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Radioiodine Uptake Studies of the Human Fetal Thyroid[1,2]

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In addition to the many excellent studies of thyroid function in the animal fetus (1), (2), (3), (4), (5), earlier reports on test doses in the human (6), (7), (8), (9), (10), and the measurement of ^{131}I in the human fetus from fallout (11), (12), (13), there is a desire for further information regarding radioiodine uptake in the human fetal thyroid. This need is recognized by clinicians confronted with requests for thyroid studies and possible treatment during pregnancy. More information on human fetal thyroids is of value for radiation protection in Public Health and is of interest to embryologists and endocrinologists. Over a period of fourteen years we have studied ^{131}I uptake in 36 human fetal thyroids. We are presenting these data now in brief form and will publish more detail of particular aspects later.

MATERIAL AND METHODS

Once all arrangements had been made for the surgical removal of the fetus, the patient was given a test dose[4] by mouth. This was usually 24 hours before the operation, but in a few cases it was 18 to 20 hours. Estimates of age by measurements were done by checking length and weight against graphs made from the present data plus that in the literature. In earlier studies the thyroid was left on the trachea, but in most instances it was dissected free and weighed.

Gamma counting was utilized and this was done in a well-type detector in a volume equal to that used for the reference (aliquot of dose) solution. The concentration of the reference solution was such as to give a counting rate approximately to that of the specimen. In larger thyroids, the specimen was divided into several portions to avoid high counting rates that might result in coincidence loss. There was very little difference in the radioactivity of different portions of the same gland, but there were sources of variation such as blood (with its

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[4]This dose varied from about 500μCi for the very early stages to 100μCi or less for the older fetal thyroids. The autographic and chromatographic studies made the required doses higher than would have been needed for uptakes alone.

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contained ^{131}I) and moisture content (which affected the measured weight). These variables were controlled as much as was practical and it appeared that differences in contained radioactivity between fetal thyroids of approximately the same stage of development were due to individual variation and not to the techniques used.

Radioautographs were made (1) by floating sections on prepared autographic "A" or NTB prepared emulsions, or (2) by dipping the slides into autographic liquid emulsion.

Chromatograms of thyroid hydrolysates were made on Whatman No. 1 paper using 2 butanol-amonium hydroxide (3:1) as the descending solvent. Compounds were identified by using standards run at the same time and the relative radioactivity was determined with a windowless strip counter. Selected regions were also counted in a well-type scintillation detector. Radioautographs were made by placing the chromatographic strip against X-ray film for suitable exposure periods.

RESULTS

Thirty-six fetal thyroids obtained over a period of fourteen years have been studied and the results are given in Table I. In twenty-one cases, *in vivo* studies were possible and these data are shown in Figure 1.

There was no detectable uptake in the four thyroids (Nos. 6a and 6b were twins) whose fetal age was less than twelve weeks. Although the glands were recognizable, they were relatively undifferentiated with only a few acini present in peripheral regions. The thyroidal uptakes of the mothers were in euthyroid range, thus tending to rule out the possibility that the fetal uptakes were negligible because of medication (stable iodine, for example).

The seven thyroids in the 12 to 13-week group had detectable uptakes, but the measurements were somewhat inaccurate. The gland was so small that dissection was possibly not complete in all cases and the contribution of the blood ^{131}I contained was variable. The autographs demonstrated radioactivity only in peripheral areas where minute follicles with droplets of colloid had been formed. The autographs of thyroid treated with acid preservatives were very much fainter than those preserved in neutral formalin. This phenomenon would indicate that at this stage the ability to bind iodine organically was just beginning. Between the third and sixth month, follicles were formed throughout the gland and the ^{131}I uptake was more uniform. The autographs were positive even in acid preservatives. The highest concentration (per cent per gram) was observed around the sixth month of gestation. We do not have any fetuses from the sixth month to term, and these at term were anencephalics. Autopsy and histologic study demonstrated pituitary tissue in each of the anencephalics.[1] Two of these thyroids had not suffered postmortem autolysis and had uptakes of 3 and 1.19.

