

Iodine Absorption, Excretion, Recycling, and Tissue Distribution in the Dairy Cow¹

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ABSTRACT

Research on iodine metabolism was reviewed with special reference to cattle and milk secretion. Iodine metabolism in the fetus and thyroid activity as related to milk secretion and iodine feeding have also been considered. Between 70 and 90% of dietary iodine is absorbed directly from the bovine rumen, reticulum, and omasum. In the abomasum, rate of iodide secretion is approximately 18 times the rate of absorption. Circulating thyroxine is not secreted into the abomasum but enters the small intestine in the bile. Most of the iodide secreted into the abomasum is reabsorbed from the small and large intestines; absorption of thyroxine averages less than 10%. The thyroid usually contains an amount of iodine equal to the daily dietary intake; extrathyroidal tissues concentrate only .006 to .04% as much radioiodine per unit weight as the thyroid. At normal iodine intake (<10 $\mu\text{g}/\text{kg}$ body weight daily), iodine losses average 30% of the daily intake in feces, 40% in urine, and 8% in milk. Milk iodine is influenced by amount and chemical form of dietary iodine, stage of lactation or milk yield, seasonal effects, goitrogens, and thyroid status. Cows secrete less iodine into milk than most other species and have an efficient iodine recycling system via the gastrointestinal tract which conserves iodine and can protect them against low dietary iodine.

INTRODUCTION

Iodine deficiency is a geographical problem (106) where feeds and water are low in iodine. Usually the first obvious sign of insufficient iodine in cattle diets is the birth of goitrous calves (46, 48). Milk yields of cows in endemic goiter areas (75) or of cows fed goitrogenic rations (48) have been improved by supplying supplemental iodine. Recommended iodine contents in ration dry matter for mature dairy cows have been set from .6 ppm (106) to .8 ppm (20), which result in 9 to 12 mg for a 500 kg cow consuming 15 kg dry matter daily. According to Bustad and Fuller's (23) estimates on the basis of thyroxine secretion rate (TSR) and radioiodine metabolism data, iodine requirements of a 500 kg cow would be 5.5 to 11 mg daily. British Agricultural Research Council recommends increasing the allowance to 30 mg/day (an equivalent of about 2 ppm in feed dry matter) when goitrogens are present (20).

For prevention or systemic treatment of mycotic infections in cattle (64, 84), iodine has been fed much above nutritional requirements. Therapeutic amounts of iodine markedly raise serum inorganic iodine (64, 80, 92, 109) and presumably, also body-tissue iodine. Recommended daily iodine intakes range from prophylactic 40 mg (84) to therapeutic doses of over 2000 mg (80). Iodine toxicity symptoms occurred in calves when dietary iodine concentrations reached 50 to 100 ppm, equal to about 500 mg I/day for 200 kg calves (109). Diets supplemented with 10 ppm increased serum iodine about 10 times over controls.

Metabolism of iodine has been studied extensively in laboratory animals (22, 41, 42). These investigations have established much of the general knowledge of iodine metabolism in mammals and have suggested the most fruitful areas of study with dairy cattle. Iodine metabo-

Received December 13, 1974.

¹ Research sponsored by the U. S. Atomic Energy Commission under Contract No. AT-40-GEN-242 with the University of Tennessee.

lism of dairy cattle has been the subject of numerous investigations, many of which have been reported or summarized in recent reviews (29, 30, 45, 133). The purpose of this article is to review iodine retention and utilization by dairy cattle as influenced by absorption, recycling, and excretion. Because of important differences among species (Table 1), this review is limited primarily to research with dairy cattle.

Model: Iodine Metabolism in Lactating Cattle

Results of many investigations suggest the iodine metabolism model in Fig. 1. A simplified model of iodine transport in dairy cattle is in Fig. 2; this model, suitable for compartmental analysis, was designed according to principles of biological research by Berlin et al. (12). Data from 18 nonpregnant Holstein cows in the 3rd mo of lactation (unpublished)² were used to derive differential equations from this model by least squares. Data were obtained by described procedures (86, 90, 92, 94) following intravenous administration of Na¹³¹I to the cows. This model was regressed to serial measurements of ¹³¹I content of plasma, thyroid, milk,

feces, and urine simultaneously; that is, the five data sets were considered together in finding a least-squares fit of the model to the data. The least-squares regression was based on a general nonlinear regression method described by Snedecor and Cochran (122). In calculating the model, it was assumed that 80% of the milk in the mammary gland was released at each milking. Regression curves and data are in Fig. 3. The total amount of iodine transferred is a function of the amount in the compartment of origin and the transfer rate. The rate constants are in Table 2. The individual compartments of Fig. 1 and 2 are considered separately in the following sections.

Gastrointestinal Tract

Absorption. Comparison of rate constants (Table 2) shows that rate of iodine flow from the gastrointestinal tract to central pool (absorption) was less than half the rate from the central pool to the GI tract (secretion). Net absorption of iodine occurs because of the much larger amount of iodine in the GI tract than in the central pool (or plasma) (Table 3). Between 70 and 80% of the daily iodide intake is absorbed directly from the rumen and an additional 10% from the omasum (10). Higher rates of absorption from the rumen which had

² These data are available on request to the authors.

TABLE 1. Species comparison of iodine secretion in milk.

