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Radioactive Iodine Concentration in the Fetal Human Thyroid Gland from Fall-out

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A study was made of the occurrence of I^{131} in human fetal thyroid glands apparently resulting from I^{131} received by the mother from nuclear weapons testing or other types of population contamination. Radioactivity compatible with I^{131} was found in the human fetal thyroid gland. The maximum concentration of I^{131} was 265 μμc per gram of fetal thyroid tissue, 29.1 μμc per gram of adult hog thyroid tissue and 22.9 μμc per gram of adult thyroid tissue. The highest activity found on a reagent blank was 10.0 μμc. The calculated maximum total radiation delivered to any human fetal thyroid gland was 0.47 rads. The average total dose was 0.05 rads. Extrapolations from data on animals suggest that it is unlikely that this quantity of radiation would produce hypothyroidism or carcinoma of the thyroid gland.

Radioactive iodine, I^{131}, from nuclear weapons testing has been reported to be present in the thyroid glands of adult cattle, swine and sheep, in the fetuses of these sheep, and in adult human beings.[1] Since I^{131} passing from the human maternal to the fetal circulation will be concentrated by the fetal thyroid gland as early as the third month of gestation,[2] we should expect the presence of I^{131} in human fetal thyroid glands. This activity results from I^{131} received by the mother from nuclear weapons testing or other types of population contamination. We wish to report on an investigation we have made of the concentration of I^{131} found in human fetal thyroid glands. The concentration of I^{131} was apparently insufficient to cause hypothyroidism or thyroid carcinoma.

Method

Sources of Specimens.—Twenty-seven human fetal thyroid glands from 25 pregnancies were obtained at the time of abortion, caesarean section, premature labor, stillbirth, or neonatal death during the period Nov. 12, 1958, to Aug. 1, 1959, from four hospitals within a radius of 10 miles of Ann Arbor, Mich.

Only fetuses aged 5 months through term stillbirth (except for one newborn infant, 3 weeks of age) were used in this study. Twelve human adult thyroid glands, not from mothers of these fetuses, were also collected from autopsies at University Hospital Nov. 19, 1958, through March 31, 1959, and analyzed. In addition, 25 adult and fetal hog thyroid glands were collected during the period Jan. 6, 1959, to July 8, 1959, from a local abattoir and used as controls. These hogs were all from Washtenaw County (around Ann Arbor, Mich.).

Data on age of fetuses, causes of death, condition of fetus, history of maternal systemic disease, maternal thyroid or iodide medication, or maternal thyroid disease were obtained at autopsy on the fetus, by examination of the medical records of the mother, and by interview of the mother. These data are presented in the table.

Preliminary Treatment of Thyroid Glands.—Most thyroid glands used in this study were dissected free of the fetus by the pathologist within one hour after delivery of the fetus. Histologic sections were obtained on many thyroid gland specimens to identify the tissue as thyroid gland. None of the sections showed a significant degree of autolysis. If chemical extraction of iodine from the thyroid tissue had to be delayed, the tissue was immediately frozen and stored at approximately −40° C until the time of analysis. The chemical extraction was always begun within a period of one hour to three days after delivery of the fetus.

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Care of Apparatus.—All apparatus and instruments used for analyses of human and hog thyroids in these experiments were stored and used separately from all other equipment in our laboratory. A second complete set of apparatus was used for recovery experiments. It was never used for unknowns. At the beginning of this study, pipettes were not isolated as described above, but in the latter part of the study separate sets of pipettes were also maintained for each type of experiment.

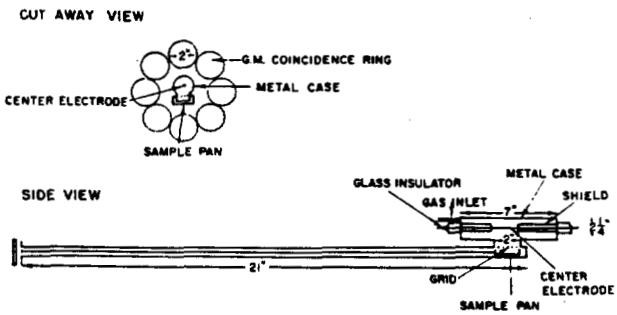

Fig. 1.—Diagram showing assembly of low-background G-M counter in which filter papers were counted.

