

RADIOLABELED CHOLESTEROL AS AN ADRENAL SCANNING AGENT

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Selective localization of a gamma-emitting compound in adrenal tissue would potentially allow the anatomical and functional assessment of that organ.

Cholesterol is the principal precursor of adrenocortical steroids (1,2). Appलगren (3) dosed mice with ^{14}C -labeled pregnenolone, progesterone, and cholesterol. Autoradiography and tissue radioassays established that ^{14}C -labeled cholesterol concentrations in the adrenal cortex exceeded that of any other tissue and concentrated to a greater extent than the other steroid analogs. The major portion of the radioactivity was present in the cholesterol ester fraction.

Nagai et al (4) have reported the use of radiolabeled adrenocortical steroid precursors in the mouse, rabbit, rat, and human, with tissue concentrations and the determination of adrenal-to-liver radioactivity ratios at various intervals. The highest adrenal-to-liver ratio was seen at 48 hr with ^3H -stigmaterol reaching a value of 27 in mice; lower values were noted with ^{131}I -labeled cholesterol and stigmaterol. A scan of one patient with Cushing's disease, 5 hr after injection with ^{131}I -stigmaterol, provided suggestive but not definitive evidence that a left adrenal adenoma was visualized.

We report here on the concentration of radioactivity in the dog adrenal using ^{125}I -19-iodocholesterol and 4- ^{14}C -cholesterol and present scan studies with visualization of the dog adrenals in vivo.

MATERIALS AND METHODS

Fifty-eight mongrel dogs weighing 7–13 kg were injected intravenously with ^{14}C - and ^{125}I -labeled cholesterol in ethanol solution. Five to 10 μCi of ^{14}C -cholesterol per kilogram of body weight were administered to 14 dogs pretreated with 40 units of ACTH gel daily for 2–4 days and continued to termination of the study period. Sixteen dogs were studied without ACTH. Six to 90 μCi of ^{125}I -iodocholesterol per kilogram of body weight were given intravenously to 13 dogs similarly treated with ACTH

and 15 dogs without ACTH. The total cholesterol administered in ^{14}C -dosed dogs was less than 1 mg and in ^{125}I -dosed dogs was 10–47 mg.

Scans were performed on eight dogs at 1–8 days after ^{125}I -iodocholesterol with the dogs under intravenous thiamylal and pentobarbital anesthesia in the prone position with a 5-in.-crystal photoscanner using a coarse, 3-in. focusing collimator. At the conclusion of the last scan on each dog, the animal was left in position and sacrificed by intravenous injection of 10–20 ml of a solution of sodium pentobarbital in isopropyl alcohol and propylene glycol*. With the aid of a narrow light beam attached to the collimator, the probe was centered over the adrenal area which had been visualized in the color dot scan obtained simultaneously with the photoscan. The adrenal area was then fixed in position by inserting probes through the posterior chest wall as close to the adrenal area as bony structures would permit at a measured distance from the center of the adrenal area. After the area of the adrenal and the probes had been exposed by dissection, the measured position of the adrenals in relation to the probes were projected onto the dot scan. After the development of the photoscan, it was superimposed on the dot scan. In addition, repeat scans were obtained after surgical excision of the adrenals in one dog maintained in the original scan position.

Radiolabeled cholesterol. The 4- ^{14}C -cholesterol was obtained from the New England Nuclear Corp., Boston, Mass. (60.9 mCi/mM dissolved in benzene). The benzene was evaporated, and the residue was dissolved in 90% ethanol to give a solution with a concentration of 100 or 200 $\mu\text{Ci}/\text{ml}$. Thin-layer

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* "Lethal" solution, Haver-Lockhart Laboratories, Kansas City, Mo.

chromatography using 95% methanol, mineral oil, and chloroform demonstrated a purity of greater than 97%.

The ^{125}I -19-iodocholesterol was synthesized (5) and dissolved in a 90% ethanolic solution with a concentration of 50–200 $\mu\text{Ci}/\text{ml}$.

