Radioiodine Metabolism in the Beagle Dog: The Importance of Age and Mode of ^{131}I Exposure*† (34023)

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(Introduced by R. O. McClellan)

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The functional status of the thyroid, like other glands of internal secretion, may change with age depending on the functions it serves during the several epochs of life. The influence of this aging process on iodine metabolism has been investigated in several species of animals (1–5), but no reference to the dog appears in these reports. As the dog is frequently used for biomedical research, the importance of age in canine iodine metabolism needs quantitation. One objective of this investigation was to determine if measurable age-related differences occur in dog ^{131}I metabolism between 6 and 48 months of age. In addition ^{131}I metabolism following inhalation, oral, or intravenous mode of admistration was compared to assess the significance of exposure route. Although other route-effect studies have been conducted (6, 7), comparison of these three routes in any one study using the dog (or any other animal) has not been reported.

Because isotopes of iodine are predominant components of recently formed fission product mixtures, they can be involved in the potentially hazardous human exposure situations in the vicinity of uncontrolled releases from nuclear systems. The present studies, in addition to their significance related to a better understanding of iodine metabolism in the dog, yield data of use in assessing potential thyroid doses in the event a human population of differing ages is exposed to isotopes of iodine by various routes of entry into the body.

Materials and Methods. Thirty purebred beagle dogs, born and reared in the kennel facility at this laboratory, were selected for use in the age and route studies. Throughout the experiment, they were maintained on the standard colony diet, a mixture of commercial feed (Krumettes, Allied Mills, Inc., Chicago, Ill.), raw ground beef, a vitamin–mineral supplement (Vionate, E. R. Squibb and Sons, New York, N. Y.) and water. This diet provided a daily intake of approximately 700 μg of stable iodine, $\approx$85% of which came from the commercial feed and 14% from the vitamin–mineral supplement. Two weeks prior to administration of ^{131}I, the dogs were transferred from the kennel facility to individual metabolism cages (90 cm high $\times$ 75 cm wide $\times$ 75 cm deep) for acclimation to limited quarters and artificial lighting. During the next 2 weeks, they were trained to accept restraint in the inhalation exposure equipment, the whole-body counting box, and the thyroid monitor.

Table I shows the experimental design and the distribution of these 30 dogs by age, sex, weight, and route of ^{131}I administration. The 18 dogs exposed (unsedated) by inhalation were each given a single, 10-min exposure in an apparatus designed for "nose-only" exposures (8). The aerosol consisted of CsCl particles contaminated with sufficient carrier-free ^{131}I to yield initial body burdens of 100–300 μCi. Particle size measurements with a cascade impactor proved the aerosols to be distributed log normally with activity median aerodynamic diameters that ranged from 1.1 to 1.4 $\mu(\sigma g = 1.8)$. A small amount of ^{131}I as vapor was also present in the exposure air.

Intravenous injections were made in the

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TABLE I. Experimental Design for the Study of the Influence of Age and Route of Exposure on the Metabolism of ^{131}I in the Beagle Dog.

	No. of dogs[a]	Age (months)	Wt (kg)	Route of adm	Form
A. Age study	6	6	5.8–10	Inhalation	CsCl + $^{131}I^-$
	6	18	7.0–13	Inhalation	CsCl + $^{131}I^-$
	6	48	8.5–12	Inhalation	CsCl + $^{131}I^-$
B. Route study	6	18	6.0–11	iv injection	$Na^{131}I$
	6	18	7.0–13	Oral	$Na^{131}I$
	6[b]	18	7.0–13	Inhalation	CsCl + $^{131}I^-$

[a] Three males and three females per group.

[b] Data obtained from 18-month-old dogs in age study also used for route comparison.

cephalic vein and oral administration was made using a gelatin capsule. For both of these routes, the ^{131}I was in sterile physiologic saline solution, pH 7.4.