Species ^a	Milk radioiodine	Milk/plasma radioiodine	Milk-bound radioiodine
	(% of dose) ^b	(Ratio)	(% of total milk radioiodine)
Cow (8, 19, 30, 39, 66, 67, 68, 72, 73, 86, 88, 91, 92, 95, 96, 105, 121)	8 (1-30) ^c	< 1:1-4:1	10
Goat (1, 26, 31, 36, 69, 117, 141)	22 (6-54) ^d	5:1-16:1	10
Sheep (24, 30, 35)	39 (30-60) ^e	29:1-92:1	...
Dog (135)	11 ^f	29:1-60:1	30-60
Rat (41, 42, 113)	40 (15-50) ^g	...	65-86

^aNumbers in parentheses are references.

^bTracer amounts of radioiodine. Results are comparable whether radioiodine is administered orally or intravenously, so both dosing methods are included.

^cAverage (range) percent of single dose in 6 to 10 days and of daily dose in milk daily.

^dPercent of single dose in 50 h to 6 days and of daily dose in milk daily.

^ePercent of single dose in 6 to 15 days and of daily dose in milk daily.

^fPercent of single dose in 12 h.

^gPercent of single dose in 8 to 24 h.

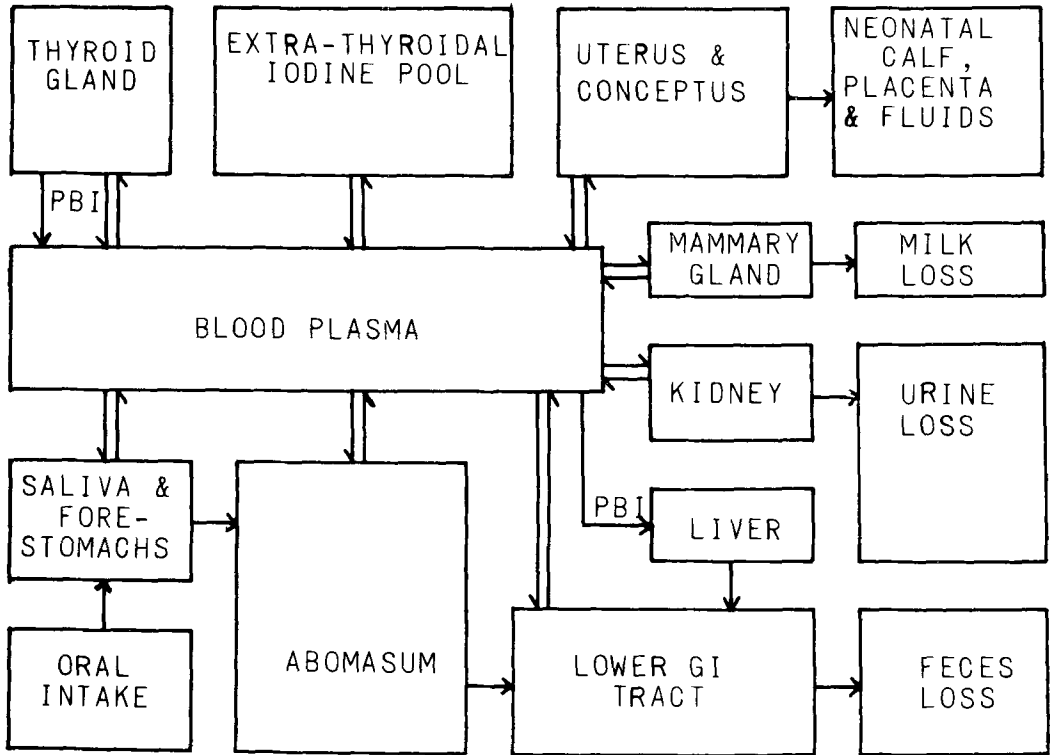


Fig. 1. Schematic diagram of the major physiological compartments involved in the recycling of iodine in the cow.

been reported (86) were caused by radioactivity-counting problems and have not been repeated in later experiments. Absorption from rumen may be influenced by the chemical form of dietary iodine. Iodine in compounds which are relatively insoluble in rumen fluid may await passage into the abomasum for absorption (104). Certain other forms of iodine, notably diiodosalicylic acid (5, 6, 86) and milk protein-bound iodine (PBI) (128), may be absorbed from the rumen in combinations metabolized differently from iodide. These differences were evident as reduced thyroid uptake and increased urinary excretion of iodine given in the organic forms. Differences in metabolism of iodide and milk PBI were consistent only when the two forms initially were placed in the rumen (128). Differential absorption posterior to the abomasum might have been reduced by gastric secretion of iodine absorbed earlier and by peptic digestion. Nutritional availability of supplemental iodine from different compounds has been reviewed by

Ammerman and Miller (2).

Abomasal concentration and secretion of iodine. Iodine is secreted by the chief and mucosal cells of the gastric mucosa (83). The abomasum is a major site for reentry of circulating iodine into the bovine digestive tract (10). Gastric concentration of iodide from plasma exceeded that of chloride in calves given daily doses of both ^{131}I and ^{36}Cl (85). Although ^{36}Cl in plasma was 6.5 times higher than ^{131}I , in the abomasum ^{131}I was 3.1 times higher than ^{36}Cl . During the first 6 h after administration to mature cows, over 65% of intravenously injected radioiodide was recovered in material draining from cannulae placed in ligated abomasa (126). Apparently only iodide is secreted into the abomasum since less than 5% of ^{131}I given as labeled thyroxine was recovered in abomasal drainage during the first 6 h (unpublished).

Radioiodine absorption and secretion by the abomasum were measured simultaneously in six steers fitted with abomasal cannulae (127).

