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CLINICAL USE OF IODINE-123

The effective clinical use of iodine-123 requires careful consideration of its decay scheme and of the degree of contamination with impurities such as other radioiodines. Biological and chemical considerations are also important. The advantages of iodine-123 rest on the lower radiation dose allowing administration of higher levels of activity and the more effective collimation and detection in comparison with iodine-131 labeled substances. An additional advantage for some radiopharmaceuticals would be a higher specific activity.

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Physical considerations

One of the principal problems with iodine-123 is the presence of other isotopes of iodine in the commercially available product. These consist primarily of iodine-124 and iodine-130. As much as 3 or 4% contamination may be present (Table 1). The effects of such contaminents on the images obtained on a gamma camera will be twofold; 1) septal penetration of the collimator and Compton scatter will degrade the image and 2) the presence of a high ratio of counts outside the window to those inside the window will reduce count rate capability at high count rates.

An examination of the spectra obtained with various collimators as performed by McKeighan, Muehllehner and Moyer is instructive (1). This study was performed with commercially available iodine-123 and illustrates the large proportion of Compton events seen with the high resolution collimator. With the 4000 hole low energy collimator the Compton background is 40% that seen with the high resolution collimator. The septal thicknesses are: hi-resolution 0.01",

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4000 hole 0.03". The spectrum as seen with the pin-hole is very significantly improved (Fig. 1).

With the high resolution collimator only 1/3 of the counts in a 20% window centered at 159 keV are due to the true 159 keV transition. The ratio of counts within the window to those outside the window could be 0.16 for this collimator, .33 for the 4000 hole collimator and 2.04 for the pin-hole collimator.

The effect on the line spread function is apparent (Fig. 2). For the high resolution collimator the effect of scatter is noted at about 15% of the peak counts while for ^{99m}Tc this is seen at the 0.5% level. With ^{123}I the effects are seen at 0.5% of peak for the pin-hole and 3% for the 4000 hole collimator.

However, when using "pure" ^{123}I the line spread function is much improved and the high resolution collimator can be effectively used.

It should be noted that delayed use of ^{123}I-labeled pharmaceuticals or studies in which images are obtained at late intervals following administration can result in greater degradation of images when using "impure" ^{123}I. This is due to the increasing percent of photons from the longer lived contaminents. In thyroid imaging, for instance, the 6 hour image may be superior to the 24 hour image despite the greater percent uptake at the later time. This is due to the fact that, on the average, nearly twice as many microcuries of ^{123}I is in the gland at the earlier time and the relative proportion of long lived contaminents (i.e., ^{124}I) is increased by a factor of about 3 at the later time (Table 2).

Chemical considerations

In principle compounds labeled with ^{131}I can be as readily labeled with ^{123}I.

The only advantages of ^{131}I are a long shelf life and its utility in long term studies, e.g. iodocholesterol for adrenal imaging. For any short term studies (24 hours or less) there is a great advantage to use of the ^{123}I label.

Because of similarities in decay characteristics, there is no advantage to the use of ^{123}I as a label for compounds that can be readily labeled with ^{99m}Tc. The latter nuclide will always be more readily available and less expensive.

There is one chemical advantage to the use of ^{123}I that should be mentioned. The parent ^{123}Xe can be used as a labeling agent by excitation labeling. This allows labeling of some materials that are not readily labeled by ^{131}I exchange reactions. The use of ICl and ICl_2 intermediates has also been described. The techniques developed are capable of production of high specific activity labeling in many instances (2).

Biological properties

The advantages accruing to the use of ^{123}I as a label depend to a large extent on the biological properties of various labeled pharmaceuticals and the clinical situation in which they may be used. They relate to the low radiation dose, the ability to do repetitive studies, the high information yields and the possibility of using the thyroid as a "sink" for liberated iodide. It is best to review the use of several radiopharmaceuticals labeled with ^{123}I in order to see what advantages exist in their use.

a) Orthoiodohippuric acid (OIH)

Renography is not extensively used by everyone but it is a useful procedure in evaluation of progress of function following transplantation and in renal cortical necrosis following shock. Ortho-iodohippurate is the most specific of labeled substances for renal evaluation. In situations where examinations must be performed repetitively the ^{123}I label has a number of advantages over the ^{131}I label. These are:

1. lower whole body radiation dose and thyroid dose.

2. lower background for repetitive studies.

3. better information density.

Where there is normal renal function the advantage of ^{123}I to ^{131}I is moderate because the major determinent is the short biological half life (Table 3). When renal function is poor, the differential becomes greater because of the favorable physical characteristics of ^{123}I.

