concentrated	1.31	2.0	2×10^{-3}	1960	648	1.00	0.98	
H_2O	1.00	1000	5.0	1280	512	1.00	1.00	1″ Collimated
Urine	1.18	1000	5.0	1242	516	0.97	1.00	Crystal; Distance 30 cm

TABLE II

DIAMETERS, VOLUMES AND NORMALIZED RESULTS OF ^{125}I DILUTIONS IN WATER SAMPLES COUNTED IN LUCITE PHANTOM (CONSTANT SAMPLE HEIGHT—43 MM).

Diameter (mm)	4.4	8.3	11.3	13.9	18.4	25.0	31.0	33.5	39.0	61.0
Volume (ml)	0.7	2.3	4.3	6.2	11.5	21.5	32.5	38.0	51.3	125.0
Normalization factor	1.80	1.75	1.45	1.40	1.20	1.10	1.00	1.00	0.90	0.65

speed was 1 mm/sec. The results (Fig. 5) show that the resolution is improved by 20% using ^{125}I instead of ^{131}I. Using two *point sources* (Fig. 5b, 5c), we obtain a separation resolution for 5 mm sources of 7.2 mm for ^{125}I and 9.0 mm for iodine-131.

These results were obtained by interpolating the count drop for a 5 mm separation (Fig. 5b) and for a 10 mm separation (Fig. 5c). Figure 5a is the resolution curve for a single 0.5-cm-diameter source.

Scanning of Superficial Organs: A small organ was simulated in the phantom, in the shape of two layers of sources (Fig. 6). The lower layer, 2 cm below the surface, consisted of 10 sources (3×3 and one extending). The upper layer consisted of eight sources (3×3 but with center cube a *blank*). The 18 sources were filled with 1 μC of ^{125}I each and with 2 μC ^{131}I each. The photoscans are shown in Figure 7. The *defect* is seen more clearly in the ^{125}I scan. This is obviously due to the stronger absorption of the 27.4 KeV ^{125}I x-ray in the upper *blank* than the 364 KeV γ-rays of iodine-131.

Scanning of Deep Organs: Six sources containing 5 μC of ^{125}I each and six sources containing 5 μC of ^{131}I each were distributed in the phantom at 1, 3, 5, 7 and 9 cm depths as shown in Figure 8. Scans were carried out at a speed of 2.5 mm/sec. The dot- and photoscans are shown in Figure 9. All six sources are clearly