Synthesis of ^{125}I -19-iodocholesterol. Figure 1 shows the structure of ^{125}I -19-iodocholesterol and 4- ^{14}C -cholesterol.

The ^{125}I -19-iodocholesterol was prepared from 19-iodocholesterol by isotope exchange. A solution of ^{125}I -NaI (5 mCi) was placed in a 25-ml round-bottom flask and the water removed by azeotropic distillation with benzene. A solution of 19-iodocholesterol (19-iodocholest-5-en-3 β -ol, 100 mg) in acetone (7 ml) was added to the flask, and the mixture was refluxed under an atmosphere of nitrogen for 4 hr. The solution was allowed to cool and poured into cold water. The resulting mixture was extracted with ether, and the combined extracts were washed with water and dried over anhydrous sodium sulfate. The ether was evaporated and the residue chromatographed over deactivated alumina. Elution with petroleum ether (bp 30–40): ether (1:1) gave ^{125}I -19-iodocholesterol (80 mg) with a specific activity of 28.25 mCi/mg (52% exchange). Thin-layer chromatography using chloroform:ethanol (1:1) gave a single spot (R_f , 0.66) coincident with the single radioactive peak appearing on the radiochromatogram.

Extraction and separation of radioactive products in the adrenal cortex. Total lipid from the adrenal cortex was extracted from both ^{14}C -cholesterol and ^{125}I -cholesterol-treated dogs with a 2:1 chloroform-methanol mixture (Folch procedure) (6). The chloroform extract was evaporated with a stream of nitrogen and the residue lipids fractionated by thin-layer chromatography on silica gel H. The solvent system of hexane, diethyl ether, and acetic acid (90:10:1 v/v) was used to separate lipids according to general class: phospholipids, sterols, fatty acids, triglycerides, and sterol esters. Inorganic ^{125}I -iodide was added to adrenal cortical tissue before extraction in a few of the studies to demonstrate complete recovery of inorganic iodide in the methanol phase and absence in the chloroform phase.

Radioassays. Upon termination of each dog study, 16 tissues were routinely removed (blood, adrenal, liver, bile, kidney, urine, urinary bladder, thyroid, thymus, fat, lung, heart, pancreas, intestines, spleen, muscle) cleaned of fat and extraneous material, and weighed. Routinely, duplicate samples of all tissues studied were processed, and more samples were obtained in tissues of special interest such as the adrenal. Adrenal cortex and medulla were separated.

With ^{14}C -labeled tissue, an effort was made to keep the weight of samples between 10 and 100 mg. After weighing, all of these specimens were placed in counting vials, digested in 0.3 ml 10% NaOH overnight and then heated for at least 30 sec in near-boiling water to complete the digestion. After cooling, three drops of 30% H_2O_2 were added for decolorization. Ten milliliters of a thixotropic liquid-counting system (7) were added and the radioactivity assayed in a Nuclear-Chicago (Mark I) liquid scintillation counter. Quench corrections were made using the external-standard, channels-ratio method. Results were expressed in dpm/mg, percent administered dose/gm of tissue*, and adrenal cortex-to-liver tissue ratios.

After the administration of ^{125}I -cholesterol, the tissues were similarly handled and counted in disposable plastic test tubes with the tissue volume

$$\begin{aligned} & * \% \text{ dose/gm calculated as follows:} \\ & \frac{\text{dpm/mg} \times 1,000 \times 100}{2.2 \times 10^6 \times \mu\text{Ci admin. dose}} \end{aligned}$$

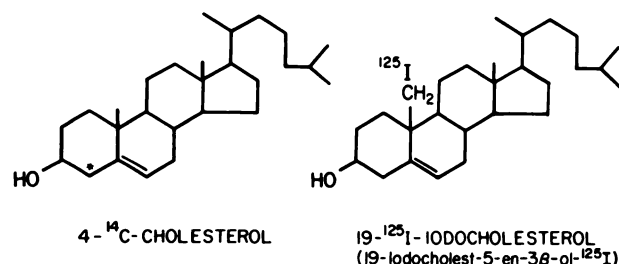


FIG. 1. Radiolabeled cholesterol formulas. Asterisk indicates position of ^{14}C .