The capability of using a low energy collimator (with "pure" ^{123}I) and the higher detection efficiency of the thin crystal of the gamma camera (80% vs 30%) for ^{123}I compared to ^{131}I means, μCi for μCi, a much higher count rate will be obtained with ^{123}I. This should improve the ability to assess renal function both in relatively normal individuals and especially where renal function is poor.

The labeling efficiency of OIH is high (~95-98%) so that large quantities of the radiopharmaceutical can be prepared. With the use of millicurie quantities "flow" studies can be performed, thus obviating the need for ^{99m}Tc studies.

This material has been used both by the Hammersmith group (3, 4) and Wellman and colleagues (5), at Cincinnati. However, both groups had to contend with other radioiodine contaminents, thus diminishing the quality of the examination. Even so, they felt that there was a definite improvement over the use of ^{131}I, particularly since renography is now routinely performed in association with gamma camera imaging.

b) Liver Studies

Studies with labeled colloids are performed routinely for morphological evaluation of the liver. Uptake of ^{99m}Tc S colloid by the reticulo-endothelial system is convenient and the radiopharmaceutical is readily available at low cost. However, functional evaluation of hepatic parenchymal cells is important in evaluation of many conditions. Rose Bengal, labeled with ^{131}I has been

available for many years for this purpose.

Again, the usual disadvantages of ^{131}I are apparent; these being the low detection efficiency and moderately high radiation dose with resultant loss in resolution and information density. The use of ^{123}I-Rose Bengal has been an obvious area of interest. There are certainly advantages to the use of ^{123}I-Rose Bengal but the biological disadvantages of Rose Bengal itself also pose some problems. Those disadvantages are:

a) renal excretion

b) relatively slow hepatic secretion

c) enterohepatic recirculation

It would therefore be appropriate to seek more specific agents. Goria (6) has evaluated the use of ^{123}I-BSP, primarily because the synthesis was easier than for Rose Bengal. It is not clear from his article, but it is probable that the ^{123}I was not "pure". BSP, however, does not meet the specifications for an ideal agent. It is potentially toxic and is not solely cleared by the liver (Fig. 3).

We have been working on the use of ^{123}I-indocyanine-green (7). It is cleared much more rapidly by the liver, does not have an enterohepatic recirculation and is not excreted by the kidneys (Table 4). Pre-clinical studies have confirmed its excellent biological properties and it is about to undergo clinical evaluation. One drawback is it's low labeling efficiency but this may be improved (Fig. 4, 5).

In consideration of these agents one should also be aware of any ^{99m}Tc labeled compounds or a ^{99m}Tc label for these above mentioned compounds that might be possible. As yet the ^{99m}Tc compounds available do not possess superior biological properties.

c) Tumor detection

We have been exploring the use of ^{123}I-labeled isoquinolines for melanoma

detection (8). While no great clinical success can be claimed at this time, the use of the ^{123}I-label has distinct advantages. At the present time ^{125}I is used as a label for this material and apparently localizes well several days after administration (9, 10). A substantial proportion of the radioiodine is liberated in vivo and the radiation dose to the choroid (46 rad/2mCi) and whole body (1 rad/2mCi) is a limiting factor. The specific activity was 3-27 mg/mCi.

The low radiation dose consequent to the use of ^{123}I and the thyroidal concentration of radioiodine can be used to advantage (Fig. 6). The thyroid can be used as a free iodine "sink", trapping that iodine liberated by metabolism of the isoquinoline. This reduces background activity and thus improving target-non-target ratios. Another possible advantage, yet to be validated, is that the potentially higher specific activity might result in earlier localization in the tumor. This has been suggested by preliminary work with the hamster melanoma model used to evaluate localizing agents and has been demonstrated in other biological systems.

d) Thrombus detection

Labeled fibrinogen detection of clots is an area of intense investigation at this time. The usual method of using the ^{125}I label and point counting has some advantages. The long half-life of ^{125}I is useful to detect thrombus formation for many days after administration. The equipment needed for detection is simple and can be used anywhere within a clinical facility.

The potential advantage of ^{123}I as a label is the possibility of visualizing the thrombi by imaging (11). The short $T_{\frac{1}{2}}$ necessitates multiple injections if a patient must be followed for a lengthy period. Since it is possible to administer multi-millicurie quantities it should be possible to follow patients for 3-4 days. With imaging systems of increased mobility, the advantages of visual demonstration of radiopharmaceutical localization are

possible even at the bedside (Figs 7-10).

e) Brain

Technetium labeled compounds are used routinely for brain tumor detection and are unlikely to be replaced by iodine labeled materials. However, there are other aspects of interest in reference to the brain such as blood flow, metabolism, etc.