Chemical Extraction of I^{131} from Thyroid Tissue.—Chemical extraction of I^{131} from thyroid tissue consisted basically of four steps: mechanical preparation of the tissue, digestion with oxidizing agents, distillation of the I^{131} out of the digest, and drying of the collected distillates. Fresh thyroid tissue was dissected free of fat and weighed. If the thyroid tissue weighed less than 1 Gm., normal rabbit serum was added to supplement the protein content to a total weight of 200 mg. (the estimated amount of protein in 1 Gm. of thyroid tissue). The tissue was minced and transferred to a digestion flask containing, in analyses of hog thyroids, 3.5 ml. and in all other experiments 2.5 ml. of chromic acid reagent, 40.0 ml. of sulfuric digestion reagents and glass beads.[3] Parts two and three of the Hycel Hormone Chemical Company's modification of the original Barker method[4] were followed, as described in their procedure manual[3] with the following two modifications. At the suggestion of Dr. Barker,[5] the distillate was collected in a trap solution containing 0.1 N sodium arsenite in 20% sodium hydroxide rather than into a solution of sodium hydroxide alone. No arsenious acid reagent was added to the centrifuge tube into which the distillate was drained.

The distillate was poured into a micro-buret and dripped slowly onto filter paper disks measuring 22 mm. in diameter. The disks were supported between slits in two waxed paper cups and a stream of warm air was used to facilitate drying.

Reagent Blanks.—Eleven reagent blanks were prepared and counted during the period from Nov. 30, 1958, through July 28, 1959. Three milliliters of stored normal rabbit serum, 2.5 ml. of chromic acid reagent, and 40.0 ml. of sulfuric digestion mixture made up the reagent blank. Digestion and distillation were carried out as described above.

Recoveries.—In order to test recovery, six additional experiments using 0.03 to 0.2 μc of I^{131} in the form of added carrier-free NaI^{131} or in the form of I^{131} already incorporated into thyroid tissue were carried out. The mean over-all recovery was 73.6% ± 6.2 (standard deviation). Counts made at various stages of the procedure showed that most of the loss occurred during drying on the filter paper.

Counting of Samples.—The filter papers containing the dried distillate were counted side by side in a windowless gas-flow Geiger counter surrounded by an anticoincidence ring of G-M (Geiger-Müller) counters 61 cm. in length and 5.7 cm. in diameter. The counting assembly was housed in a cave of old iron bricks with a minimum thickness of 8 in. A diagram of this assembly is seen in figure 1.

The background count in the counting chamber not canceled by coincidence counts from the ring of Geiger counters was approximately 1.6 counts per minute.

Each sample was counted for four hours or more and background counts were run overnight. Since the counts occurring in the counting chamber not canceled by a simultaneous pulse from the coincidence ring increased proportionally with an increase in the counts canceled by the coincidence ring, all uncanceled counts were standardized to a canceled count of 25 counts per minute, an average value. Samples showing activity greater than twice the background count were recounted weekly until the fall in count rate showed a plateau.

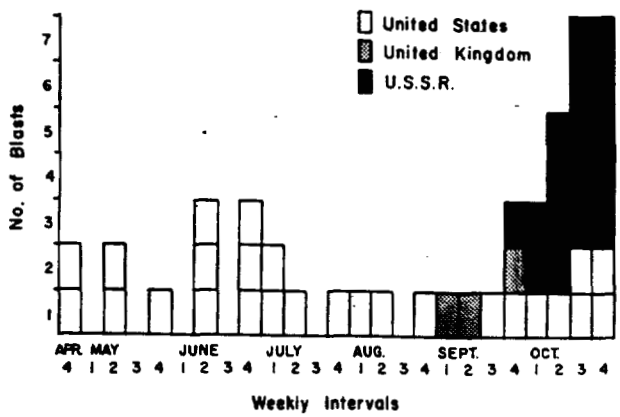

Fig. 2.—Frequency of atomic blasts in 1958.

A line of best fit was calculated from the data, assuming a single isotope decay rate. From this line the half-life of the radioisotope counted was determined. Because the half-lives thus determined agreed closely with the half-life of I^{131}, the activity of each sample was calculated back to the day of fetal delivery, using the decay rate of I^{131}.

The over-all efficiency of the counting system was found by drying a known volume of a solution of I^{131} containing a known number of disintegra-

tions per second on filter paper, as described above. This standard was then counted in the usual manner. The over-all efficiency of the counting system was thus found to be 14%. This value included the loss of activity during the drying process, about 26%. With this knowledge the number of micromicrocuries of I^{131} per gram of fetal thyroid tissue and per total thyroid gland was calculated.