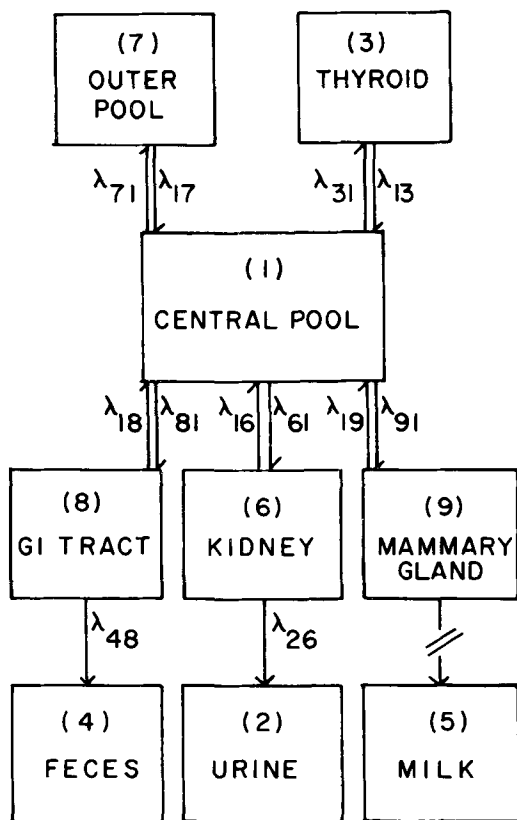


Fig. 2. Compartmental model of iodine transfer in dairy cows. λ subscript numbers correspond to numbers arbitrarily assigned to compartments. The first digit refers to the compartment of deposit, the second to compartment of origin.

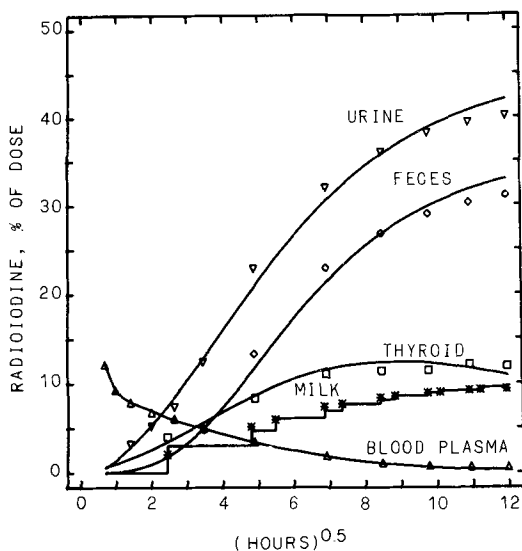


Fig. 3. Radioiodine clearance from blood plasma, uptake by thyroid gland, and cumulative excretions in milk, urine, and feces of Holstein cows during 144 h after single intravenous ^{131}I doses. Plasma by regression constituted $37.1 \pm 1.0\%$ of the central pool.

Differential equations derived from the transport model in Fig. 4 (unpublished) were simultaneously regressed to data sets obtained from abomasal and from intravenous administration of radioiodine. The model was fit to observations of abomasum, excreta, omasum, and rumen contents at slaughter (7 h) as well as

TABLE 2. Rate constants describing movement between compartments in the model of iodine metabolism of dairy cattle (Fig. 2).

Compartments and direction	λ	SE
	(per hour)	
λ_{61} Central pool to kidney	1.80 ^a	.07
λ_{16} Kidney to central pool	1.57	.05
λ_{31} Central pool to thyroid	.0258	.0013
λ_{13} Thyroid to central pool	.00502	.00091
λ_{71} Central pool to outer pool ^a	.837 + .172 λ_{61}	...
λ_{17} Outer pool to central pool	.645	.066
λ_{91} Central pool to mammary gland	.173	.003
λ_{19} Mammary gland to central pool ^a	.576 + 8.074 λ_{91}	...
λ_{81} Central pool to GI tract	.145	.039
λ_{18} GI tract to central pool	.068	.016
λ_{26} Kidney to urine ^a	.14515 - .05126 λ_{61}	...
λ_{48} GI tract to feces	.0321	.0077

^aLinear dependencies were estimated from the behavior of these parameters in the neighborhood of the least-squares best fit.

TABLE 3. Comparison of distributions of radioiodine in blood plasma and gastrointestinal (GI) tract contents of yearling calves killed 24 h after the last of seven oral or subcutaneous doses.^a

Location	Type of dosing	
	Subcutaneous	Oral
	— (% of daily dose) —	
Blood plasma	15.0 ± 1.9 ^b	14.4 ± 1.1 ^c
Rumen-reticulum	6.4 ± 1.0	34.2 ± 3.6
Omasum	1.2 ± .2	9.6 ± 1.1
Abomasum	9.1 ± 1.8	6.8 ± .7
Small intestine	7.8 ± 1.8	9.1 ± .8
Large intestine	8.9 ± 1.6	16.6 ± 1.2
Total GI tract	33.4	76.3

^aJ. K. Miller (unpublished).

^bMean ± SE for six 202-kg calves.

^cMean ± SE for five 240-kg calves.

serial measurements of radioiodine contents of plasma and abomasal drainage. To give proper weight to data points, a log-transformation was used in the analysis. Regression curves and data are in Fig. 5 and Table 4. Although iodine was absorbed from abomasal contents (87), the rate constant for secretion of iodine from the central pool into the abomasum was 18 times the rate for the reverse direction (Table 5).