^{123}I-iodoantipyrine has been utilized on a small scale at UCLA for the study of brain perfusion (12). This material has a lipid/water partition coefficient of 2.0. It's initial distribution is in the brain rather than other cranial structures as it readily penetrates the blood brain barrier. It therefore is an index of cerebral perfusion. Experience is limited but studies indicate that the compound should be useful for detection of ischemic areas such as subdural hematoma, cerebrovascular accidents, etc. The authors suggest that another area of use is in the quantitative evaluation of compensatory collateral perfusion following a cerebrovascular accident as an aid in prognosis (Fig. 11). The use of an ^{131}I label would result in a blood radiation dose 20x higher.

Other uses

We have been looking at the use of ^{123}I as a label for aromatic amino acids (iodophenylaline, iodotryptophan) and catechol amines where it can substitute for a methyl group. Iodinated amino acids have been previously studied by others (13, 14). While pancreatic localization was rather good in rodents, it did not appear particlarly good in larger animals. Iododopamine does not appear to localize in adrenal medulla so well as the carrier free ^{11}C compound but further investigation is required. There are definite advantages to use of ^{123}I over ^{11}C.

Conclusions

There is no question that ^{123}I is superior to ^{131}I as a label for studies

of short term (<48 hours). In evaluation of an increased role for this nuclide in medicine one should consider whether the compound can be labeled with ^{99m}Tc. For some compounds it is clear, at least at the present time, that ^{123}I is the label of choice, e.g. - orthoiodohippuran, iodoantipyrine.

For future development it is important to know what the availability and cost of ^{123}I will be. In addition, rapid, kit-type synthetic processes must be developed to efficiently utilize the materials.

For full utilization of the physical advantages attendent upon ^{123}I compound applications "pure" ^{123}I, free of other radioiodine contaminents is necessary.

Figures

1. Effect of collimation and radiocontaminents on spectrum of ^{123}I as seen by a gamma cameral crystal. BNL neg. #8-909-74
2. Line spread function for ^{123}I with several collimators. The effect of radiocontaminents can be noted. BNL neg. #8-908-74
3. Comparison of ^{99m}Tc colloid and ^{123}I-Rose Bengal liver images in a dog. Central defect seen in colloid scan fills in with the ^{123}I label late following administration of the label and is obviously a gall bladder. BNL neg. #10-160-74
4. Serial Scintiphotos of ^{123}I-ICG distribtution in a normal dog. BNL neg. #7-48-74
5. Serial scintiphotos of ^{123}I-ICG distribution in normal dog and in dog with complete bile duct obstruction. BNL neg. #7-47-74
6. Localization of ^{123}I-isoquinoline in hamster melanoma and thyroid at hours following administration. BNL neg. #1-656-74
7. Venogram of the lower extremity of a dog showing acute block of the femoral vein. BNL neg. #10-157-74
8. ^{123}I-fibrinogen camera image discloses thrombus and some radioactivity in the gall bladder. BNL neg. #10-156-74
9. Normal ^{123}I-fibrinogen images in man. BNL neg. #10-153-74
10. Multiple thrombi disclosed by ^{123}I-fibrinogen. BNL neg. #10-154-74
11. Comparison of distribution of ^{99m}Tc-pertechnetate and ^{123}I-iodoantipyrine in man. The ^{123}I activity was 7 millicuries. BNL Neg. #9-927-74