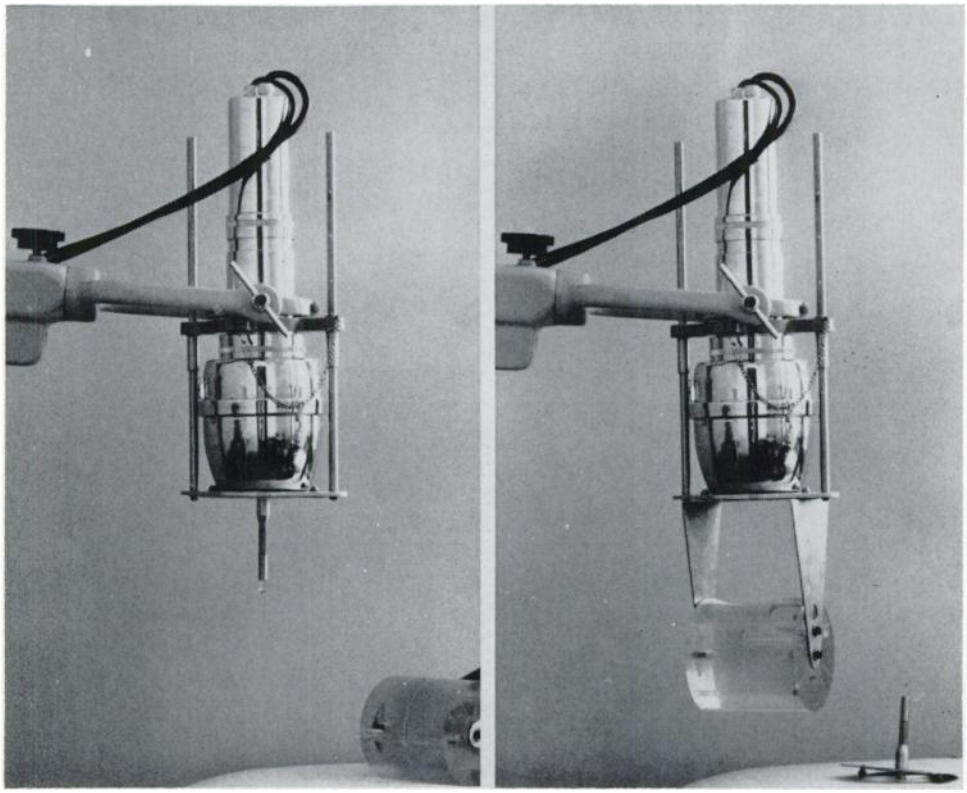

Fig. 1. Detector and phantom used for thyroid uptake measurements. Left: Distance pointer in position. Right: Phantom in position.

seen with ^{131}I on both the photo- and the dotscans. All sources can be seen on the dotscan (with ^{125}I also), but the sources that were 7 cm and 9 cm deep cannot be seen on the photoscan using optimum contrast setting. At first sight this seems to be an obvious advantage of ^{131}I; but, these findings suggest that by using ^{125}I it might be possible to estimate the depth of a source by carrying out anterior and posterior scans. This is demonstrated by the localization of pulmonary metastases of thyroid carcinoma as shown in the following paper.

DOUBLE-ISOTOPE COUNTING TECHNIQUE

Iodine-125 and iodine-131 can easily be counted simultaneously, using relatively simple equipment. The high voltage and the amplifier gain are chosen so that the base full scale will be 1 MeV for ^{131}I and 300 KeV for iodine-125. Using the base settings as described in section 1, for ^{125}I there is a 20% contribution from the ^{131}I peak count rate in a well counter. (Packard 3042 single-channel Gamma Spectrometer), and a 40% contribution with DS5-1 probe with one inch crystal (Nuclear Chicago DS5-1 probe with 132A Analyzer Computer). The ^{131}I activity is determined as usual, as there is no contribution from the ^{125}I radiation at the ^{131}I level. The ^{125}I activity is determined as follows:

$$C_{125} = C'_{125} - (C_{131} \times P).$$

where, C_{125} are the actual net ^{125}I counts at the ^{125}I level,
C'_{125} are the sample net counts at the ^{125}I level,
C_{131} are the sample net counts at the ^{131}I level, and
P is the relative contribution of ^{131}I counts at the ^{125}I level.

$$P = \frac{A_{125}}{A_{131}}$$

where, A_{125} is the net ^{131}I standard counts at the ^{125}I level, and
A_{131} is the net ^{131}I standard counts at the ^{131}I level.

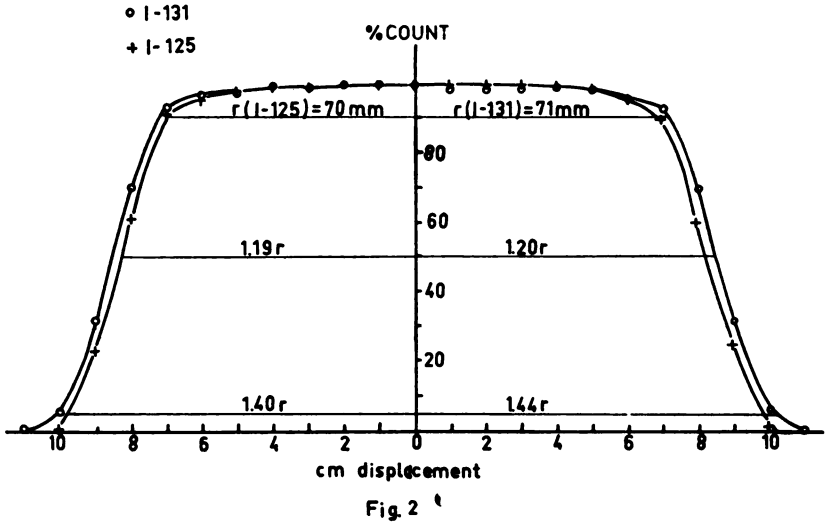

Fig. 2. Field of view of detector.