Table 6 shows (a) that high dietary iodine (100 and 1000 mg/day) did not reduce abomasal radioiodine secretion (126, unpublished) but effectively blocked thyroid uptake and (b) that thiocyanate reduced radioiodine uptake by both the thyroid and abomasum (103). Lewitus and Shaham (77) consider the gastric stomach to be a reservoir which concentrates plasma

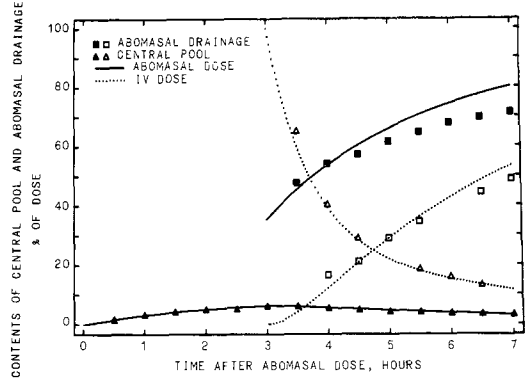


Fig. 5. Radioiodine in central pool and abomasal drainage after abomasal infusion of ¹²⁵I and intravenous injection of ¹³¹I in steers fitted with abomasal cannulae. Abomasal dose was given at zero time; at 3 h, the intravenous dose was given and the abomasal cannulae were opened. Plasma was found by regression to constitute 17.4 ± 2.2% of the central pool.

iodine and then gradually returns it to plasma for uptake by the thyroid. Initial plasma radioiodine and urinary losses were increased by anions which inhibit iodine concentrating systems (69, 88), including the abomasum (103). The iodine concentrating action of the abomasum may promote conservation of iodine by transferring it from vascular to extravascular compartments, thus preventing its excessive loss in urine.

Other gastrointestinal tract iodine recycling. Radioiodine, whether given orally or parenterally, has been found in rumen contents of 220-kg calves at slaughter 24 h after the last of seven daily doses (Table 3). Presence of rumen iodine after subcutaneous administration shows that iodine enters the rumen directly via saliva and/or secretion through the epithelium. Only 6.4% of the daily subcutaneous dose was recovered from the rumen 24 h after last administration as compared with 9.1% in the much smaller volume of the abomasum. Saliva/plasma iodine concentration gradients averaged only .7 in calves (as compared with 30 to 40 in man (22)). Radioiodine concentration in rumen contents was about half that in blood plasma, indicating that forestomach fluids do not concentrate iodine in the bovine.

Some of the thyroxine from plasma constantly is being degraded or conjugated in the liver and secreted via bile. Consequently, 30

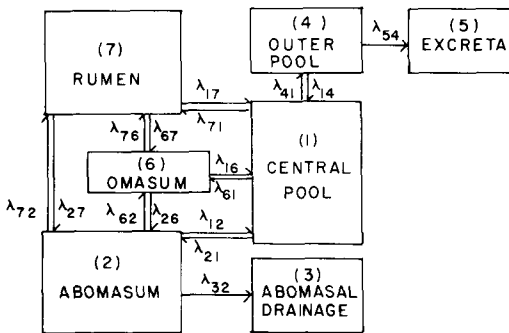


Fig. 4. Compartmental model of iodine transfer in steers fitted with abomasal cannulae.

TABLE 4. Observed and calculated regression values of radioiodine contents in various compartments of the model of iodine secretion by the bovine abomasum (Fig. 4) at slaughter.

Compartment	Dosing method			
	Intravenous		Abomasal	
	Observed	Calculated	Observed	Calculated
	(% of dose)			
Rumen	3.0	3.1	4.0	4.1
Omasum	3.1	3.1	2.1	2.1
Abomasum	14.4	13.0	6.7	6.9
Excreta	.49	.57	.17	.15

min after intravenous injection of labeled thyroxine, the highest ^{131}I concentrations in bovine gastrointestinal tract contents were in the anterior one-sixth of the small intestine (10). Recovery of ^{131}I from cannulated bile ducts of two calves during 24 h after injection intravenously of labeled thyroxine averaged 24.3%, and fecal ^{131}I from six intact calves averaged 18% of the dose (142). Considering the delay in passage from bile duct to rectum, we assume that most of the iodine originating from thyroxine passes through in a bound form.

About 10% of thyroxine added to the digestive tract may be reabsorbed as measured by (a) elevation of plasma PBI from orally given as compared with intravenously administered thyroxine (99), (b) the amount of thyroxine given orally as compared with that given intravenously which inhibited thyroidal ^{131}I release (11), and (c) the slow increase in plasma

radioactivity after oral dosing with ^{131}I -labeled thyroxine (112). Percentage absorption of thyroxine from thyroglobulin or thyroprotein was similar to that of crystalline thyroxine (99).

Fecal excretion of iodine. Cumulative fecal excretion of ^{131}I during 6 days after intravenous administration of Na^{131}I averaged 32% of the dose for 18 cows (Fig. 3). This is within the range of 13 to 33% (average 22%) of single doses over 7 days (6, 66, 68, 72, 91, 92, 94, 105) and within the range of 24 to 46% (average 30%) daily of doses administered each day (67, 72, 86, 96). Fecal radioiodine during 7 days after single intravenous administration of labeled thyroxine averaged 52% of the dose (86, 94, 96). The appearance in feces of approximately twice as much radioiodine given as thyroxine as compared with that given as iodide indicates that hormonal iodine secreted into the digestive tract is an important source

TABLE 5. Transfer coefficients describing movement between compartments in the model of iodine secretion by the bovine abomasum (Fig. 4).