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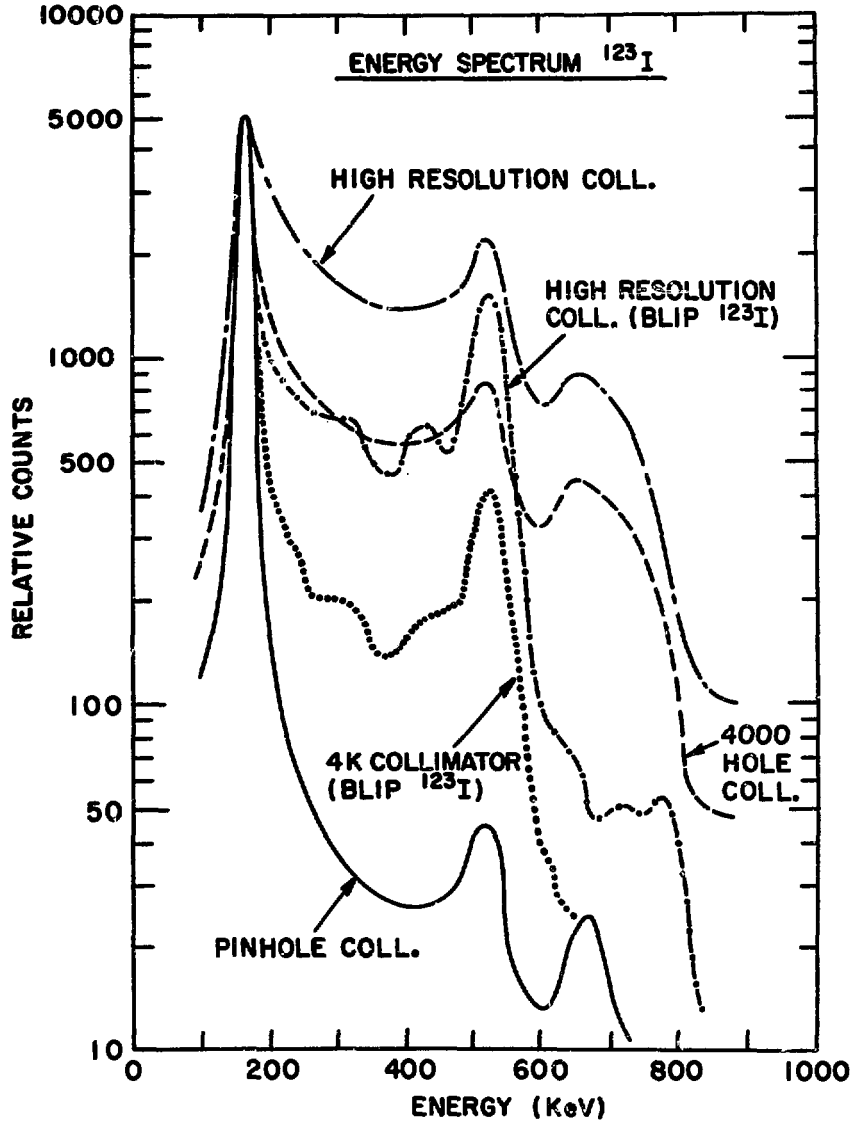
ENERGY SPECTRUM ^{123}I
HIGH RESOLUTION COLL.
HIGH RESOLUTION COLL. (BLIP ^{123}I)
4K COLLIMATOR (BLIP ^{123}I)
4000 HOLE COLL.
PINHOLE COLL.
RELATIVE COUNTS
ENERGY (KeV)
10000
5000
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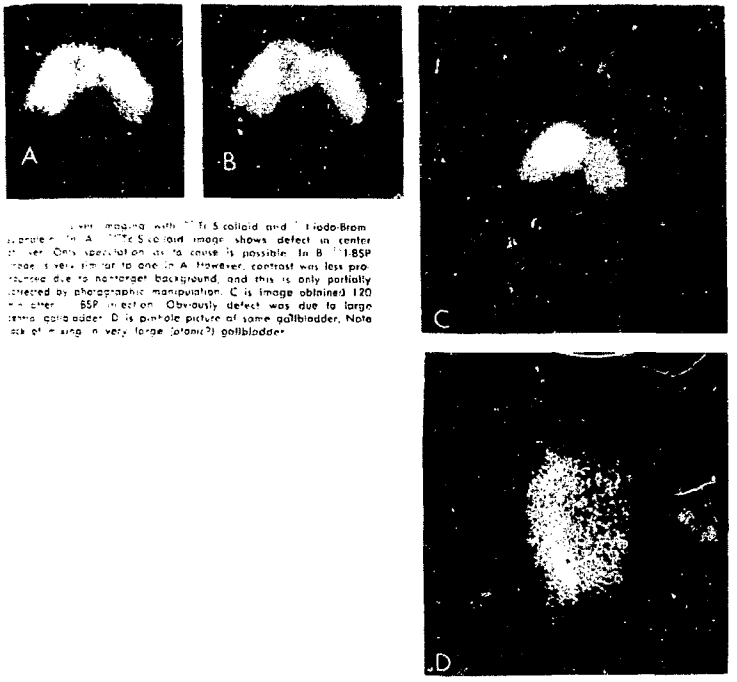
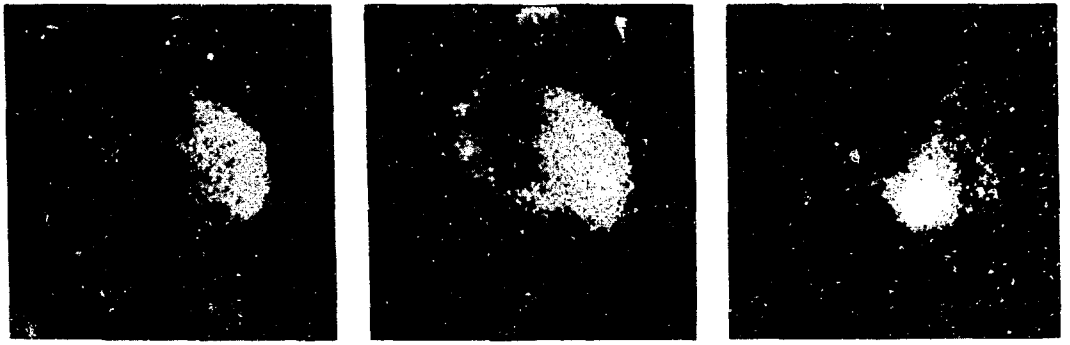