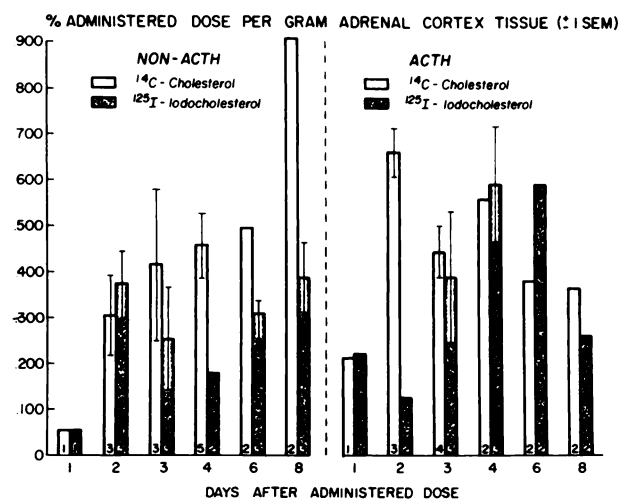


FIG. 2. Mean percent dose in adrenal tissue is indicated by bars. Standard error of mean is represented for intervals with three or more dogs. Number of dogs is indicated at base of each column. Adrenal gland mean weight with ACTH was 705 mg; without, 585 mg.

being maintained at 2 ml. Counting was done in an automated well counter and correction made for decay and counting efficiency. Standards of the original solutions were made and counted identically to the tissues. Counts were accumulated for a sufficient period of time to insure a statistical counting error of less than 5% and at least a 95% confidence level.

RESULTS

Although the lack of a minimum of three dogs at each interval between the administration of the tracer dose and the time of sacrifice does not permit dogmatic conclusions, certain trends are suggested by the data obtained.

Radioactivity concentrations in the adrenal cortex. The adrenal cortices of the ^{14}C -cholesterol-dosed dogs without ACTH appear to show a slow increase in mean cortical radioactivity concentration for the period of the study (Fig. 2). In contrast, the adrenal cortices of the ^{125}I -cholesterol dogs show no higher concentration of radioactivity at 8 days than at 2 days. The average radioactivity concentrations after ^{125}I -cholesterol was at a lower level than after ^{14}C -cholesterol at most intervals with the difference between these two groups becoming progressively greater to 8 days. With ACTH, the mean concentration of radioactivity in the adrenal cortex after ^{14}C appeared to plateau at 2 days and after ^{125}I at 4 days (Fig. 2).

Radioactivity ratios (adrenal cortex to liver). Both the ACTH- and nonACTH-stimulated ^{125}I -iodocholesterol dog groups attain higher mean adrenal-to-liver activity concentration ratios than the ^{14}C -cholesterol groups (Fig. 3). The ^{125}I -iodocholesterol-dosed dogs without ACTH attained mean ratios 2–3.5

times that of ^{14}C -cholesterol, and these ratios were not attained until the sixth to eighth days. With ACTH in ^{125}I -iodocholesterol dogs, mean ratios were 2.5–5 times greater than after ^{14}C -cholesterol, reaching these favorable levels by the third day. The highest mean ratio of 168 was seen in ACTH-treated ^{125}I -iodocholesterol dogs.

Results in other extra-adrenal tissues. All other tissues sampled showed the same or lower concentration of radioactivity than the liver after ^{125}I -cholesterol. To conserve space, only the adrenal-to-kidney ratios are presented in Figs. 4 and 5. Kidney was chosen because the ^{125}I radioactivity in kidney would be expected to be unusually high as a result of the excretion of the ^{125}I from ^{125}I -cholesterol. The high adrenal to extra-adrenal ratios seen in ^{125}I -iodocholesterol dogs appeared to be due to lesser initial radioactivity concentration and a more rapid clearance in extra-adrenal tissues. Figure 5 illustrates this difference in concentration between ^{14}C -cholesterol and ^{125}I -iodocholesterol in the kidney. With adrenocortical radioactivity of ^{125}I -cholesterol remaining at relatively high levels during the study, indirect evidence of rapid extra-adrenal clearance of ^{125}I -iodocholesterol is seen in the rapid excretion of ^{125}I in the urine and stool (Fig. 6). The 50% excretion level was noted within 3 days with ACTH and nearly reached that level in 6 days without ACTH. In contrast, the total-body half-time excretion for ^{14}C -cholesterol has been reported to be 62 days in dogs and 75 days in humans (8,9).