Compartment and direction	λ	SE
λ_{21} Central pool to abomasum	.632	.048
λ_{12} Abomasum to central pool	.0341	.009
λ_{32} Abomasum to abomasal drainage	.741	.045
λ_{41} Central pool to outer pool	.467	.171
λ_{14} Outer pool to central pool	.574	.161
λ_{54} Outer pool to excreta	.0078	.00204
λ_{16} Omasum to central pool	.225	.124
λ_{62} Omasum to abomasum	.796	.335
λ_{26} Abomasum to omasum	.201	.076
λ_{72} Abomasum to rumen	.0963	.0219
λ_{27} Rumen to abomasum	.386	.126
λ_{17} Rumen to central pool	.065	.0987

TABLE 6. Effect of dietary iodine and thiocyanate on thyroid radioiodine uptake and recovery of radioiodine in abomasal drainage during 6 h after intravenous administration.

Treatment	Material	
	Thyroid	Abomasal content
	(% of dose)	
Control ^a	1.7	66.7
100 mg I/day ^{a,b}	.13	63.6
1000 mg I/day ^{b,c}	.0002	69.6
10 g NaSCN/day ^{c,d}	.57	26.0

^aAverage of three animals.

^bIodine supplements fed daily for at least 14 days beginning before radioiodine dosing.

^cAverage of four animals.

^dThiocyanate fed beginning 2 days before radioiodine dosing.

of fecal iodine. However, iodine from inorganic sources also is excreted in feces since one-third of the total excretion during 7 days after a single radioiodide dose can be recovered during the first 24 h, which is insufficient time for formation and release of labeled thyroid hormone in cattle (6). Most of the radioiodine in feces was in a bound or nonexchangeable form (85). Total fecal iodine increased in almost direct proportion to increased supplemental stable iodine (92).

Urinary Excretion of Iodine

Cumulative urinary ¹³¹I excretion by 18 cows averaged 40% of a single intravenous Na¹³¹I dose in 6 days (Fig. 3). Within the normal dietary iodine intakes for cattle (<10 µg/kg body weight per day), reports of urinary excretion of radioiodine given as iodide averaged 49% (range 34 to 73) of a single dose during 7 days (6, 66, 68, 72, 91, 92, 94, 105) and 30% daily of a daily dose (72, 86, 96). Radioiodine concentrations in urine tended to parallel the nonprotein-bound ¹³¹I of blood during 7 days after single doses (66). Since urinary radioiodine excretion can be increased by 50% at daily iodine intakes above 2 mg/kg body weight (96) and more than doubled at much higher intakes, urinary excretion can exceed the daily dose for short periods (72). Urinary iodine excretion increased in direct proportion to plasma-nonbound iodine in cows

fed 40 to 800 mg supplemental iodine daily (92).

Renal tubular reabsorption of iodide was qualitatively similar to that of chloride; was not greatly affected by perchlorate, thiosulfate, or large amounts of stable iodide; and was considered as predominantly passive (137). Some iodide may also be reabsorbed from urine in the bladder (3). Retention of iodine is reduced by high dietary chloride (9) and potassium (132), presumably because of increased urinary excretion. Under *Abomasal concentration and secretion*, we have discussed increased urinary loss caused by anions inhibiting other iodine concentrating systems and a possible interrelationship between the kidney and gastric stomach.

Secretion of Iodine in Milk

Mammary gland and iodine metabolism. Many studies of milk iodine have been reported in relation to public health (44, 52, 57, 82), and in some European countries milk is considered the most important natural source of iodine in the human diet (14, 110). Iodine in the diet and in milk has also been viewed as a potential hazard because high iodine could be toxic to sensitive persons (139), and part of the iodine in the environment may be radioactive (74).

Secretion of iodine in milk has been investigated by chemical procedures (14, 15, 16, 47, 51, 53, 75, 107, 110), with radioiodine during single or chronic administration (18, 25, 29, 30, 38, 39, 71, 72, 73), following experimental contamination of pastures with ¹³¹I (8, 34, 121), and after accidental or fallout contamination of pasture (37, 61). Total radioiodine excretions in milk, urine, and feces during 7 or more days after a single dose compared well with average steady state excretions during daily administration (17, 26, 72). Equilibrium between iodine intake and secretion in milk occurs after 7 to 10 days of daily dosing (14, 30, 72, 96). Results of 17 reports show total percentages of radioiodine intake secreted in cows' milk averaged 8% (range 1 to 30) and rarely exceeded 10% (Table 1). Cumulative secretion of ¹³¹I in milk during 6 days after an intravenous dose averaged slightly less than 10% of the dose (Fig. 3).

In the cow, unlike the rat (41), entry of iodine into the mammary gland is not depen-

dent on active secretion of milk. On the contrary, ^{131}I concentrations were higher in halves of cows' udders distended by 24 h accumulations of milk and in a nonsecretory condition than in opposite halves of udders milked before intravenous radioiodine administration (90). These results indicate that iodide enters the cow's mammary gland independent of milk synthesis. Much of the iodine in milk is available for reabsorption following secretion into the mammary gland. Net absorption of radioiodine from infused cows udders, as estimated by that not recovered in milk, averaged 82% at 7 h (90) and 94% when not milked until 16 h after dosing (95). In this study residual milk, containing an unknown amount of iodine, was not recovered; so true absorption percentages were less than the amount not recovered. Knutsson (62) measured over 90% absorption of ^{131}I from a goat's udder during 19 h using polyethylene glycol as a nonabsorbed reference material. Indirect evidence indicates iodine in protein-bound form is not absorbed from the cow's udder (90).