Immediately following administration of the ^{131}I and at selected intervals thereafter, the retained body ^{131}I burden was determined by whole-body counting using a system in which the dogs were supported 84 cm above two shielded 10.2 cm long $\times$ 2 cm diameter NaI(Tl) crystals laid on their side. The thyroid ^{131}I burden was determined with a specially designed thyroid monitor consisting of a 5.1 cm long $\times$ 5.1 cm diameter NaI(Tl) crystal shielded by a 5 cm thick cylindrical lead shield. During the counting period, the dog's neck rested on the end of this shield resulting in a source-to-crystal distance of 18 cm which could be varied by moving the crystal.

Whole-body and thyroid counting were performed on all dogs in the age and route studies at frequent intervals during the first 700 hr after ^{131}I administration. The counting data were corrected for physical decay, calculated as percentages of initial body ^{131}I burden, and plotted versus time to obtain thyroid ^{131}I uptake-retention and whole-body retention patterns.

An ancillary experiment, involving nine 8.6 – 10.8-kg beagles given ^{131}I intravenously, was performed to obtain early-time tissue distribution data and detection efficiency values for the thyroid monitor. These dogs were sacrificed in pairs at 1, 2, and 4 days and as a group of three at 8-days postinjection. The thyroid area was monitored immediately before and after sacrifice; the thyroid was dissected out and the area was monitored again to determine the contribution of extrathyroid activity. The thigh area of each dog was also monitored to determine the ^{131}I activity present in an area remote to the thyroid. Observed activity in the thigh area was $\approx$1.2 times that in the neck area after removal of the thyroid. For all subsequent thyroid monitoring the thigh area was monitored to facilitate a correction for extrathyroid ^{131}I in the neck.

The ^{131}I content in each of the nine excised thyroids was determined by gamma ray spectroscopy and related to the activity observed with the thyroid monitor just prior to sacrifice. Consistent results from all nine dogs yielded a mean observed counting rate of 10,200 cpm/μCi of ^{131}I (SD = 120 cpm/μCi ^{131}I). Complete necrotomies were performed on all dogs and all tissues were analyzed by gamma ray counting to determine the distribution of ^{131}I throughout the body at 1–4 days postinjection.

Results. Tissue distribution data, obtained from the nine dogs sacrificed at 1–8 days after intravenous injection (shown in Fig. 1), are expressed as percentage of sacrifice body burden to show the relative amounts of ^{131}I in the various tissues samples. The relative amount of ^{131}I in the thyroid increased during the first few days postinjection and then leveled off when it reached approximately two-thirds of the existing body burden. The extrathyroid ^{131}I was distributed throughout the body with a large fraction in the carcass (a composite sample of bone, muscle, and

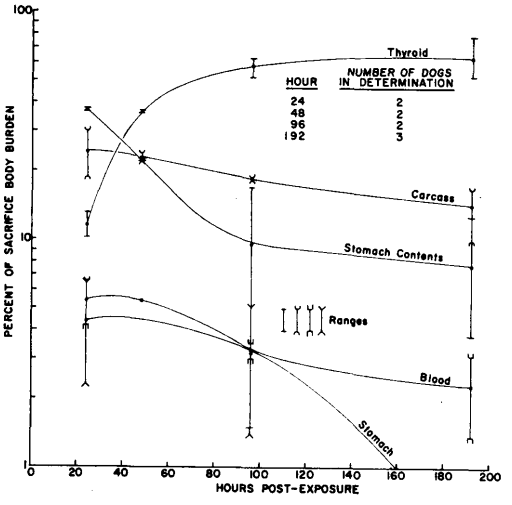

FIG. 1. Relative distribution of ^{131}I in the tissues of beagle dogs at various times after an intravenous injection of $Na^{131}I$ in physiological saline solution.

pelt) and smaller fractions associated with the stomach, stomach contents, and blood.