Adrenal cortex and bile radioactivity concentrations of ^{14}C -cholesterol were nearly the same both with and without ACTH (mean adrenal-to-bile ratios at < 5 days = 0.7 with and 0.9 without ACTH).

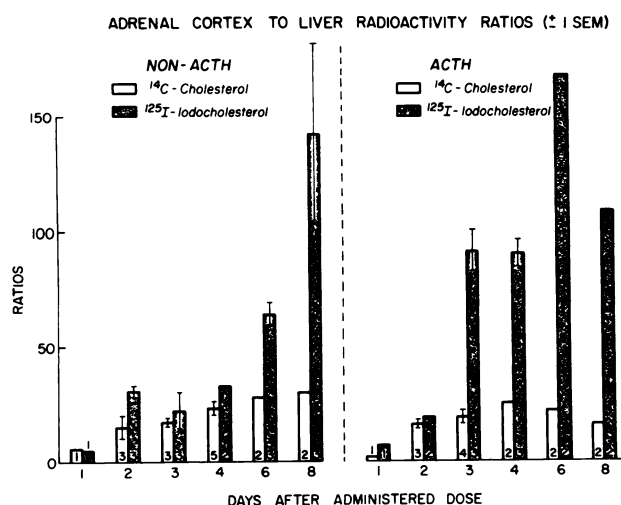


FIG. 3. Adrenal cortex-to-liver radioactivity ratios. SEM indicated as on previous graph.

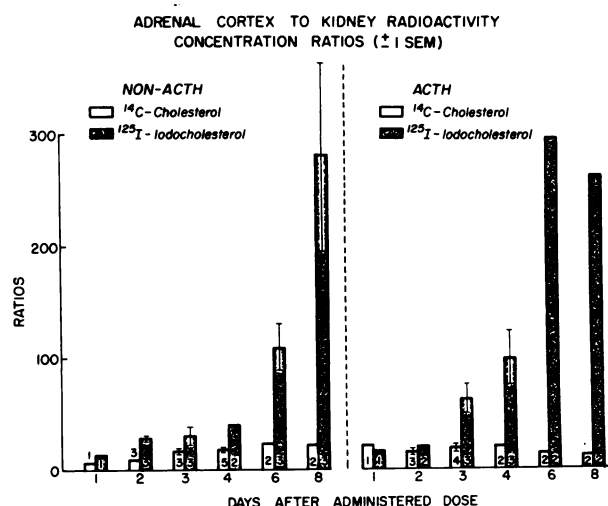


FIG. 4. Adrenal cortex-to-kidney radioactivity ratios. SEM as previously.

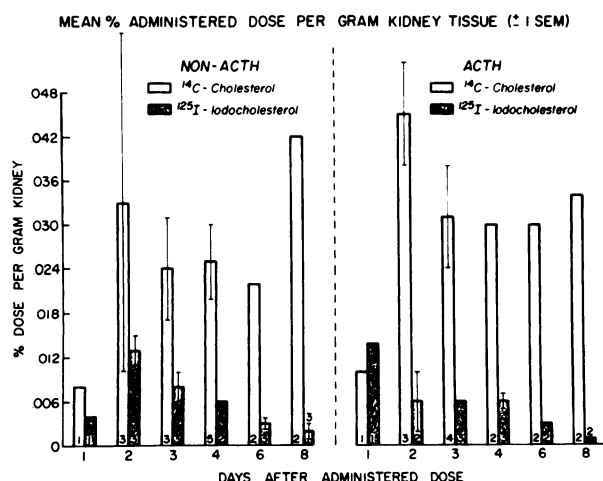


FIG. 5. Percent dose/gm kidney tissue. SEM as previously.