Results

Nuclear Weapons Testing.—Figure 2 is a bar graph presenting the frequency of nuclear blasts during 1958 by the United States, Great Britain, and Russia.[6]

A maximum atmospheric concentration of I^{131} would be expected to occur during the last week of October. Our sampling began less than two physical half-lives after the last blasts. We have not been informed of the occurrence of any further nuclear weapons testing during the period of November, 1958, to August, 1959.

Data on Human Fetuses and Their Mothers.—The table presents data on human fetuses and their mothers. Repeated counting of extracted material from seven fetal thyroid glands collected over the period Nov. 24, 1958, through May 12, 1959, gave values of radioactive half-life ranging from 7.5 to 9.8 days and averaging 8.4 days, roughly the half-life of radioactive iodine, I^{131} (8.1 days).

Although the median I^{131} content of the reagent blanks was equivalent to only 2.1 $\mu\mu$c, the maximum I^{131} content was equivalent to 10.0 $\mu\mu$c. This maximum is higher than the fetal thyroid gland I^{131} concentration of all but eight fetuses. Excluding the dates Nov. 30, 1958, to Dec. 23, 1958, however, the activity of reagent blanks never exceeded 3.5 $\mu\mu$c per gram. Only two human fetal thyroid glands were obtained during the above interval. Excluding these two fetal thyroid glands, only eight fetal thyroid glands failed to exceed the maximum reagent blank activity of 3.5 $\mu\mu$c. These eight glands are scattered fairly uniformly throughout the period Feb. 27, 1959, to July 24, 1959.

Figure 3 presents a comparison of the concentration of I^{131} in the human fetal thyroid gland to the concentration in human adult and hog thyroid glands, and in reagent blanks during the same period of sampling.

It is important to note that the plot in figure 3 on a semilog scale minimizes the apparent fetal thyroid gland peak concentrations of I^{131} and tends to emphasize small variations in activity in samples containing little activity. The following observations from figure 3 are noteworthy.

1. These four groups of samples may be listed in order of average decreasing concentration of radioactivity as follows: fetal thyroid gland, hog thyroid gland, human adult thyroid gland, and reagent blanks. Generally, the fetal thyroid I^{131} concentration is 2 to 10 times greater than the human adult thyroid I^{131} concentration and shows greater variation. One group of pooled hog fetal thyroids showed a 58% greater concentration of I^{131} than was found in the mother's thyroid.

It is of interest that the twin human fetuses 13 and 14 showed only a 9% difference and twin fetuses 25 and 26 showed only a 39% difference in concentration of I^{131}. The total thyroid gland I^{131} content of the twins in each instance was roughly the same, even though the concentration of I^{131} differed.

2. Fetal thyroid gland I^{131} concentration decreased during the period December, 1958, through March, 1959, with an apparent half-life of about 20 days.

3. The variation in concentration of I^{131} from one fetal thyroid gland to the next is roughly tenfold to twentyfold during the period from November to February. The variation in concentration then appears to become less as the concentration in all specimens falls between February and May.

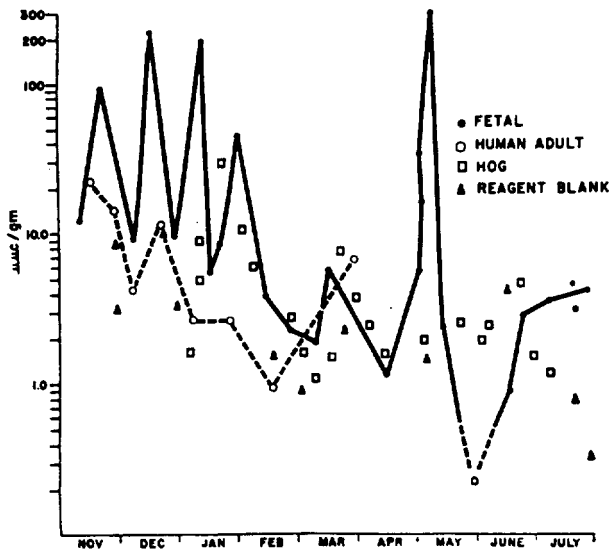

Fig. 3.—Comparison, by month, of concentration of I^{131} in thyroid gland specimens and in reagent blanks.

4. The concentration in fetal thyroid gland specimens in May builds up progressively through four successive specimens to a peak hundredfold increase, with no similar rise in hog thyroid gland or reagent blank I^{131} concentration.