The uptakes at term were the highest of all of the fetal thyroids, but the percent per gram was lower than at the five to six month period. The follicles

[1]We are indebted to Mr. J. C. Peterson, a sophomore medical student, Summer Fellow, for making the histological study.

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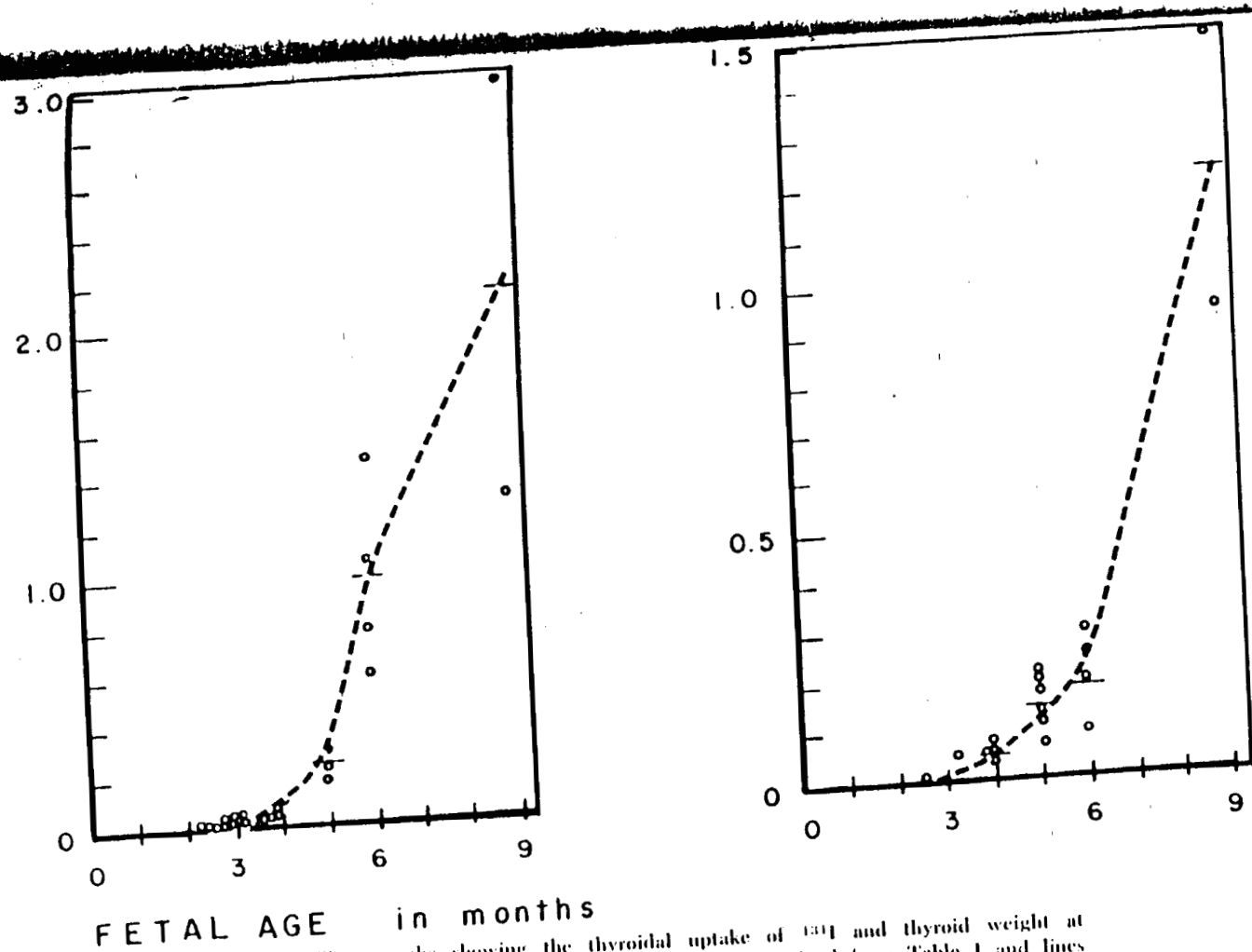