After ^{125}I -cholesterol, adrenal cortex to bile radioactivity concentration ratios were near unity at the first day but reached activity levels of 2–61 over the period of 2–8 days. The thyroidal concentration of radioactivity from ^{125}I -cholesterol exceeded that from ^{14}C -cholesterol by a factor of 2–100 times, despite the administration of 15 drops of Lugol's solution in drinking water each day from 5 days before dosing to the sacrifice of the dog.

Radioactive products in adrenal cortices. Adrenal cortical radioactivity in both ^{14}C - and ^{125}I -cholesterol-dosed animals was completely recovered in the chloroform phase, and none appeared in the methanol phase. This suggests the absence of any significant levels of free ^{125}I -iodide in adrenal tissue after ^{125}I -cholesterol administration. Thin-layer chromatography of the lipid fractions resulted in an 80–85% recovery of ^{14}C -cholesterol in the ester fraction. The remainder migrated as free cholesterol.

The distribution of radioactivity in the lipid extract from ^{125}I -cholesterol-treated dogs showed considerable variation. A significant portion (25–35%) always appeared with the cholesterol ester fraction. Small amounts (4–6%) of radioactivity migrated similarly to free cholesterol. A high, but variable, amount of radioactivity (15–40%) remained at the origin. Rechromatography of ^{14}C -cholesterol gave similar results in successive runs. However, the same procedure resulted in less consistency and significant variation with ^{125}I -cholesterol. Two-dimensional thin-layer chromatography of ^{125}I -cholesterol adrenal tissue, using the previously-mentioned solvent system first (see Methods), and ether, acetic acid and acetone (40:15:1.5) in the second system, resulted in 45% radioactivity in the cholesterol ester fraction.

The variability in distribution of ^{125}I radioactivity and the failure to migrate with lipids on rechroma-

tography is most likely the result of radiochemical instability of iodocholesterol during analysis. Nevertheless, there is little doubt that a portion of the radioactivity in the adrenal after injection of ^{125}I -iodocholesterol exists as iodocholesterol ester.

Scintillation scans. Table 1 presents the details on the eight dogs that were scanned. The adrenal scans of Dogs 1, 2, and 3 were negative; of 4, 6, 7, and 8, positive; of 5, equivocal. The dogs with positive scans differ from those with negative scans (with the possible exception of Dog 5) in that the positive scan dogs all received more than 300 μCi of ^{125}I , had a radioactive cholesterol "specific activity" of 13–53 μCi of ^{125}I /mg of cholesterol, and tissue concentrations of greater than 1.0 μCi /gm of tissue. It is of particular interest that in the most strikingly positive scan Dog 6 received the largest dose (923 μCi), had the highest tissue concentration of ^{125}I -cholesterol, and received the highest specific activity

19- ^{125}I -IODOCHOLESTEROL URINE AND STOOL EXCRETION IN 8 DOGS

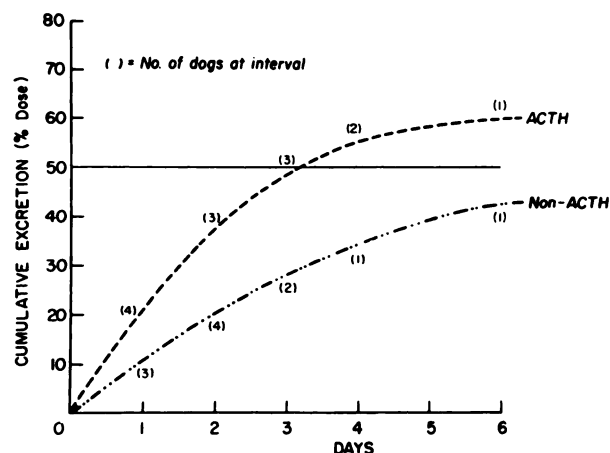


FIG. 6. Cumulative excretion without correction for physical decay.