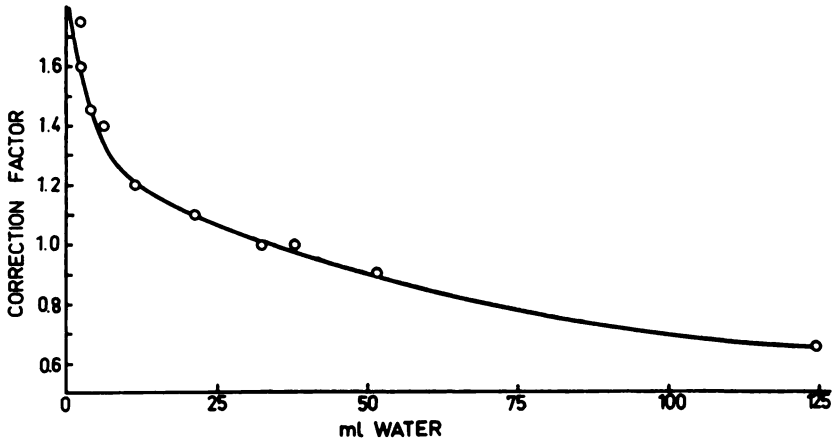

Fig. 3

Fig. 3. Variation of count rate of ^{125}I standards vs. standard volume. (Normalized to 32.5 ml volume).

DETERMINATION OF TRACER DOSE

First, we have to establish the necessary tracer dose of ^{125}I that must be administered to the patient, in order to obtain equal statistical counting accuracy as with ^{131}I, when equal time periods for counting are used. For this purpose we have to consider: (a) photon signals per disintegration, (b) crystal efficiency, (c) background, (d) absorption within the thyroid, and (e) absorption in the

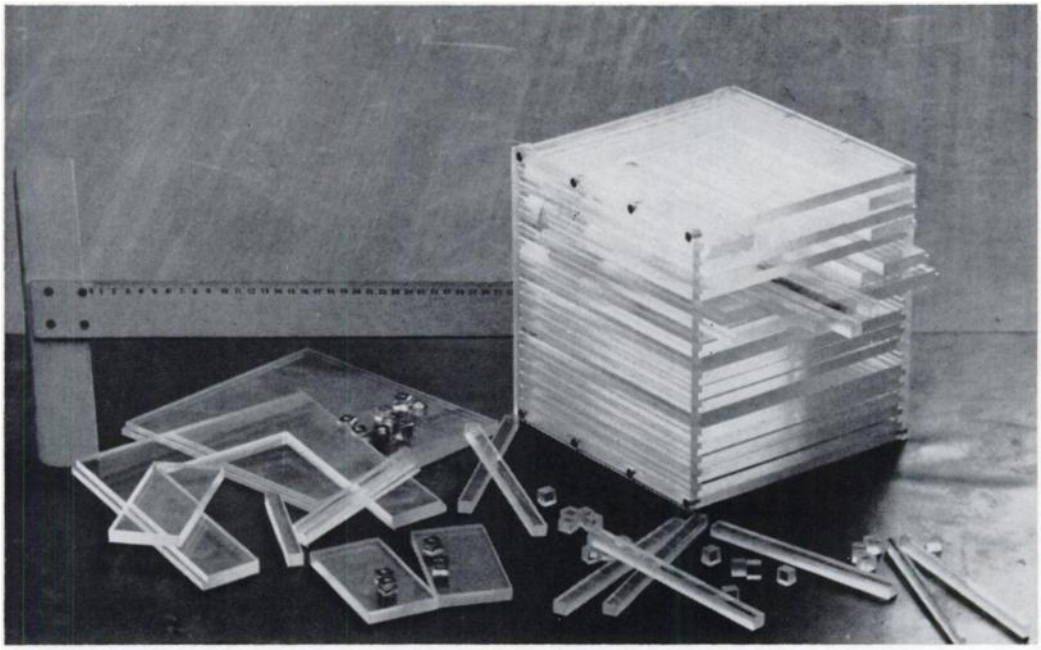

Fig. 4. The scanning phantom, partly disassembled.