...ver imaging with ...Tc S colloid and ...I Iodo-Brom ...ophle ... In A, ...Tc S colloid image shows defect in center ...ver. Only specification as to cause is possible. In B, ...I-BSP ...age is very similar to one in A. However, contrast was less pro...nounced due to nontarget background, and this is only partially ...corrected by photographic manipulation. C is image obtained 120 ... after ... BSP injection. Obviously defect was due to large ...stone, as is added. D is pinhole picture of same gallbladder. Note ...ize of ... and ... very large (stone?) gallbladder.

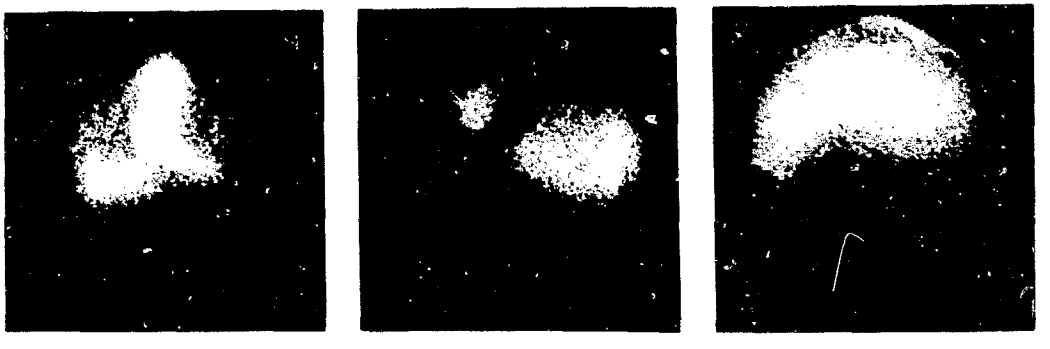


(A) 15 minutes (B) 40 minutes (C) 95 minutes

(D) 15 minutes (E) 40 minutes (F) 80 minutes

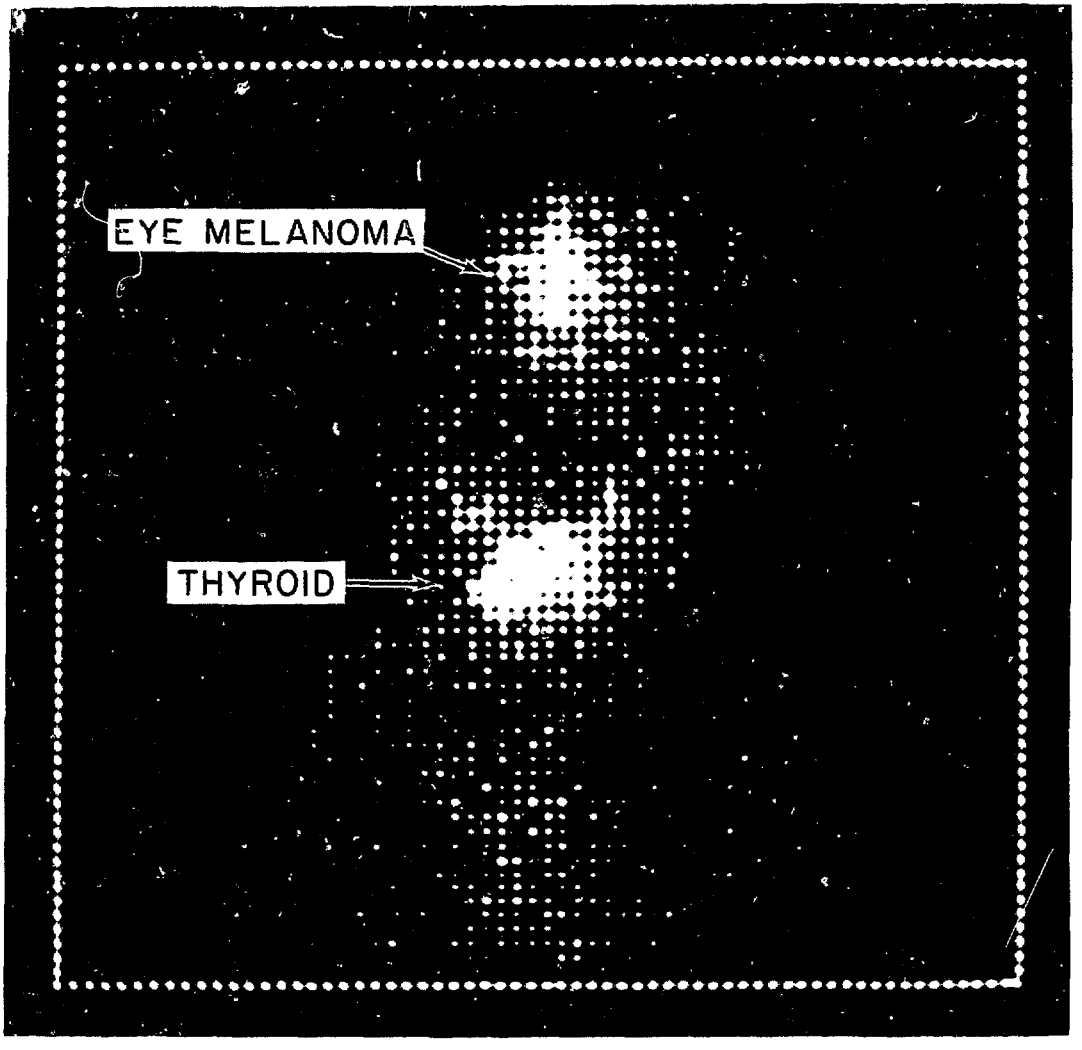
SERIAL SCINTIPHOTOS OF HEPATOBILIARY SYSTEM. COMPARISON OF NORMAL WITH COMPLETE BILE DUCT OBSTRUCTION. (A,B,and C) COMPLETE BILE DUCT OBSTRUCTION, (D,E,and F) ARE NORMAL.