TABLE 1. ^{125}I -19-IODOCHOLESTEROL DOG ADRENAL SCANNING DATA

Dog No.	Total dose (μCi)	Dose/kg (μCi)	Tissue conc. (μCi /gm)	Days after dose	Adrenals visualized
1	85	6	0.05	3	No
2	251	20	0.65	3	No
3	180	10	0.13	1	No
4*	304	30	1.22	2	Yes
5*	500	45	0.58	3	Yes?
6*	923	90	3.75	8	Yes
7	390	50	1.73	3	Yes
8	612	75	1.60	6	Yes

* ACTH treated.

material. The highest specific activity ^{125}I -cholesterol preparation to date was only one-third the specific activity of the ^{14}C -cholesterol used in these studies.

Figure 7 is a photograph (PA views) of three negative scans (Dogs 1, 2, and 3); Fig. 8 is a photograph of three positive scans (Dogs 7, 4, and 6); and Fig. 9 is a photograph of scans in Dog 8 showing the adrenals before and no adrenals after excision.

DISCUSSION

In the dog, the right kidney is more cephalad than

the left, and the adrenals are separate from, and medial to, the cephalad portion of the kidneys. The adrenals are anatomically as close as 0.5 cm, and our experience in scanning dog adrenals has shown that the adrenals must be separated by a distance of 1–2 cm to be distinguished as separate organs. In each instance when increased radioactivity was seen clearly to the left of the midline clear space, the measured distance from the needle inserted before the dissection revealed that this area of increased radioactivity on the left (Dogs 2, 3, and 4) corre-

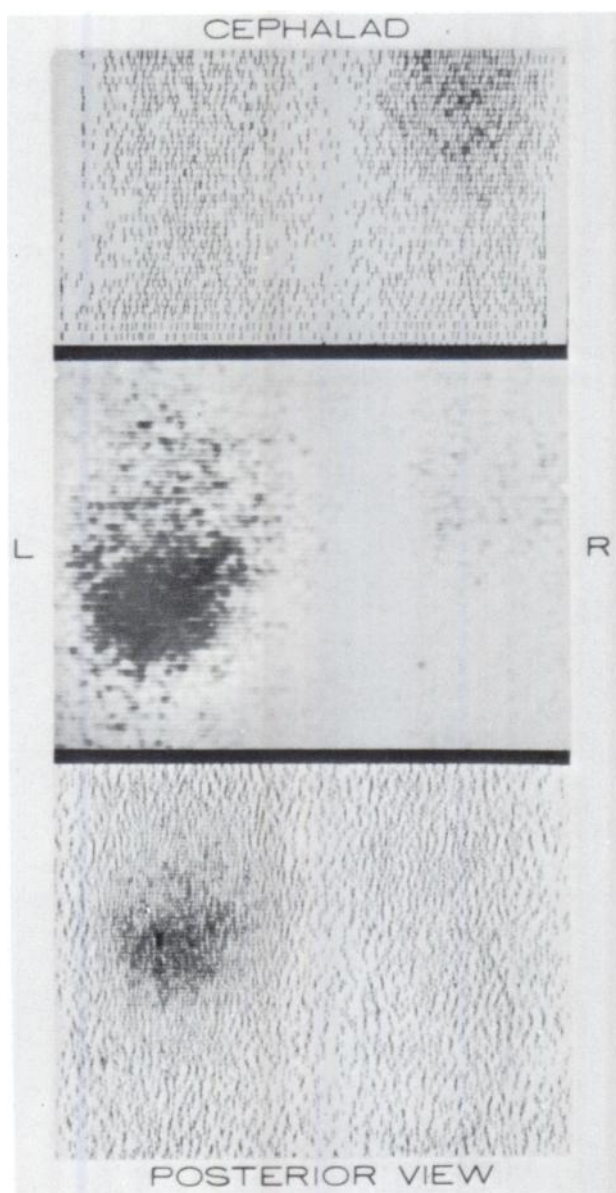


FIG. 7. Negative scans in Dogs 1, 2, and 3 (top to bottom). Increased concentration to left of midline clear space in Dogs 2 and 3 was in region of posterior tip of spleen. Increased activity to right of midline clear space in Dog 1 was lateral to adrenal gland.