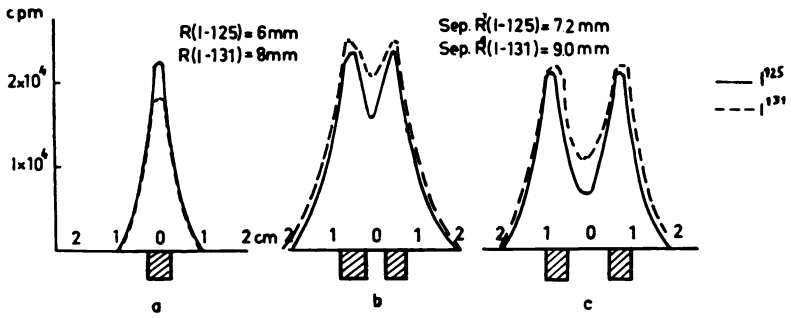

Fig 5

a - Single source, diameter 0.5 cm.
b - Two source, diameter 0.5 cm. (separation of sources 0.5 cm.)
c - Two source, diameter 0.5 cm (separation of sources 1.0 cm.)

R = Resolution = i.e. the width of the curve in mm. at 50% of peak count
¹ = Interpolated separating resolution.

Fig. 5. Resolution curves for ^{125}I and ^{131}I.

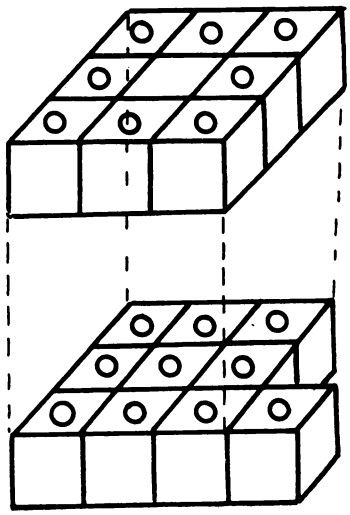

Fig. 6. The two layers of the simulated small organ, with *cold lesion* in upper layer.

tissue between the thyroid and neck surface. The ratio of photon signals per disintegration of ^{125}I to ^{131}I (SR) = 1.36 : 0.81 = 1.68 (1). According to Myers (1) it can be assumed that the ^{125}I to ^{131}I crystal efficiency (C.E.) is two to one. If the number of photons emitted from radioiodine distributed evenly through-