I^{131} Content and Fetal Age.—Histological study of human fetal thyroid tissues demonstrated that colloid-containing follicles were clearly evident in all specimens past 4 months of fetal age. Our data suggest that the fetal thyroid gland weight increases until 7 months of age and then reaches a plateau. No correlation is apparent between I^{131} concentration in the human fetal thyroid and age of the fetus or weight of the thyroid gland after the fourth month of gestation.

Correlation of I^{131} Content of Fetal Thyroid with Condition of Fetus and Thyroid Status of Mother.—No relation was observed between the cause of death in the fetus and the I^{131} concentration of the thyroid gland. Fetus 4, with the second highest concentration of I^{131} in his thyroid gland, died at

6 months of age after premature birth with cerebral agenesis and possible hyaline membrane disease. Fetus 7, with one of the lower concentrations of I^{131} in thyroid tissue, died after a full-term birth with hydrocephaly and a meningocele.

The mothers of fetuses 3 and 7 had taken desiccated thyroid during pregnancy. The mother of fetus 20 had been given compounds containing organic iodine, and the mother of fetus 24 had had inorganic iodine during pregnancy. All of these fetuses had low concentrations of I^{131} in their thyroid glands, in spite of the fact that the thyroid glands of fetuses 3 and 7 were collected at the time when the concentration of I^{131} in thyroid gland specimens was running high. There is insufficient data, however, to allow one to conclude that medicament containing iodine ingested by the mother or injected into the mother during pregnancy decreased the I^{131} concentration in fetal thyroid gland.

Data on Human Fetus

Fetuses, No.	Delivery Date of Specimen	Weight of Fetal Thyroid Specimen Obtained, Gm.	Estimated Amount of Whole Thyroid Gland, Lobes	First Count Obtained, Cpm	Interval Between First Count and Delivery Date, Days	Activity in Disintegrations Per Minute	Physical Half-Life of Isotope, Days
1	11/12/58	0.38	½	0.1	31	0.7	Cannot be calculated
2	11/24/58	0.18	½	3.1	6	22.6	7.9
3	12/10/58	0.77	2	1.3	6	9.5	Cannot be calculated
4	12/19/58	0.28	2	11.9	5	86.9	9.1
5	1/ 1/59	0.62	2	1.3	4	9.5	8.4
6	1/14/59	0.39	1	16.0	4	117.0	7.5
7	1/17/59	1.06	1	1.2	5	8.5	Cannot be calculated
8	1/22/59	0.37	1½	0.6	5	4.6	...
9	2/ 2/59	0.48	2	6.4	2	39.6	7.5
10	2/15/59	0.66	1 3/5	0.5	3	3.9	...
11	2/27/59	0.37	1 3/4	0.2	4	1.3	...
12	3/10/59	0.37	2	0.2	3	1.2	...
13 twins	3/17/59	0.40	2	0.5	3	3.4	...
14	3/17/59	0.54	2	0.6	3	4.3	...
15	4/16/59	1.01	1 4/5	0.3	2	2.1	...
16	5/ 4/59	0.36	1	0.5	3	3.3	...
17	5/ 5/59	0.41	½	3.1	3	22.5	...
18	5/ 5/59	0.63	2	1.9	5	13.8	8.6
19	5/12/59	0.55	2	34.6	3	253.0	9.8
20	5/14/59	0.61	1	0.3	4	2.1	...
21	6/ 1/59	0.43	1½	...	1	...	...
22	6/19/59	1.05	2	0.2	4	1.4	...
23	6/25/59	0.59	2	0.3	4	2.4	...
24	7/ 9/59	0.95 used 1.43 total	2	0.5	7	3.8	...
25 twins	7/20/59	0.44	2	0.3	3	2.0	...
26	7/20/59	0.26	2	0.3	4	1.8	...
27	7/28/59	0.07	1½	0.1	6	0.4	...

* Values were rounded to significant figures after calculations were performed.

Calculated Irradiation Dose Delivered to Human Fetal Thyroid Gland.—Certain assumptions are made in calculating the dose of radiation in rads delivered to fetal thyroid glands. These assumptions are: that all beta radiation from thyroid I^{131} was absorbed in fetal thyroid tissue; that radiation from gamma rays may be ignored; that, as in fetal sheep,[16] the concentration of I^{131} in fetal thyroid tissue rises exponentially from day 50 to 150 and then remains constant with a constant intake of I^{131}, and that no decreased concentration of I^{131} in human fetal thyroid gland resulted from irradiation of the fetal thyroid gland. We are aware of the fact that the I^{131} intake from fall-out is not constant; that we do not know the concentration of fetal thyroid I^{131} during the actual period of weapons testing; and that calculation of the dose with use of these assumptions does no more than set an upper limit to fetal thyroidal I^{131} under the specific conditions of our study.