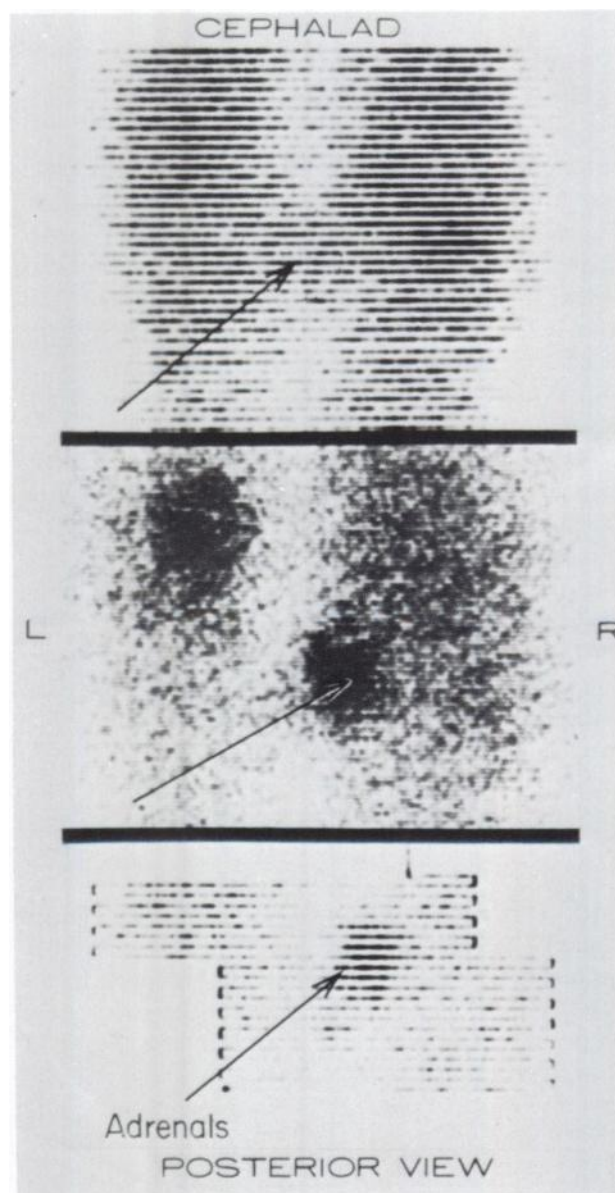


FIG. 8. Positive adrenal uptake of ^{125}I -cholesterol is indicated by arrows in photoscans of Dogs 7, 4, and 6 (top to bottom). Unusual activity to left of midline clear space in Dog 4 is posterior spleen tip.

sponded to the location of the posterior tip of the spleen located against the posterior abdominal wall on the left. Similarly, the increased area of radioactivity seen clearly to the right of the midline clear space in Dog 1 was cephalad and lateral to the adrenal.

The location of the "hot" spot produced by adrenal radioactivity was always within the midline clear space but small differences in the location of the adrenals on the scan, within the side-to-side axis, were easily explained by slight rotation of the dog during scanning because of the relatively pointed anterior chest wall. Other slight differences in the resolution of the images of the adrenals on successive scans can be accounted for by the fact that the adrenals were somewhat beyond the focal length of the collimator because of the prominence of the dorsal spine in the dog.

Our fractionation of 4- ^{14}C -cholesterol in the adrenal cortex showed 80–85% in the ester form. This agrees with the findings of many investigators who report the ester fraction to be 80–90% (1,2). The total cholesterol content of dog and human adrenals has been reported as 2–6% of the total percent wet weight (1,2). The 4- ^{14}C -cholesterol studies in the adrenal cortex, therefore, suggest that cholesterol is a logical agent to consider labeling with a gamma-emitting nuclide for adrenal scintiscanning.