Iodine enters milk primarily as iodide (66). Although 3% of ^{131}I administered intravenously as labeled thyroxine appeared in milk during 7 days (86, 94, 96), its form in milk was not determined. Radioactivity was found only as iodide in goats' milk after administration of ^{131}I either as labeled iodide or iodinated casein (141). Milk from thyroprotein-fed cows produced no rise in metabolic rate when fed to humans (120) or guinea pigs (118).

Iodine in cows' milk as naturally secreted is only about 10% bound, unavailable to anion exchange resin or removed by protein precipitants (66, 71, 72, 90, 94, 96, 101). Although after ^{131}I administration as iodide, the proportion of bound ^{131}I in blood increased with time, bound ^{131}I which was in milk 6 h after dosing remained relatively constant (101). The bound fraction can be increased by incubating *in vitro*, delayed milking, or intramammary administration (90). Although 16% of total ^{131}I naturally secreted in milk was removed with the cream, nearly all of the ^{131}I in cream was in the nonfat (serum) portion (65, 72).

Effect of dietary iodine on iodine in milk. Milk from cows in endemic goiter areas contains lower iodine ($<10 \mu\text{g/liter}$) than milk produced in nongoiter areas ($>20 \mu\text{g/liter}$) (13, 108). Iodine concentrations in market milk

have increased in recent years because of widespread use of supplemental dietary iodine (52) and iodine containing sanitizing agents (54, 58). Post-milking teat dipping with iodophor solution increased milk iodine $184 \mu\text{g/liter}$ (54).

Milk iodine content varies linearly with intake in the normal dietary range if other conditions are equal (14, 47, 107). Iodine concentrations in milk of cows fed 0, 40, 81, 162, 405, or 810 mg supplemental iodine daily as ethylenediaminedihydroiodide (EDDI) averaged 8, 361, 895, 1559, 2036, and 2393 $\mu\text{g/liter}$ (92). Iodine concentration in milk increased in direct proportion to increasing supplemental iodine through 162 mg daily. Apparently the capacity of the cow's mammary gland to secrete additional iodine is reduced between intakes of 162 and 405 mg iodine daily (57, 92). In contrast, urinary iodine concentration increased approximately four to seven times at the two highest EDDI amounts and was proportional to plasma iodine. When iodine intake of two cows was raised from 5 mg to 2 g daily (a 400-fold increase), milk iodine concentration increased less than 30 times (25). Decreased percentage transfer of iodine by the mammary gland also was demonstrated with radioiodine as iodine intake was increased above normal. Massive iodine intakes reduced ^{131}I concentrations in milk by one-third when 1.3 g (96) and by one-half when 2 g (25) or 4 g (72) were fed daily.

Effect of chemical form of dietary iodine on milk iodine. Potassium iodate has been reported superior to iodide for raising milk and blood iodine of cows (75, 107). However, Lengemann (68) found that $\text{K}^{125}\text{IO}_3$ doses gave lower radioiodine in milk and blood than K^{131}I , which suggested a delayed absorption of the iodate. Iodine from diiodosalicylic acid was only about 20% as available as iodide for transfer to milk (86). No significant differences between sodium iodide and elemental iodine (19, 39), methyl iodide, or sodium iodate (19) in milk transfer were reported. When 81 mg supplemental iodine were supplied as potassium iodide or EDDI, average milk iodine concentrations were 379 and 895 $\mu\text{g/liter}$ (92). Experiments, thus, indicate that the percentage of dietary iodine which appears in milk may be influenced by the chemical form of the iodine.

Effect of stage of lactation or production on

iodine in milk. The relationship between milk production and radioiodine concentrations in milk has not been consistent (34, 39, 90, 121). Greater total radioiodine secretion in milk of higher producing cows has been related to the larger volume of milk (39, 90). However, radioiodine concentration in milk was reduced proportionally to increased milk yields when thyroxine was fed (96). An inverse relationship has been reported between milk yield and iodine concentration in milk (14, 51). Lower iodine concentrations in milk during pasture as compared with stall-feeding periods accompanied higher yield on pasture (16). Iodine concentrations are higher in colostrum than in normal milk (25, 53), but this may be related to higher protein. Iodine concentrations of normal milk rise with declining milk yield as lactation progresses (14, 51), especially if the diet is supplemented with iodine (124). When the diet is deficient in iodine, depletion of iodine reserves may mask the normal tendency for milk iodine concentration to increase with advancing lactation (124). Concentrations of chemical iodine (14) and radioiodine (91) in small volumes of milk produced by sick cows may be abnormally high.

Seasonal effects on iodine in milk. Effects of production or stage of lactation can be obscured by seasonal effects (73); seasonal effects in turn are complicated by dietary variations (21). Chemically-measured iodine concentrations in milk were highest in winter and dropped to lowest during spring and summer (14, 16, 44, 52, 119). Lower iodine concentrations in summer than in autumn to spring months were shown by chemical (82) and radioiodine (39) measurements. However, a stimulus coinciding with spring which raised amounts of ^{131}I in blood and milk has also been reported (73). Broadhead et al. (21) related maximum iodine concentrations in creamery milk in Scotland and Yorkshire during March and April and minimum values in August and September to differences in supplemental iodine fed. Seasonal differences in the Netherlands were not explained by iodine intake (16).