Although dogs in the age and route studies were not sacrificed, data from whole-body and thyroid counting showed a similar relationship between the amount of ^{131}I in the thyroid and whole body. Figure 2 shows the whole-body retention (R_t) and thyroid uptake-retention for one of the dogs in this experiment. The spread between the two curves indicates the amount of extrathyroid ^{131}I. The curve drawn through the whole-body retention data is a two-component exponential function, $R_t = C_1e^{-k_1t} + C_2e^{-k_2t}$, fitted to the datum points by computer using a least squares, nonlinear curve fitting program. Parameters of this two-component equation were compared for all dogs in the experiment. The bottom curve, representing uptake and retention of ^{131}I by the thyroid, was fitted by eye to the data points. For comparison, three parameters were used to describe important areas of this curve: the time to 90% maximum uptake (an indicator of the rate of uptake), the maximum uptake, and the biological half-life of ^{131}I in the tyyroid following maximum uptake. In some dogs, there was an increased rate of loss from the

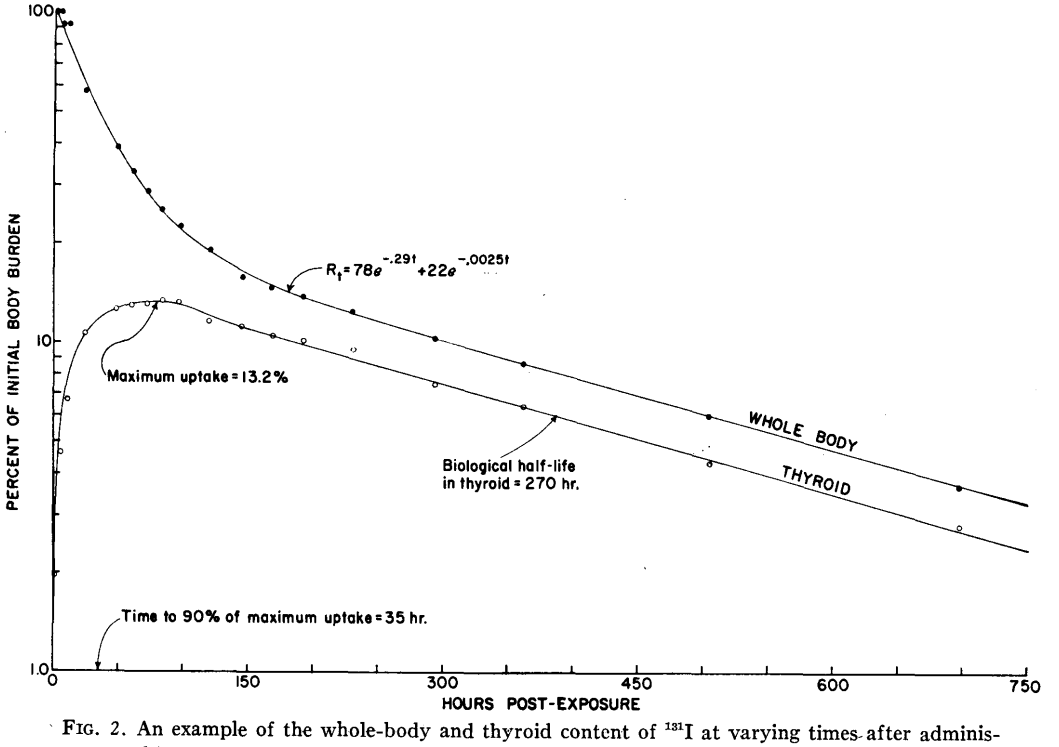

FIG. 2. An example of the whole-body and thyroid content of ^{131}I at varying times after administration of ^{131}I to a dog. The parameters selected for comparison among the various age and route groups are noted.

TABLE II. Thyroid-Uptake Retention and Whole-Body Retention of ^{131}I Following Inhalation of ^{131}I by Dogs in the Age-Effect Study.

	Age of dogs		
	6	18	48
Maximum thyroid ^{131}I uptake (%IBB)[a]	11 ± 2[b]	12 ± 3	13 ± 5
Time to 90% of maximum thyroid ^{131}I uptake	34 ± 9	42 ± 10	34 ± 9
Half-life of thyroid ^{131}I (hr)	250 ± 97	220 ± 57	260 ± 52
First component intercept C_1 (%IBB)	81 ± 6	77 ± 5	87 ± 4
Half-time of first component (hr)	24 ± 4	29 ± 18	30 ± 18
Second component intercept C_2 (%IBB)	19 ± 7	22 ± 6	17 ± 3
Half-time of second component (hr)	230 ± 85	260 ± 33	280 ± 27

[a] IBB = initial body burden.