(A) 15 minutes (B) 60 minutes (C) 80 minutes

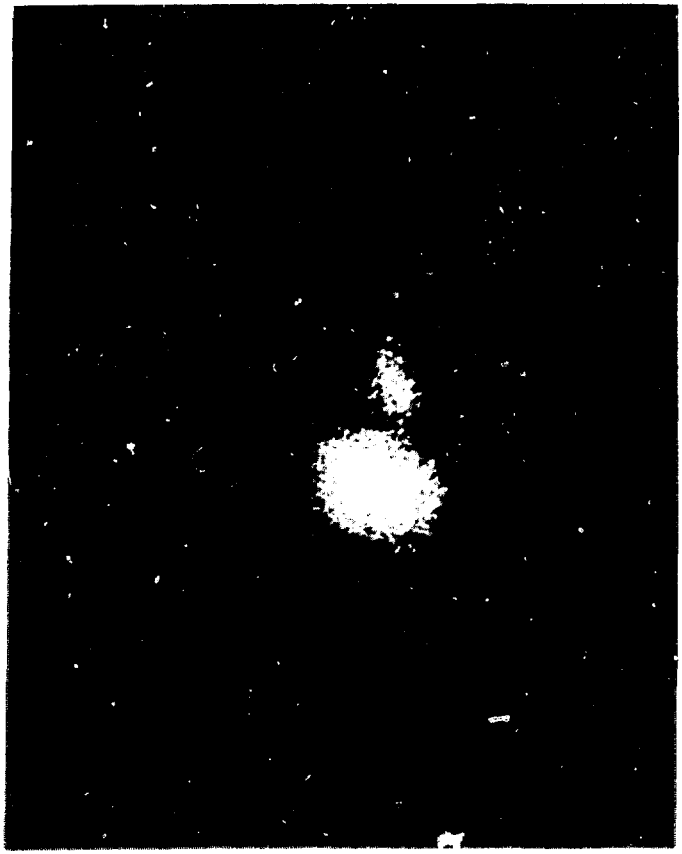


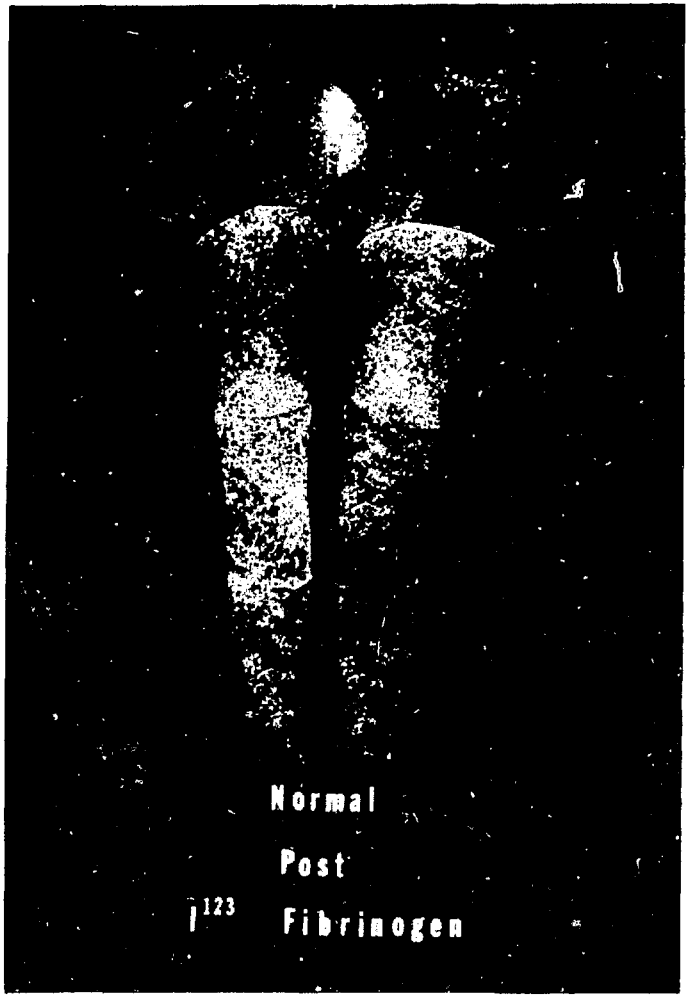
(D) 2 hours (E) 24 hours (F)

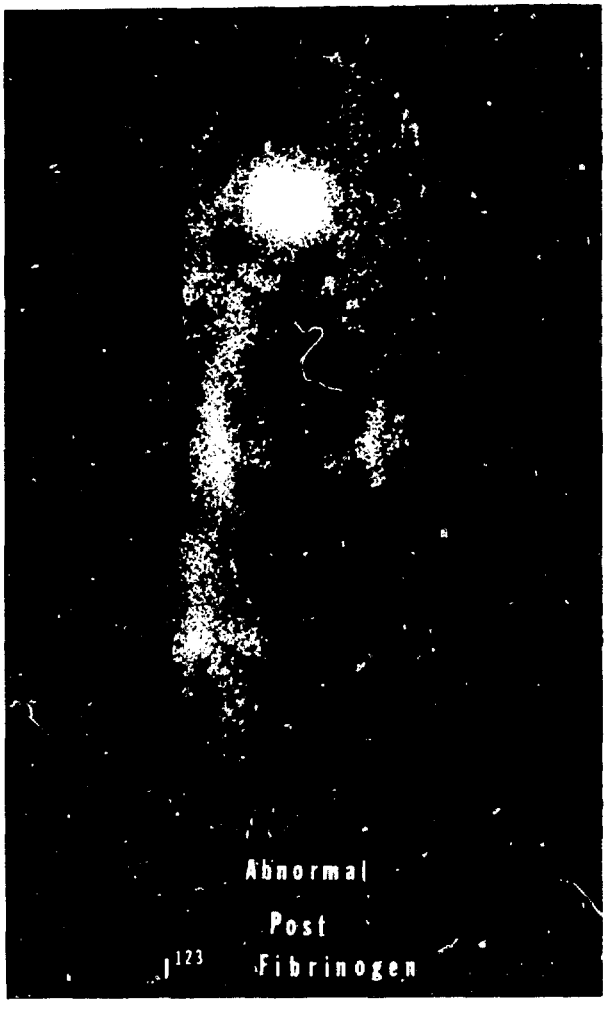
SERIAL SCINTIPHOTOS OF HEPATOBILIARY SYSTEM IN NORMAL DOG. (A – D) SHOWS EXCRETION OF ^{123}I ICG FROM LIVER INTO BILIARY TREE. (E) 24 hour SCINTIPHOTO WITH RESIDUAL ACTIVITY IN THE GALL