Fig. 4. Two graphs showing the thyroidal uptake of ^{131}I and thyroid weight at different times during fetal development. The data were obtained from Table I and lines are drawn, by inspection, through the means. The horizontal extension of the line at the mean indicates the range of fetal age included in this calculation.

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at term were well formed and filled with colloid. The epithelium was moderately flattened and did not show signs of hyperactivity.

It thus appears that although the ability of the fetal thyroid to concentrate iodine increased at a rapid rate from the third month, the maximum per cent per gram was reached at about the sixth month as from this time the gland increased more rapidly in mass. The concentration of radioiodine increased from 1.25% per gram during the three to four month period to 1.7 for the following month, and reached a peak of about five near the sixth month. At term, the per cent per gram was only two. We had only two usable anancephalic cases and whether their thyroid function was normal could be questioned. However, a lower concentration at term has been reported for the monkey (3), and the one anencephalic of our cases that lived for a few days after birth had a 24 hour uptake as high as that of the usual newborn.

Actually, the concentrating ability of the fetal thyroid is very low as compared to the newborn for the first three or four days. This has been found to be as high as 70% (Van Middlesworth, 1954 (14), Ogborn, et al., 1960 (15), Martmer et al., 1956 (17), Fisher, et al., 1962 (18), and Morrison, et al., 1963 (21)) under certain conditions. A diagram of these fetal values is shown in Figure 2 along with estimates from our experience and from the literature for the values during childhood and adult life.

In instances where it was not certain that the fetus would have to be removed, we did not give radioiodine to the mother. We were able to obtain the thyroid in good condition and were able to incubate it in Tyrode's balanced salt solution with glucose. We were not able to estimate from the incubation what the % uptake would have been *in vivo* because of the many differences including the non-uniform permeation of the isotope in the *in vitro* condition. Where penetration was uniform, good radioautographs were obtained with some organification in that the ^{131}I persisted even after acid preservation. This phenomenon showed that had Na I-131 been given *in vivo* under usual conditions, definite uptake by the thyroid would have occurred.

Our chromatography studies revealed, as found by Yamazaki, *et al* (8) that at the time of earliest uptake the thyroid did not bind ^{131}I to thyroglobulin. By the twentieth week however, ^{131}I was found in the organic fractions although most was in monoiodotyrosine. Later, there was an increase in the relative amount in the diiodotyrosine, triiodothyronine, and tetraiodothyronine fractions. These results are summarized in Table II. The relative radioactivity is indicated only roughly as the more exact calculations in percentage of the total have not been completed.

SUMMARY

Thyroidal uptake of ^{131}I in 36 human fetuses has been studied. There was no detectable uptake before the third month. From the third to the fourth month the uptake varied from 0.001 to 0.04% per gland with an average of 0.025, or approximately 1% per gram of thyroid. During the next month, the per cent per gland averaged 0.2 and the percent per gram of thyroid averaged almost two. The highest concentration was 5% per gram for the five to six month period.