Effects of goitrogens on iodine in milk. Goitrogenic substances in feed may influence iodine concentrations in milk. A corn silage-soybean oil meal diet was goitrogenic (48), and milk from cows on such a diet contained only 8

$\mu\text{g I/liter}$ (47). Goitrogens are of two classifications, those which block uptake of inorganic iodide and those which inhibit organic binding of iodine by the thyroid gland (140). Belonging to the first classification, perchlorate (70) and naturally-occurring goitrogens including thiocyanate or its precursors in plants of the genus *Brassica* (51, 102, 110) and nitrate in sudan grass (105) inhibit iodine transfer into milk. Methylthiouracil, of the second classification, increased milk iodine concentrations (15). The action of certain goitrogens in depressing radioiodine concentrations in milk relative to plasma has been interpreted as an indication that secretion of iodine in the cows' milk is at least in part an active process (67). Since thiocyanate is also secreted into the milk (51, 110, 136) and it can inhibit resorption of iodine from the mammary gland as well as secretion (95), a possible alteration in the form of iodine which affects its availability for transfer (102) should also be considered.

Effect of thyroxine on iodine secretion in milk. There is evidence for an inverse relationship between circulating thyroxine and concentration gradient of iodide to milk from plasma. Concentrations of radioiodine in cows' milk can be reduced by exogenous thyroxine given intravenously (67), subcutaneously (116), or orally (96). Exogenous thyroxine also inhibited transfer of iodine from the mammary gland to blood plasma (67). Markedly hypothyroid cows yielded only 53% as much milk containing almost twice as much of a radioiodine dose as their normal controls (88). Treating the hypothyroid cows with exogenous thyroxine increased milk yield and reduced secretion of radioiodine into milk. Effects of thyroxine on milk/plasma radioiodine concentration gradients were similar to those of perchlorate (70) and thiocyanate (39), but to a lesser degree. Because of other marked differences between thiocyanate and thyroxine (88), it seems illogical to explain their similar effects on milk/plasma radioiodine ratios as an effect on the mammary epithelium. We have found that thyroid-stimulating hormone, which increases thyroid uptake of iodine, has no effect on milk iodine (unpublished).

Fetal Concentration and Circulation of Iodine

Measurable amounts of iodine were first detected in fetal bovine thyroids about day 60

of gestation (138). Chemical iodine concentrations in fetal thyroids averaged 160 $\mu\text{g/g}$ of tissue through day 138 of gestation, and total thyroid iodine was almost directly proportional to fetal thyroid mass and body weight. More iodine was accumulated by fetal thyroids after day 140 than could be accounted for by increased thyroid mass. By day 240 of gestation, iodine concentrations averaged 1.05 mg/g of fetal thyroid tissue as compared with 1.38 mg/g for four mature cows (138). Total fetal thyroid iodine present as thyroxine remained relatively constant at 30% between days 72 and 265 (63). Near-term fetal thyroids contained about twice as much ^{131}I at concentrations per gram of tissue six to seven times greater than maternal thyroids 24 h after dosing (40). At day 7 after dosing, fetal/maternal ratios averaged only 1.1 for total thyroid radioiodine uptake and 2.5 for concentration per gram of tissue (5, 93).

Fetal serum thyroxine concentrations averaged about one-third the maternal at day 90 of gestation but had increased to more than double the maternal concentration in the second and third trimesters (50). Thyroxine-binding globulin was fully saturated in the second and third trimester fetus but only about two-thirds saturated in the dam. It was suggested that this could provide a gradient for transfer of thyroxine from the fetal to maternal side of the placenta (50). Thyroid deficiency symptoms in a thyroidectomized cow appeared to be partially relieved during the last 10 wk of gestation, suggesting passage of thyroid hormone from fetal to maternal circulation (123). However, work with sheep (33) and rabbits (43) showed negligible placental transfer of thyroxine in either direction. Bidirectional passage of triiodothyronine has been reported in sheep with fractional transfer in the fetal to maternal direction exceeding that in the maternal to fetal direction by 10 times (32).

Average near-term fetal/maternal blood serum radioiodine concentration ratios increased from slightly above one at 24 h (40) after a single dose of radioiodine to the dam to over five at 7 days (5, 89). Seven days after the dams were dosed, radioiodine concentrations in chorionic and amniotic fluids, respectively, averaged 2.9 and 6.2 times that of maternal plasma radioiodine concentrations (5). Elevated circulating radioiodine (93), PBI (76), and thyroxine

(50) in the neonatal calf cleared rapidly during the first few days after birth. These results indicate that the unborn fetus lacks an efficient means of iodine disposal; excreted iodine enters the fluid enveloping the calf and is available for recycling. After birth the fetus can eliminate accumulated iodine by normal urinary and fecal excretions.

Thyroid Uptake and Release of Iodine

Prenatal development, anatomy, and physiology of the thyroid gland, biochemistry of thyroid hormone production (23, 133), and factors influencing thyroid uptake of iodine (134) have been reviewed. Reported peak thyroid ^{131}I accumulations of single doses vary from 20% (range 7 to 35) for mature cows (25, 30, 68, 125) to 35% (range 27 to 42) for calves (6, 78, 79) and 42% (range 22 to 86) for heifers (115). After 6 to 14 daily doses, radioiodine accumulations by cow thyroids averaged 120% (range 79 to 200) of the daily intake (25, 67, 68, 71). Much of the variation probably resulted from variable stable iodine intakes since amounts of iodine normally included in dairy rations markedly inhibited thyroid ^{131}I uptake (125). Peak ^{131}I uptake by thyroids of 18 cows which were fed a commercial concentrate feed containing iodized salt averaged only 10% of the dose (Fig. 3).