[b] Mean values ± SD.

thyroid for a short period of time soon after reaching maximum uptake. This resulted in a slight hump in the curve (Fig. 2) before the straight line exponential loss began. Biological half-lifes for ^{131}I reported here refer to the slope of this curve beyond the hump.

Mean values for the seven parameters from the three groups in the age study are presented in Table II with their corresponding standard deviations. The mean maximum uptake of ^{131}I by the thyroid ranged from 11 to 13% of the initial body burden and was 90% complete by a mean of 34–42 hr after administration of the isotope. The exponential loss of ^{131}I from the thyroid after maximum uptake corresponded to a mean biological half-life of 220–260 hr. The similarity in all dogs between the second component half-time for whole-body retention and the thyroid biological half-life suggested that the rate of ^{131}I secretion by the thyroid approximated the rate of ^{131}I excretion from the body for all times following maximal uptake. The large standard deviation values attested to the considerable amount of variability among dogs in each group.

These results failed to demonstrate any statistically significant age-related effects on ^{131}I metabolism in the beagle dog for ages between 6 and 48 months. An analysis of variance showed, at a 95% confidence level, that these dogs could collectively be considered as samples from one population with a single mean value for each of the parameters investigated. Similar data from the route study are given in Table III. Route-related effects on ^{131}I metabolism in the 18-month-old beagle dogs were not detected among the inhalation, oral or intravenous injection groups when an analysis of variance was performed at a 95% confidence level.

Discussion. The dietary iodine intake of the dogs studied was ≈700 μg/day, a level twice that recommended for the adult dog (breed unspecified) by the NAS-NRC Committee Report on the Nutrient Requirements of the Dog (9). Consideration of the inverse relationship between excess dietary iodine and the maximum percentage uptake of ^{131}I by the thyroid suggested that the values observed in this study might be lower than those of beagle dogs maintained on lower dietary iodine levels. In this context, Toft *et al.* (10) observed that dogs fed 450 μg of iodine/day had maximum thyroid ^{131}I uptakes of 10% at 2 days after ^{131}I administration whereas dogs fed 50 μg of iodine/day had corresponding ^{131}I uptakes of 72%.

A period of elevated thyroid function has been observed in the very young of many animals (11–15), coincidental with stages of rapid growth. It is during this time that a number of age-related differences are noted in the iodine metabolism. That the iodine metabolism did not noticeably differ among dogs ranging from 6 to 48 months old in this study may be related to the fact that the 6-month-old dogs had already completed about four-fifths (8 kg/10 kg) of their expected adult growth. Gilmore *et al.* (16), reported a general increase in the diameter of the canine thyroid follicle up to 4 months of age;

TABLE III. Thyroid-Uptake Retention and Whole-Body Retention of ^{131}I for 18-Month-Old Dogs in the Route-Effect Study.

	Route of adm		
	Inhalation	Intravenous injection	Oral
Maximum thyroid ^{131}I uptake (%IBB)[a]	12 ± 3[b]	13 ± 2	13 ± 3
Time to 90% of maximum thyroid ^{131}I uptake	42 ± 10	39 ± 13	41 ± 6
Half-life of thyroid ^{131}I (hr)	220 ± 57	310 ± 67	250 ± 69
First component intercept C_1 (%IBB)	77 ± 5	76 ± 15	80 ± 10
Half-time of first component (hr)	29 ± 18	20 ± 3	22 ± 8
Second component intercept C_2 (%IBB)	22 ± 6	24 ± 6	23 ± 6
Half-time of second component (hr)	260 ± 33	250 ± 73	260 ± 80

[a] IBB = initial body burden.

[b] Mean values ± SD.

a larger thyroid in the young, in terms of grams per kilogram of body weight was noted as suggesting an early phase of elevated activity. It appears that if age-effects are to be demonstrated, perhaps selection of younger dogs in the neonatal to 4 month age range may be in order.