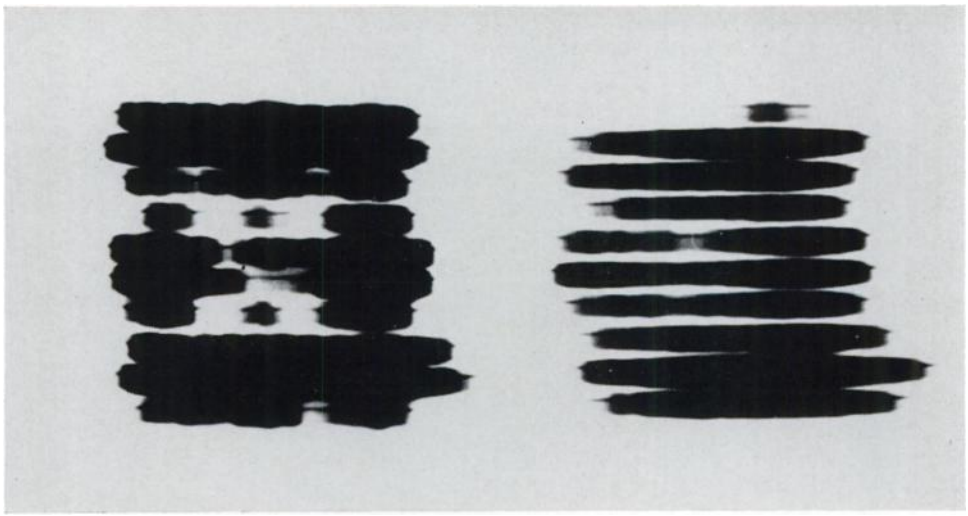

Fig. 7. Photoscan of *small organ*. Left: With ^{125}I. Right: With ^{131}I.

out a thyroid 1 cm thick is N_0, then the number of photons escaping from the thyroid surface is:

$$N = N_0 \times \frac{1}{l} \int_0^l e^{-\mu_a x}\, dx, \text{ or } \frac{N}{N_0} = -\frac{1}{\mu_a l}\,(e^{-\mu_a l} - 1),$$

where μ_a is the linear energy absorption coefficient. In water μ_a (^{125}I) = 0.301 cm^{-1} and μ_a (^{131}I) = 0.110 cm^{-1}. These figures are obtained from the experimentaly determined half thickness of ^{125}I (2.3 cm) and ^{131}I (6.3 cm), (1). Assuming a thyroid of thickness l = 1.5 cm, and substituting the constants in the above equation, it can be calculated that 80% of the ^{125}I photons and 93% of the ^{131}I photons escape from the thyroid surface. Assuming that the tissue layer between the thyroid and neck surface is 0.5 cm thick, the fraction $\frac{N^1}{N_0}$ of photons penetrating this layer can be calculated from the equation

$$N^1 = N_0 \times e^{-0.5\mu_a}\ .$$

That is, 86% of the ^{125}I photons and 95% of the ^{131}I photons penetrate this layer. The overall relative penetration of ^{125}I photons compared to ^{131}I photons in the thyroid and overlaying tissue is:

$$A = \frac{0.80 \times 0.86}{0.93 \times 0.95} = 0.78$$

Before entering the crystal, the photons must penetrate its aluminum housing. The thickness of this layer is 0.08 cm for most standard crystals. The absorption of the ^{131}I photons in this thin layer is negligible, while a considerable fraction of ^{125}I photons will be absorbed therein. This fraction equals (1 − F) = (1 − $e^{-3 \times 0\ 08}$) = 0.22. [The linear absorption coefficient of 27.4 KeV photons in aluminum is 2.97 cm^{-1} (NBS Handbook 85).] As the counting efficiency of a system is determined by the square of the count rate divided by the background,

we arrive at the overall ratio R by calculating

$$R = \frac{(SR \times CE \times A \times F)^2}{B}$$

where B is the background ratio. With our equipment the background was 7 cpm, and 14 cpm at the ^{125}I and ^{131}I settings respectively. Thus,

$$B = 7 : 14 = 0.5.$$

Substituting the calculated constants, the relative counting efficiency is

$$R = \frac{(1.68 \times 2.00 \times 0.78 \times 0.78)^2}{0.5} = 8$$

DOSIMETRY

The radiation dose absorbed by a 30 gm thyroid was calculated by the method described in "Radiation Dosimetry" (8, 9).

The parameters E_β (^{125}I) and k (^{125}I) were calculated using the decay scheme for ^{125}I as published by Myers (1).

$\bar{E}_\beta$ (^{131}I) = 0.178 MeV

$\bar{E}_\beta$ (^{125}I) = 6.85 keV , from 3.77 keV L-capture x-rays
+ 13.76 keV , from I.C. electrons
20.6 keV
= 0.0206 MeV.