BLADDER. (F) ^{99m}Tc SULFUR COLLOID SCINTIPHOTO TAKEN AFTER (E).


EYE MELANOMA
THYROID


a




Normal
Post
I^{123} Fibrinogen

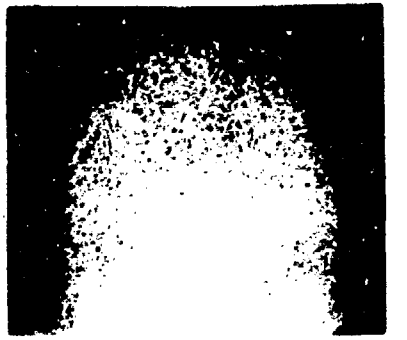

Abnormal
Post
I^{123} Fibrinogen

CNS PERFUSION SCAN

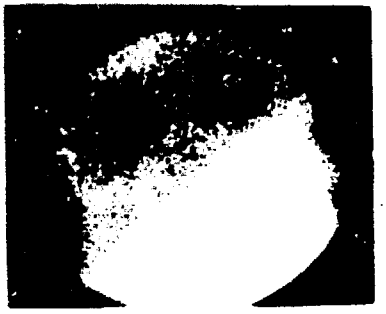
^{99m}Tc

^{123}IAP

3 Min.



22 Min.



66.8

5 Min.

TABLE 1

Decay Characteristics of Some Radioiodines
(No./100 disintegrations)