Our results show that the dog adrenal cortex indeed does have the capability to achieve satisfactory radioactivity concentrations with ^{125}I -19-iodocholesterol similar to 4- ^{14}C -cholesterol both with and without ACTH. More surprisingly, the less "physiologic" radioiodinated analog of cholesterol appears to maintain high adrenal radioactivity. At the same time, the extra-adrenal radioactivity rapidly diminishes, resulting in higher target-to-nontarget ratios than can be attained with the "physiologic" ^{14}C -cholesterol. ACTH may allow these favorable ratios to develop two or three days sooner and also is associated with a more rapid excretion of the injected radioactivity. Scans of the dog were satisfactory for detecting the adrenal glands despite the small size (mean weight with ACTH = 705 mg, without = 585 mg) which is at the limits of resolution of conventional scintiscan equipment. Finally, it appears that a significant portion of ^{125}I -cholesterol behaves the same as ^{14}C -cholesterol and is probably stored as the ester. The iodocholesterol analog may be recognized as unphysiologic by extra-adrenal tissue and therefore not metabolically utilized. However, it appears that at least in the earliest step of steroidogenesis, the adrenal cannot distinguish between iodocholesterol and cholesterol as it concentrates ^{125}I -iodocholesterol equally as well as ^{14}C -cholesterol.

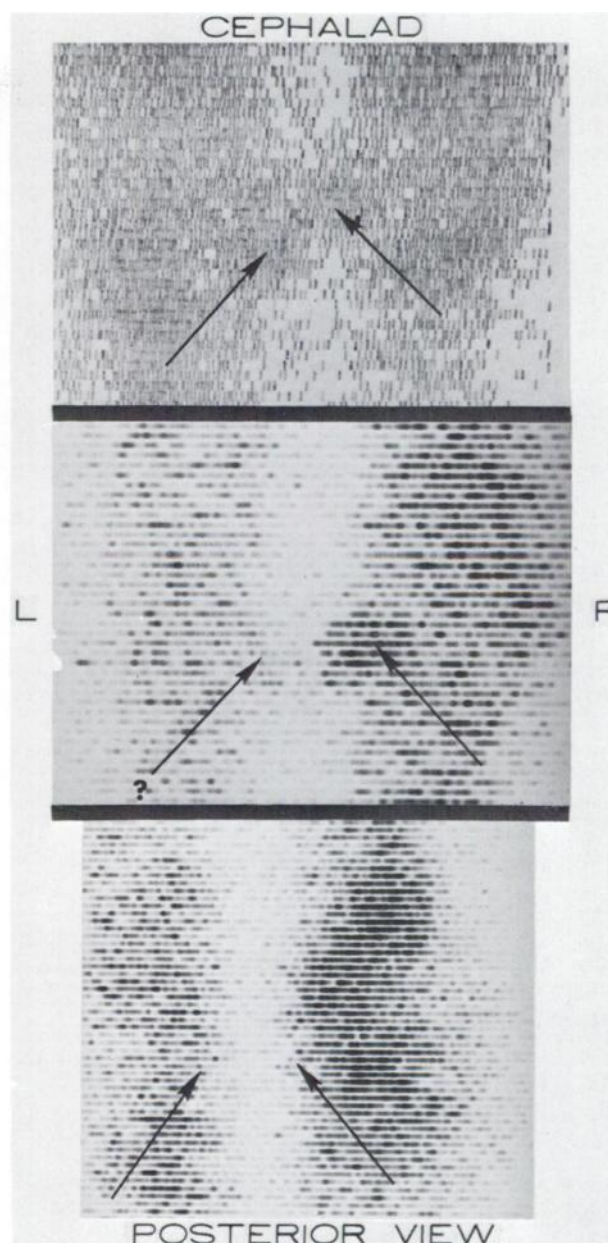


FIG. 9. Positive scans in Dog 8 with dot scan (top) showing two adrenals. Middle scan, taken later, shows only one definite adrenal on right. Lower scan shows absence of adrenal activity after excision (arrows).

We are presently exploring the possible diagnostic usefulness of this new compound in man.

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