First, in order to calculate the maximum possible absorbed dose to a fetal thyroid gland we assumed that the intake of once-labeled diet throughout the gestation period was constant at a level which resulted in the maximum observed concentration of 265 $\mu\mu$c/per gram. Two formulas must be used; one to calculate the cumulative dose during the initial period of exponential increase in I^{131} concentration; the second to calculate the cumulative dose after the concentration of I^{131} reaches a plateau. The dose to the thyroid gland during the initial period from 50 to 150 days is given by the equation, $D\beta = 73.8 \times \bar{E} \times C_o \times T(\frac{1}{2}) \times [1 - \exp.(\frac{-0.693\ t}{T(\frac{1}{2})})]$,

where $D\beta$ = absorbed beta dose in rads,

$\bar{E}\beta$ = average energy of the beta particle disintegration in mev,

C_o = concentration of the isotope in microcuries per gram of thyroid tissue,

t = time of exposure in days, and

$T(\frac{1}{2})$ = doubling period of the I^{131} concentration in days.

Substituting into the formula we have

$D\beta = 73.8 \times 0.19 \times 2.65 \times 10^{-4} \times 20 \times [- \exp.(\frac{-0.693 \times 100}{20})]$, so that

$D\beta = 0.04$ rads to the thyroid between 50 and 150 days.

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The second formula, $D\beta = 51.2 \times \bar{E}\beta \times C_o \times t$ expresses the absorbed dose between 150 and 270 days where the symbols are the same as above.

Then $D\beta = 51.2 \times 0.19 \times 265 \times 10^{-4} \times 120$ and $D\beta = 0.31$ rads to the thyroid between 150 and 270 days. Adding 0.04 rads delivered during the initial build-up period to the subsequent 0.31 rads accumulated during the last 120 days of intrauterine life, the calculated maximum cumulative dose to any fetal thyroid in our series is 0.35 rads. Correcting this for a chemical recovery of 74% the dose becomes 0.47 rads.

A second calculation, the mean observed exposure dose, was performed with the data used to obtain a more realistic figure. The mean observed exposure dose we took to be the dose in rads to a fetal thyroid if the gestation period corresponded to the nine-month period of our study and the concentration of I^{131} in the gland varied as shown by our values. This calculated dose was obtained by averaging the fetal thyroid I^{131} concentrations gravimetrically, then applying the preceding equations. The total corrected dose obtained was 0.05 rads.

es and Their Mothers*

I^{131} Content of Fetal Thyroid Gland at Delivery		Age of Fetus, Mo.	Condition of Fetus	Remarks About Mother
μμc/Gm.	μμc/Thyroid Gland			
12.0	18	7	Died 10 days after premature birth	...
94.4	68	6½	Caesarean section because of diabetes with complications	No information
9.2	7	6	Stillborn-macerated fetus	Taking thyroid pills
216.0	60	6	Neonatal death; cerebral agenesis; hyaline membrane disease	...
9.6	6	9	...	...
180.0	148	8½	Lived 12 hr.; hyaline membrane disease	No history
5.5	12	9	Neonatal death due to hydrocephalus; meningocele	On thyroid; previous thyroidectomy
8.5	4	6½	...	History noncontributory
44.5	21	9	...	...
3.7	3	9	Rh incompatability; lived 4 hr.	History noncontributory
2.2	1	9	Stillborn, term	History noncontributory
1.8	1	5½	...	Fourth pregnancy lost
5.4	2	6½	Asphyxia; abruptio placenta	History noncontributory
5.1	3	6½	Same, twins	...
1.1	1	9	Amniotitis	...
5.3	4	6	Persistent fetal atelectasis; prematurity	...
31.7	52	9	Persistent fetal atelectasis; died 48 hr. after delivery	History noncontributory
15.0	10	9	Stillborn	...
265.0	147	9*	Anoxia; intrauterine death; cord prolapse	History noncontributory
2.2	3	9	Intrauterine death	...
		7½	Premature labor; neonatal death	Endometritis; I.V. pyelogram
1.8	1	9	Death within 24 hr. of delivery; cord about neck; aspiration of amniotic fluid	History noncontributory
2.6	2	9¾	Polycystic kidney and hydroureter	History noncontributory
3.3	5	9	Hydrops fetalis	Took cough medicine for 2 days
2.7	1	9	...	History noncontributory
4.4	1	9	...	History noncontributory
3.8	0.4	5	Premature infant; dead on arrival in emergency	History noncontributory; arrested pulm. tbc.