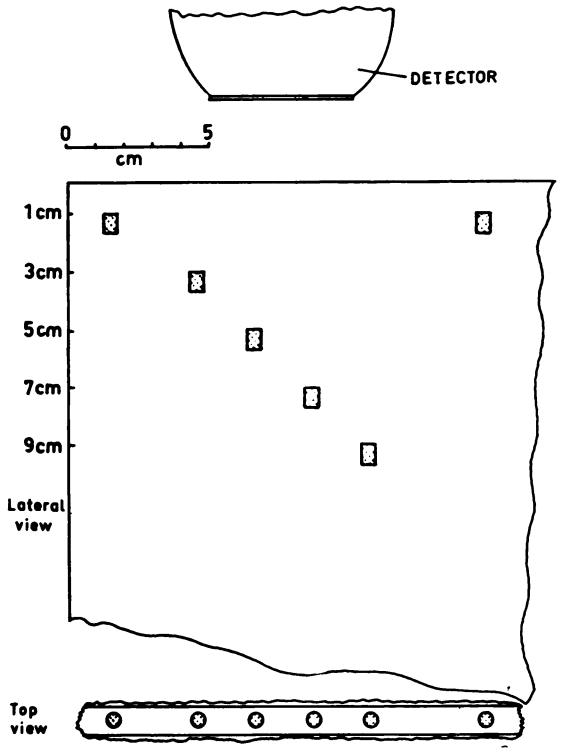

Fig 8

Fig. 8. Distribution of sources in phantom for localization of deep *hot lesions*.

T_{eff} (^{131}I) = 6 days [1]

T_{eff} (^{125}I) = 17 days [8]

[1]Assuming a biological half-life T_b of 24 days.

k (^{131}I) = 2.18 r/mc/h at 1 cm

k (^{125}I) = 1.0 × 0.68 (27.4 KeV capture x-rays) + 1.0 × 0.68 (27.4 KeV I.C. x-rays) + 0.6 × 0.07 (35.4 KeV unconverted gamma-rays = 1.40 r/mc/h at 1 cm

g (geometric factor) = 14.6

m = 30 gm

The total dose absorbed by the thyroid equals

$$D(\beta + \gamma) = \frac{T_{eff}}{m} (73.8 \bar{E}_{\beta} + 34 \times 10^{-3} \times g \times k) \text{ rads}/\mu C \text{ in thyroid.}$$

For ^{131}I, $D(\beta + \gamma)131 = \frac{6}{30} [(73.8 \times 0.178) + (34 \times 10^{-3} \times 14.6 \times 2.18)]$
= 2.84 rad/μC

For ^{125}I, $D(\beta + \gamma)125 = \frac{17}{30} [(73.8 \times 0.0206) + (34 \times 10^{-3} \times 14.6 \times 1.40)]$
= 1.25 rad/μC

The ratio q of the ^{131}I dose/μC to the ^{125}I dose/μC is $\frac{D(\beta + \gamma)131}{D(\beta + \gamma)125} = 2.27$

These results differ slightly from those reported by Harper *et al* (10).