	^{123}I 13.3 h - E.C.	^{124}I 4.2 d - E.C., β^+	^{126}I 13 d - E.C., β^+, β^-	^{130}I 12.4 h - β^-
γ keV	159 (83.5)	603 (66)	386 (33.5)	669 (99.6)
	27.5 (47.2)	511 (49.6)	667 (32.8)	538 (99.3)
	27.2 (24.2)	1692 (13.8)	27.5 (22.5)	743 (86.7)
	31 (12.7)	644 (10.3)	27.2 (11.5)	144 (34.6)
	31.8 (2.6)	714 (9.1)	31 (6.1)	1150 (12)
	530 (2)	722 (6.9)	480 (4.2)	Others (1.62)
	Others (1)	1540 (4.2)	750 (3.6)	
		1361 (2.1)	511 (2.6)	
		1370 (1.2)	31.8 (1.3)	
		2260 (1.5)	Others (1.7)	
		1326 (1.0)		
		X-rays (65.6)		
		Others (3.1)		
Δi (β)	0.0591	0.4504	0.3132	0.6282

TABLE 2

Comparison of Simultaneous Administration of $Na^{131}I$ Orally and $Na^{123}I$ Intravenously

	Thyroid uptake, % (±SD)		Ratio
	^{123}I	^{131}I	$^{123}I/^{131}I$
2 Hours			
All patients(21)	13.7±11.6	13.9± 4.4	1.16±0.27
Euthyroid(17)	10.1± 6.6	8.5± 5.9	1.23±0.22
6 Hours			
All patients(21)	21.4±16.8	18.7±14.9	1.16±0.17
Euthyroid(17)	16.1± 8.5	14.2± 8.4	1.16±0.12
24 Hours			
All patients(29)	27.0±15.7	25.6±16.3	1.11±0.31
(28)*	27.0±16.0	26.1±16.4	1.05±0.10
Euthyroid(25)	23.1± 9.1	21.8± 9.4	1.11±0.33
(24)*	22.8± 9.1	22.2± 9.4	1.04±0.09

*One euthyroid patient had a ratio of 2.67 at 24 hours, probably a technical error. Elimination of this one patient changes the results as indicated.

Radiation Dose With Labeled OIH

	Rads/mCi			
	Normal kidney function		Absent kidney function	
	Kidney	Whole body	Kidney	Whole body
^{123}I (pure)	0.014	0.009	0.143	0.143
^{123}I (5% ^{124}I)	0.019	0.012	0.528	0.528
^{131}I	0.075	0.030	11.470	11.470
$^{131}I/^{123}I$		3.33		80.2

Assumptions –

$T_{1/2}$ = 20 min (normal)
ECF distribution
Max fractional renal conc. = renal clearance × transit time = 0.19
100% in bladder for 2 hours

TABLE 4

Characteristics of $^{123/131}$I-labeled Compounds for Study of Liver-Function

			I-Ioglycamic-acid (I-IGA)	I-Bromsulphalein (I-BSP)	I-Rose-Bengal (I-RB)	I-Indocyanine-green (I-ICG)
Chemical purity			pure	pure	impure	pure
Blood-clearance (t/2)			30′	3.1-10′	6-9′	3.1′
Liver-excretion (t/2)			6.3′	20′	90-284′	
Hepatic-excretion-efficiency			~10%	~90%	30-50%	~90%
Hepatic-to-plasma-reflux			no	no yes	no yes	
Diffusion into extravascular space			yes	no yes	no yes	no
Intestinal reabsorption			no	partial	partial	no
Conjugation/transformation			*no*	*partial*	*partial*	*no*
Urinary excretion			yes (5%)	yes (5%)	yes	no
Interference by bilirubin			yes	yes	yes	no
Radiation-exposure (rad/100μCi)	liver	^{131}I	0.006	0.05	0.1	
		^{123}I	0.0006			
	whole body	^{131}I	0.02	0.01	0.001	
		^{123}I	0.0028			
Gall bladder-visualization during test-time			regular ⩾5′	irregular ⩾15′	irregular ⩾25′	
Test-period			40′	60′	60-120′	