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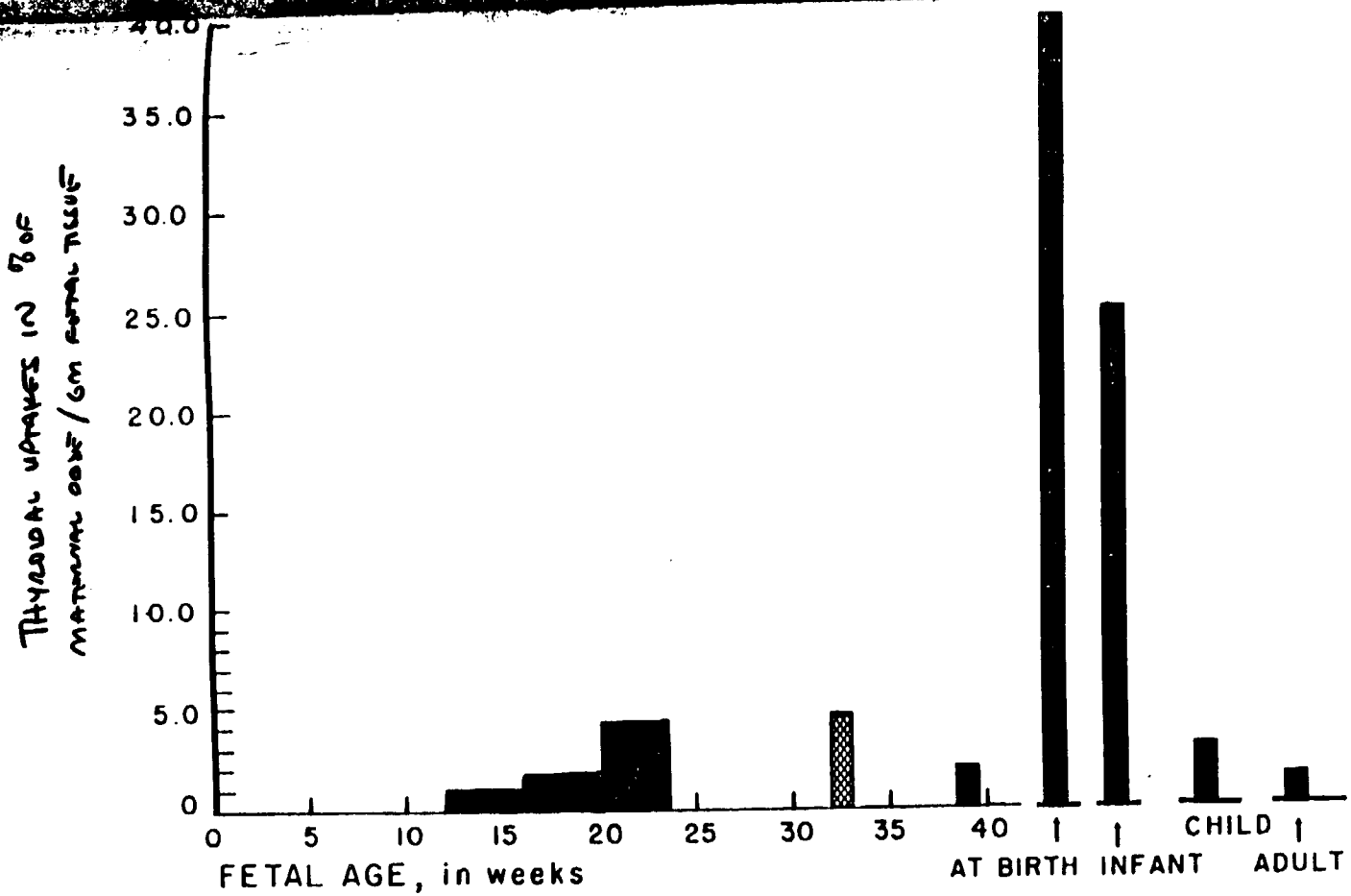

Fig. 2. Representative values of thyroidal uptakes in percent per gram at different times during fetal development, at birth, in infancy, during childhood and in the adult. The fetal values are from Table 1, except for the 32 week figure which is from Chapman, *et al* (6). The other values are estimates from the literature, such as in references 14, 15, 16, 17, 18, 19, 20, and 21.