Comment

Radioactivity in Reagent Blanks.—As the activity in reagent blanks was not sufficient to identify I^{131} by repeated countings, we have no proof that the radioactivity is from I^{131}. For purposes of comparison, however, it was assumed that the counts were from I^{131} and activity was extrapolated to zero time and converted to micromicrocuries.

As the activity in reagent blanks roughly paralleled (at a lower level) the I^{131} concentration in thyroid tissue, it is reasonable to assume that the activity came from air fall-out into reagent bottles or from fall-out I^{131} entering the blood stream of the rabbit from which the carrier serum protein was obtained. Carrier protein was added to reagent blanks and to other samples with insufficient amounts of tissue protein, because recoveries have been found [4] to be lowered when insufficient protein is present initially.

Identification of I^{131} as the Source of Radioactivity.—The identification of I^{131} as the source of the majority of the radioactivity in the samples of thyroid glands by the technique of radioactivity half-life determination did not furnish unequivocal proof that I^{131} was the major source of radioactivity in these samples. At least seven other radioisotopes have similar half-lives. Only Ag^{111} (radioactive silver) and Sn^{125} (radioactive tin) are products of fission. As neither of these isotopes are concentrated by the thyroid gland similar to I^{131} (half-life = 8.1 days), it is unlikely that any radioisotope other than I^{131} accounts for the radioactivity found in our thyroid gland samples. Moreover, the radioactivity material finally counted had first been isolated from the thyroid tissue by a multi-step chemical procedure specifically designed to isolate and recover iodine.

Relative Radioactivity of Four Groups of Samples.—Extrapolating from studies in fetal sheep and cattle, the human fetal thyroid gland would be expected to show a higher concentration of I^{131} than the human mother's thyroid gland during the third trimester. Barnes and colleagues [16] found that the thyroid glands of offspring of dams fed 0.15 μc of

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I^{131} per day showed 1.8 to 2.9 times the I^{131} concentration of their mothers' thyroid glands after 130 days of pregnancy. Gorbman and co-workers [7] demonstrated that the concentration of I^{131} was six to seven times greater in the fetal thyroids of cattle than in their mothers' thyroids, although the total content of I^{131} was only twice that of the mother's thyroid gland. Histologically the thyroids of these cattle appeared much less active than those of their fetuses. He believed that a disparity of thyrotropic hormone concentrations in the fetal and maternal circulation was the most reasonable explanation for the disparity in thyroidal function between the mother and its near-term fetus. It is probable that Hodges and colleagues [2b] demonstrated, after tracer doses of I^{131} to mothers, a lower concentration of I^{131} in fetal thyroid than in maternal thyroid glands of human beings, because the fetuses they studied were younger than ours. We are not aware of any other studies demonstrating the relative I^{131} concentration in human fetal thyroid gland in comparison with human adult thyroid gland. It should be stressed, however, that our finding of a concentration of I^{131} in fetal thyroid amounting to 2 to 10 times the concentration in human adult thyroid gland does not necessarily hold strictly for any individual mother and her fetus. Our adult human thyroid glands were not from mothers of the fetuses studied.

Our data showing a concentration of I^{131} in the thyroid glands of swine higher than in the thyroid glands of human adults complement the data of Van Middlesworth. Swine in Memphis showed a thyroid concentration of I^{131} from fall-out 5 to 10 times the concentration in adult human beings in Memphis during 1958.[8]

Fall in Fetal Thyroid Gland I^{131} Concentration After Nuclear Weapons Testing.—Our data show no significant decrease in thyroid gland I^{131} concentration during the first month after cessation of nuclear weapons testing. Van Middlesworth [9] demonstrated that rats fed I^{131}-tagged diets were almost in equilibrium, as judged by the fact that the I^{131} content of their excreta was 90% of the intake, by the 16th day on the tagged diet. Bustad and co-workers [10] feeding adult sheep a constant daily intake of I^{131}, found that the concentration of I^{131} in their thyroid glands reached an initial plateau after 10 to 40 days, with a mean of 17 days.

It is logical to suppose, therefore, that the apparent absence of decrease in fetal I^{131} concentration in the first few weeks after cessation of weapons testing and the apparent subsequent decrease in fetal thyroid I^{131} activity between December, 1958, and March, 1959, with a half-life of approximately 20 days, was also related to the time taken for establishment of I^{131} equilibrium between mother and fetus.