The transport of iodine to the thyroid from various portals of entry could be influenced by the availability of iodine to the blood stream. In contrast to intravenous injection, the oral and inhalation routes involve passage of iodine across an epithelial boundary. In a study dealing with the kinetics of ^{131}I passage through the respiratory mucosa of the monkey, Perrault *et al.* (17), found that the diffusion time was brief, 2–10 min. They concluded that inhalation of iodine as a vapor equaled an intravenous injection of the isotope. In humans, Morgan *et al.* (18), using methyl iodide labeled with ^{131}I, also observed that pulmonary retention of soluble iodine was short, approximately 2 sec. The failure of our study to demonstrate route-related effects may be explained by such extermely short pulmonary retention times and the solubility of the iodide ion in body fluids.

For persons interested in hazard analysis, the question of prime interest is "Was there a significant difference in the absorbed dose to the thyroid for dogs in the different experimental groups?". The parameters discussed to this point all relate to the absorbed dose but none by itself gives an accurate assessment of dose. Therefore, average cumulative absorbed β dose to the thyroid were calculated for the first 32 days for each dog using the following equation:

$$\text{rads}_\beta = \frac{51.2\,\bar{E}_\beta A_0}{W} \int_0^t T(t)\,dt,$$

where: 51.2 = (dis/MeV) (g/μCi) (rads/day); $\bar{E}_\beta$ = average β energy of ^{131}I, 0.187 MeV; A_0 = initial body burden in μCi; W = thyroid weight (g); and $T(t)$ = thyroid ^{131}I burden expressed as a fraction of A_0.

The expression $A_0 \int_0^t T(t)dt$ was evaluated graphically by plotting on linear graph paper μCi in the thyroid uncorrected for physical decay against time and determining the area under the curve through 32 days postexposure with a planimeter. Since these dogs were not sacrificed, it was necessary to estimate thyroid weight using a ratio of thyroid weight to whole-body weight (7.2×10^{-5}) determined from 75 dogs sacrificed at this laboratory at an age of between 400 and 900 days.

Radiation doses to the thyroid varied from 130 to 1700 rads mainly because of differences among dogs in initial body burdens. The absorbed doses were normalized by expressing them as rads per microcurie of initial body burden and the resulting mean values are presented in Table IV. If the gamma ray component were also considered, the results would be $\approx$10% higher. An analysis of variance performed on all five groups of dogs

TABLE IV. Radiation Dose to the Thyroid of Beagle Dogs during the First 32 Days Following Inhalation, Ingestion, or Intravenous Injection of ^{131}I.

Age of dogs (months)	Av (rads/μCi of IBB[a])	SD
A. Inhalation		
6	4.4	1.4
18	6.3	1.7
48	6.7	2.0
B. Intravenous injection		
18	6.0	1.5
C. Oral administration		
18	5.5	1.6

[a] IBB = initial body burden.

indicated that, at a 95% confidence level, similar thyroid doses per microcurie were experienced by all dogs in this experiment regardless of age or route of administration. These results are in good agreement with results for the individual parameters selected for study.

Summary. Seven parameters associated with ^{131}I whole-body retention and thyroid uptake-retention were chosen to characterize iodine metabolism in the beagle. No statistically significant differences in these parameters were observed in groups of beagle dogs ranging in age from 6 to 48 months. The 6-month-old dogs may have been too old to demonstrate a period of elevated thyroid function such as that reported for several other species. The influence of the mode of administration of ^{131}I on the resulting iodine metabolism was also investigated. Exposure of 18-month-old dogs to ^{131}I by the oral, inhalation, or intravenous injection routes produced no statistically significant differences in ^{131}I metabolism, probably because of extremely short pulmonary retention times and the solubility of the iodide ion in body fluids. Absorbed doses to the thyroid for dogs in this investigation ranged between 130 and 1700 rads. When these doses were expressed as rads per microcurie of initial body burden, an analysis of variance showed that similar thyroid doses per microcurie administered were experienced by all dogs in the experiment regardless of age or route of ^{131}I exposure. The average dose administered was 5.8 rads/μCi.

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