Could be converted from %/gm to μCi/gm to rads/gm

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TABLE I

% OF MATERNAL DOSE IN TOTAL FETAL THYROID

MATERNAL UPTAKE

Fetal Number	Age - wks. by meas.	Age - wks. by hist.	Length cm C-R	Body wt. gram	Thy. wt. mg.[6]	C^{131}-I fetal thy.	Autograph	Mother C^{131} uptake 4 hr	Mother C^{131} uptake 24 hr
4	8	7	2.7			0	−	12	
6a	10	8	4.2	5.2		0			20
6b	10	8	4.4	5.3		0	−		22
7	12	10	6.4	14.5		0	±		
15	12	10			4.8	0.003	±	11	26
12[1]	13	12	8.0	37.0	5.2		+		
8	13	12	8.0	30.0	(7.0)	0.001	+		38 (48 hr)
10	13	11	7.0	21.0	(5.0)	0.010	+		29
3	13	13	7.2		(8.0)	0.034	+		30
9	13	12	7.6	26.0	(7.0)	0.030	+		
27[2]	13	14	7.0	21.0	(5.0)	0.001[2]	−		
17	14	13	8.2	38.0	(15)	0.03	++	12	26
2	14	13	8.0		(20)	0.03	++		35
19	15	13			41	0.03	++		
18[1]	15	15	10.1	65.0	(23)		++		
5	15	15	10.1		(23)	0.04	++		30
1	15	15	9.8	100.0	(45)	0.04	++		
13	15	15	10.8		58	0.025	++		
36[3]	16	14	13.0	160	(70)				
34[4]	17	16	13.5	160	50	0.004[3]	−		
23	18	17	14.0	170	(80)	0.003	+		

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14[1]	18	18	15.0	247	110		+++		
33	20	18	17.0	315	150	0.3	+++		
35[1]	21	20			204		++		
32[3]	21	18	18	420	187	0.24	−		
11	21	22	18	341	78	0.22	+++		
24a[5]	22	23	18.5	470	274	0.175[5]	−		
24b[1]	22	23	17.0	360					
16	22	20	19.0	440	96	0.8	+++	(61 −	4 days)
25	23	23	20.0	605	220	1.1	+++		
26	23	22	19.0	670	200	0.6	+++	18	
22	24	23	20.5	486	(225)	1.5	+++	10	41
29[1]	24	20		600	216		++		
21[3]	38	term[7]	39.0	1940	(1000)	0.7[3]	+	18	
20	38	term[7]	33.0	3155	944	1.3	+++		19
31	38	term[7]		2850	1500	3.0	+++		
28[3]	40	term[7]		3920	736	0.3[3]	−		
30	4 days post partum[7]				870	40	++++		

[1] *In vitro* study.
[2] Iodine-131 given as triiodothyronine; autograph was negative. Autograph was positive however, after incubation with Na^{131}-I.
[3] Post mortem autolysis
[4] Lymphocytic infiltration
[5] Iodine-131 given as radioiodinated human serum albumin, autograph was negative. Autograph positive after incubation with ^{131}-I as NaI.
[6] Thyroid weights in parentheses are estimates based on body weight and C-R height.
[7] Anencephalic

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During this time, the uptake per gland was about 1%. Near term, the percent per gland increased to two, but the concentration was less than at the sixth month. The maximum concentration was about five times that of the adult thyroid, but this concentration is much lower than that found for the first few days after birth.

TABLE II

CHROMATOGRAPHY RESULTS

Fetal Age	*Fetal Number*	*Relative ^{131}I Content*				
		I	*MIT*	*DIT*	*T3*	*T4*
20 weeks	33	+	+++++	++++	−	−
22 weeks[1] (*in vitro*)	29	+++++	++	±	−	−
24 weeks	22	++	++++	++++	−	−
Anencephalic at term	31	++	+++	++++	±	±
Anencephalic at term[2]	28	++++	++	+++	+	±
Anencephalic P. P. 1 week	30	+	+++	+++++	●	+

[1]Incubated with $Na^{131}I$
[2]Autolysis

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