Fetus-to-Fetus Variation in Thyroidal I^{131} Concentration.—We have no good explanation for the tenfold to twentyfold fetus-to-fetus variation in thyroidal I^{131} concentration. Variation of similar magnitude has been observed by others, however, in sheep and man. Bustad and co-workers [10] found a tenfold variation from sheep to sheep on the same day in the same group fed the same diet with a fixed content of I^{131}. Comar and colleagues [1c] found that in May, 1955, 30% of the adult human thyroid gland samples had less than 0.0008 mμc of I^{131} from fall-out per gram, whereas 11% had more than 0.01 mμc per gram, a one-hundred-twenty-five-fold variation. Although all our thyroid gland specimens were from patients and hogs within a 50-mile radius of Ann Arbor, the intake of I^{131} from fall-out is certainly more variable than intake on a regular diet of fixed I^{131} content. The 9% difference in human fetal thyroid I^{131} concentration in one set of twins and the 39% difference in another set of twins, give some idea of the order of magnitude of variation in I^{131} concentration that may be found under ideal conditions. The fact that the total I^{131} content of the thyroid glands of twins differed much less than thyroid glands of unrelated fetuses suggests that variations in weights of the thyroid glands from fetus to fetus might be a factor in these differences. The larger thyroid glands of twin fetuses showed the lowest concentrations of I^{131}.

Peak of Radioactive Concentration in May, 1959.—The peak fetal thyroid I^{131} concentration in May, 1959, is noteworthy. The magnitude of this concentration equals the concentration found during the month after cessation of nuclear weapons testing. We have several reasons for believing that this peak of I^{131} concentration does not represent contamination of specimens with I^{131} in the laboratory. The peak is made up of four fetal thyroid glands delivered and extracted on different dates. Each successive specimen shows a regular and progressive increased concentration over the previous specimen. A reagent blank and a hog thyroid specimen prepared and counted during this same interval do not share this increased I^{131} concentration. Hogs in this area are fed grain kept in drums. Milk from cows on the same farms is mixed with this grain. We were able to find radioactivity in milk but the radioactivity did not have a half-life compatible with I^{131}.

Van Middlesworth [8] demonstrated the presence of increased I^{131} radioactivity in the thyroid glands of Seattle sheep at the end of April and in Seattle cattle in May. Increased concentrations of radioactivity were also observed during May and June by the United States Public Health Service in connection with their 12 milk sampling stations.[11]

In vivo counting over the thyroid gland of the mother of the fetus with the greatest thyroid activity detected no evidence of thyroid radioactivity. She gave no history of having I^{131} for tracer studies or treatment in the past.

If this May peak in fetal thyroid I^{131} concentration was from fall-out, the source of atmospheric contamination apparently was not a nuclear weapons blast.

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In spite of these data arguing against laboratory contamination of the fetal thyroid, or I^{131} administered to the mother by her physician, these sources of contamination are still a possibility. The very rapid build-up and fall-off of activity in these fetal thyroid glands sampled in May are difficult to explain on any other basis.

Correlation of I^{131} Content of Fetal Thyroid with Condition of Fetus and Thyroid Status of Mother.—It is not surprising that fetus 4, with cerebral agenesis, was able to concentrate I^{131} avidly in his thyroid gland. Yamazoki and colleagues [12] have just reported that in two anencephalic fetuses of mothers given tracer doses of I^{131} the thyroid was able to synthesize the normal thyroidal iodine compounds.

It is logical to expect that if the mother were given desiccated thyroid during pregnancy her own thyroid gland's accumulation of I^{131} from fall-out would be suppressed. The average dose of desiccated thyroid to the mother, however, would not be expected to suppress fetal thyroid gland activity [13] unless iodine from the thyroid medication diluted I^{131} in fetal thyroids. We have no explanation, therefore, for the fact that the thyroid glands of fetuses 3 and 7 showed relatively low concentrations of I^{131} at a time when other fetuses showed high concentrations.

It does seem evident, however, that all fetal and maternal factors which might affect the concentration of I^{131} by the fetal thyroid gland appear to be dwarfed in their significance by variations in the concentration of I^{131} in fall-out.

Radioactivity in Human Fetal Thyroid Required to Produce Hypothyroidism.—As we have observed no histological changes in the fetal thyroid gland specimens compatible with I^{131}-induced decrease in thyroid function, and as fetuses tested during maximum fall-out concentrations concentrated I^{131} well in their thyroid glands, we have no evidence that even the maximum I^{131} concentration in a fetal thyroid gland observed in this series was sufficient to produce hypothyroidism by the time of counting.