Seasonal effects of greater thyroid activity in winter and spring as compared with summer and fall have been shown by measurement of PBI (7) and TSR (78, 98, 114). Rising environmental temperatures depressed thyroid ^{131}I release rate (59) and plasma butanol-extractable ^{131}I (18); differences were much less when heifers were maintained at constant temperatures for extended periods (60). Thyroxine secretion rate of Holstein heifers decreased markedly within 35 days after they were changed from cool (3 to 18 C) to hot (24 to 35 C) environmental temperatures (129). Apparently thyroid activity is inhibited directly by high environmental and body temperatures rather than by accompanying depressed feed intake (81). Slight reductions in the secretion rate of thyroid-stimulating hormone with increasing temperatures were not statistically significant (49). Thyroid ^{131}I uptake measurements showed little seasonal effect (125) or highest uptake in summer (79). Lodge et al.

(79) suggested thyroid ^{131}I uptake is not a good indicator of thyroid activity but merely shows its storage capacity. Radioiodine uptakes (25, 125) were highest at the beginning of lactation but decreased in later lactation. Mixer et al. (98) reported that TSR of 12 Holstein and Guernsey cows declined from 1.76 mg/day at the beginning of lactation to 1.62 mg at mid lactation, then rose to 1.66 mg at 9 mo. Swanson (124) reported that TSR of 14 Holstein cows gradually increased from 1.50 mg/day at about 1 mo to 1.74 mg at 6 mo of lactation, but these differences were not statistically significant.

Seasonal effects had a much greater influence on TSR than stage of lactation (98). Diurnal effects on thyroid activity in dairy cattle were not revealed by measurements of plasma PBI and thyroxine ^{131}I disappearance (143). Thyroid activity on a body-weight basis decreased with growth (60). Daily TSR of Holstein heifers increased only .64% for each 1% increase in body weight (100). Jerseys had more active thyroids on a body-weight basis than Holsteins or Brown Swiss as measured by thyroid ^{131}I release rate (60).

Thyroid-inhibiting action of a number of naturally occurring goitrogens, notably those in plants of the genus *Brassica* (55, 56), is well known. Volatile compounds in members of the lily family (onions, garlic, etc.) may also be goitrogenic (28). Certain forages contain factors which induce adjustments in thyroid activity with sudden change in type of forage fed (1, 131). A goitrogenic effect of large amounts of soybean meal in dairy cattle rations was shown by research in Maryland (46, 48, 130), but a similar ration did not reduce TSR of lactating cows significantly below those supplemented with iodine (124).

Work with rats (41, 42) and goats (36) showed thyroidal ^{131}I uptake was significantly lower in lactating than in nonlactating animals. Within lactating goats, correlations were negative between milk yield and thyroid ^{131}I uptake and also between milk yield and TSR (36). These results suggest that under conditions of minimal iodine intake, lactation could be self-limiting because iodine lost in milk would be unavailable for thyroid hormone production (4).

When cows with 10-mo lactations averaging 8,178 kg were fed low iodine diets from 8 wk

prepartum, milk yields were not reduced below comparable cows fed the same ration supplemented with 100 mg iodine daily. Incipient iodine deficiency, however, was indicated by reduction of concentration of iodine in milk from 53 to 14 $\mu\text{g}/\text{liter}$ within 28 wk (124). Statistically insignificant correlation coefficients between TSR and milk iodine loss ($r = .06$) or milk yield ($r = .38$) were calculated from Swanson's data (124, unpublished) for seven cows fed the low iodine diet. Milk/plasma iodine concentration gradients are much lower for cows than goats (Table 1). Cattle apparently also can adapt to low iodine intakes by reducing iodine losses in milk, urine, and feces (92, 124). Recycling of iodine through the abomasum (Fig. 5) plays an important role in conservation of iodine. Iodine reserves should be increased during the dry period which would decrease probability of low dietary iodine affecting lactation in cows.

Iodine in Extrathyroidal Tissues

Of 20 nonthyroid tissues removed from mature cows at slaughter after six to eight daily radioiodine doses, none had higher radioiodine concentrations than blood plasma (97). However, abomasal tissue, which concentrates iodine, was not analyzed in this study. If average uptakes are 100% of the daily dose by 40-g thyroid glands after 6 days, nonthyroid tissues concentrated only .006 to .04% as much radioiodine per unit weight as the thyroid gland. Nonthyroid tissue radioiodine concentrations, as percentages of concurrent plasma concentrations, averaged in descending order: uterus and cartilage, 77; skin with hair, ovary, mammary gland, lung, kidney, and lymph node, 63; salivary gland, pancreas, adrenal, hoof, heart, spleen and liver, 38; and skeletal muscle, 14. Radioiodine concentrations in mouse muscle averaged only 16 to 25% of plasma radioiodine concentrations, but stable iodine was 40% higher in muscle than in plasma (27). Thus, radioiodine concentrations in body tissues after short dosing periods may not reflect accurately long-term storage of dietary iodine. Tissue concentrations of ^{125}I given for 6 days to dairy cows as ^{125}I -labeled EDDI averaged 10% higher than ^{131}I given simultaneously as NaI (92). Inflamed or diseased tissues concentrated 24 to 218% more radioiodine than corresponding normal tissues (97), possibly because of infil-

trating leucocytes. Pincus and Klebanoff (111) reported that phagocytosing leucocytes concentrate iodide, fixing it to ingested particles or organisms in a form precipitable by trichloroacetic acid. A possible microbiocidal involvement (111) may be another important function of iodine in the body in addition to its role as a necessary component of thyroxine.

ACKNOWLEDGMENT

Appreciation is expressed to Joan Ellis, Ruth Kerr, and Lana Melton for editorial assistance, obtaining and checking references, and typing two revisions of the manuscript.

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