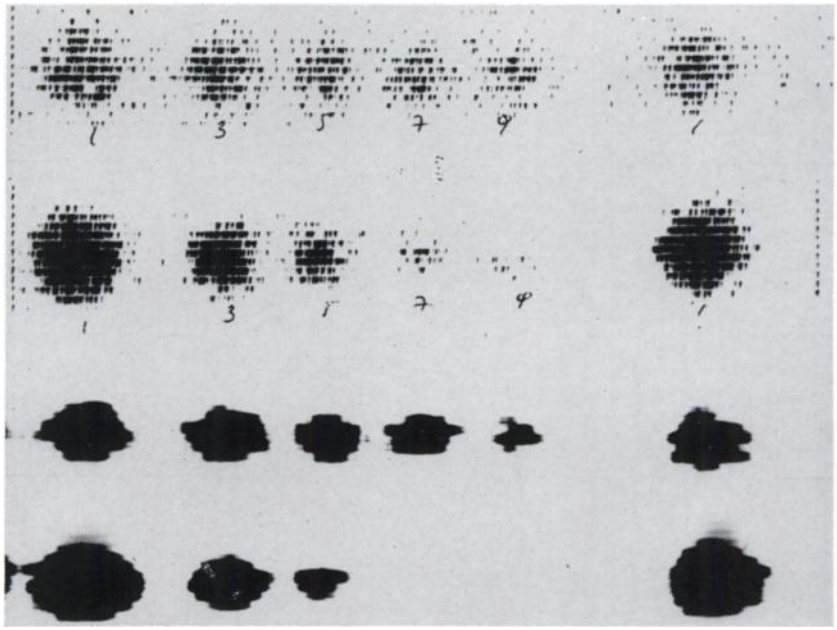

Fig. 9. Dotscan and photoscan of *deep lesions*. Top and third row with ^{131}I, second and fourth row with ^{125}I.

Assuming a biological half-life of 50 days, and that the ^{125}I tracer dose is one eighth of the ^{131}I tracer dose, (sect. 4) the radiation to the thyroid may be reduced by a factor of 10 using ^{125}I for routine radioiodine thyroid uptake measurements.

SUMMARY

The physical aspects of the use of ^{125}I for thyroid diagnosis have been studied.

1. It has been shown that for *in vitro* studies (urine and plasma) the effect of density on assay is negligible.

2. Using a 32.5 ml water standard and a five-inch, lucite neck phantom, thyroid uptakes may be measured with an accuracy of ± 10% for thyroids in the 20 to 55 gm weight range, and ± 20% for 15 to 75 gm range.

3. The scanning resolution is improved by 20% for ^{125}I in comparison with iodine-131.

4. The possibility of estimating the depths of sources is indicated.

5. Iodine-125 and ^{131}I easily may be used for double-tracer techniques.

6. The tracer dose of ^{125}I may be reduced by a factor of six, compared to ^{131}I, without altering counting statistics.

7. For thyroid studies, the radiation dose to the thyroid may be reduced by a factor of ten.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the valuable technical assistance of Mrs. Sarah Kornitzer-Baron, Mr. E. M. Reich, and Mr. I. Koffler.

REFERENCES

1. Myers, W. G., and Vanderleeden, J. C.: Radioiodine-125. *J. Nuclear Med.* 1:149-164, 1960.

2. Bakhle, Y. S., Prussoff, Wm. H. McCrea, J. F.: Precaution in the use of iodine-125 as a radioactive tracer. *Science.* 143:799-800, Feb., 21, 1964.

3. Eldridge, I. S., and Crowther, P.: Absolute determination of I-125 in clinical applications. *Nucleonics* 22. 6:56-59, June, 1964.

4. Levy, L. M., Estrellado, T. T., Okazie, O., and Stern, M. S.: The use of I-125 in clinical nuclear medicine. *J. Nuclear Med.* 3:183, 1962.

5. Endlich, H., Harper, P., Beck, R., Siemens, W., and Lathrop, K.: The use of I-125 to increase isotope scanning resolution. *Am. J. Roentg. Rad. Therapy and Nuclear Med.*, 87:148-155, 1962.

6. Fellinger, K., Hofer, R., and Vetter, H.: Szintigraphie der Schilddruse mit Jod-125. *Nuclear Medizin, III.* 1:20-26, 1962.

7. Ben Porath, M., Hochman, A., and Gross, J.: Scanning with iodine-125. Proceedings of the IAEA symposium on medical radioisotope scanning in Athens, Greece (April 20-24, 1964). II:71-77. IAEA, Vienna, 1964.

8. Loevinger, R., Holt, J. G., and Hine, G. J.: Internally administered radioisotopes. *Radiation Dosimetry.* Edited by G. J. Hine and G. L. Brownell, Academic Press pp. 803-871, 1956.

9. Loevinger, R., Japha, E. M., and Brownell, G. L.: Discrete radioisotope sources. *Radiation Dosimetry,* Edited by G. J. Hine and C. L. Brownell, Academic Press, pp. 694-794, 1956.

10. Harper, P. V., Siemens, W. D., Lathrop, K. A., and Endlich, M. E.: Production and use of I-125. *J. Nuclear Med.* 4:277-289, 1963.