Could subtle radiation damage in the fetal thyroid produce hypothyroidism later in life? It is difficult to extrapolate from the few pertinent animal experiments to man.

Bustad and colleagues [14] found no evidence of hypothyroidism in the offspring of sheep fed 5μc per day throughout pregnancy and during breast-feeding of these offspring for four months. The offspring were then fed 5μc of I^{131} a day for five years and killed. The calculated total dose of irradiation received by a representative animal was 30,000 rads for the entire 5 years of life.

If any type of extrapolation from these data to our data on the human fetus were justified, it seems unlikely that even the maximum concentration of I^{131} found in human fetal thyroid would have resulted in hypothyroidism.

Radioactivity in Human Fetal Thyroid Required to Produce Neoplasm.—It is impossible for us to conclude that radiation from I^{131} in our fetal thyroid glands was sufficient to produce neoplasms, as none were observed in our histological sections. It is also dangerous to extrapolate from the few pertinent animal experiments to man. Bustad and colleagues,[14] observed the development of thyroid adenomas under the conditions stated above from daily I^{131} intake in four of five sheep receiving an estimated total dose of 30,000 rads. A metastasizing fibrosarcoma involving the thyroid gland was found in the fifth sheep. Six ewes exposed to 0.15 μc per day and 25 nonirradiated controls showed no involvement. This dose of irradiation, however, is greatly in excess of the doses observed here and therefore not pertinent to our observations.

Summary

Twenty-seven human fetal thyroid glands from 25 pregnancies, 12 human adult thyroid glands, 25 adult and fetal hog thyroid glands, and 11 reagent blanks were analyzed for I^{131} activity from fall-out.

Radioactivity compatible with I^{131} was found in the human fetal thyroid gland. The maximum concentration of I^{131} was 265 $\mu\mu$c per gram of fetal thyroid tissue, 29.1 $\mu\mu$c per gram of adult hog thyroid tissue, and 22.9 $\mu\mu$c per gram of adult thyroid tissue. The highest activity found on a reagent blank was 10.0 $\mu\mu$c. Data on fetal pathology, age of fetus, thyroid status of mother during pregnancy, and frequency of nuclear weapons testing have been examined for correlation with the degree of concentration of I^{131} in fetal thyroid.

The calculated maximum total radiation delivered to any fetal thyroid gland was 0.47 rads. The average total dose was 0.05 rads. Extrapolations from others' data from animals suggest that it is unlikely that this quantity of radiation would produce hypothyroidism or carcinoma of the thyroid gland.

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Miss Patricia Dahlstrom carried out all counting measurements used in this study. Katherine Elzinga, Jean Cofell, and Sharon Owings participated in the chemical extraction of I^{131} from thyroid tissue.

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Cardiotoxic Thyroid and Radioactive Iodine

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A study was made of 43 patients with heart disease who could not be restored to a comfortable state of ambulation by treatment with digitalis, diuretics, low-sodium diet, and other medication. In this group there were 5 men and 20 women with definite evidence of thyroid abnormalities. In none of the 25 was the hyperthyroidism diagnosed clinically, although it was looked for by both history and physical examination; the evidence was obtained in each case by the radioactive iodine (I^{131}) tracer technique. The diagnostic and therapeutic use of I^{131} is exemplified in the history of a 53-year-old man with angina pectoris. It is believed that by careful adjustment of I^{131} dosage the patient can be brought to a state of normal rather than subnormal thyroid function. The procedure outlined gave marked improvement in all patients but two who died of myocardial infarction.

Thyroid disease can usually be diagnosed clinically, even when there is minimal evidence of thyrotoxicosis and the thyroid is not palpable. It is accepted that this diagnosis frequently calls for effort and attention on the part of the clinician, and occasionally the diagnosis is elusive even with the most experienced. Diagnostic skills in recent years have been supplemented by laboratory procedures that have made it possible for the clinician to verify an opinion and institute proper therapy in the presence of thyroid disease that affects the heart.

In the early 1930's many papers were published [1] that advocated total thyroidectomy as a treatment for heart disease. This procedure did not meet with universal enthusiasm from physicians and was eventually dropped as a subject in the literature. Somewhat later, in the early 1950's, radioactive iodine (I^{131}) was used in the treatment of heart disease; the rationale for this procedure was similar to that used earlier by those who had advocated surgical removal of the thyroid gland. Two large series of cases were reported in 1955,[2] one of 1,070 and one of 231 cases. These two series included 814 cases of angina pectoris, 428 cases of congestive heart failure, and 59 cases of combined congestive

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