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See pp 419 & 420 for estimates of $T_{1/2}$ I^{131} in fetus. See p 423 [illegible] p 421 – placenta [illegible] large "external" [illegible] highly energetic short-lived radionuclides?

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STRUCTURAL AND FUNCTIONAL DEVELOPMENT OF THE HUMAN FOETAL THYROID

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SUMMARY

1. Certain aspects of the functional and physical development of the foetal thyroid gland have been studied in thirty-seven human foetuses after administration of ^{131}I to the mother at varying times before termination of pregnancy. The radioactivity in different intra-uterine tissues was also measured.

2. The growth and iodine-trapping function of the human foetal thyroid gland was found to be age-dependent, certainly up to the 23rd week of gestation, while the estimated biological half-life of radioiodine was much shorter than that of the adult up to the 19th week of gestation.

3. The data obtained were used to calculate irradiation doses to the foetal thyroid and gonads produced by isotopes of iodine entering the maternal circulation.

The use of radioiodine in clinical and experimental medicine is now well established and the short-lived isotope of iodine ^{132}I has been used by a number of workers studying thyroid function during pregnancy (Pochin, 1952; Halnan, 1958; Aboul-Khair *et al.*, 1964). Although the doses used by these investigators were described as being within permissible limits (in respect of irradiation to the foetal thyroid and gonads) the data on which this view was based is inadequate primarily because of our ignorance of the biological half-life of iodine in the foetal gland. The investigation reported in this paper was designed to study how the human foetal thyroid gland develops its capacity to trap iodine and so obtain more accurate estimates of irradiation doses to the foetal gonads and thyroid following the administration of radioisotopes of iodine, either by accident or intention, to pregnant women.

MATERIALS AND METHODS

The study was carried out in thirty-seven patients with normal pregnancies in whom therapeutic termination was performed on medical or psychiatric grounds. No foetus showed any developmental abnormality.

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In twenty-nine of the patients hysterotomy was carried out at varying time intervals (3, 6, 12, 24, 48, 96 or 144 hr) after the intravenous injection of 20–40 μCi of ^{131}I in the form of carrier-free sodium iodide. During the operative procedure 20 ml uterine venous blood was removed and care taken to obtain the uterine contents without rupturing the membranes. In the twenty-nine cases foetal length and weight were measured and foetal age derived from these measurements together with consideration of the menstrual data. The period of gestation ranged from 13 to 23 weeks. The foetal thyroid gland was dissected out, weighed on a torsion balance, and homogenized in a polythene tube containing 5 ml of 3 N-sodium hydroxide solution. The radioactivity in the homogenate was measured by counting for 100 sec. Counts of the homogenate were checked against a standard and the percentage uptake of radioiodine per milligram foetal thyroid was calculated after allowing for background radiation. The thyroidectomized foetus was then homogenized, an aliquot weighed and the radioactivity counted for 100 sec. By checking against a standard and correcting for background counts, the percentage concentration of radioiodine per gram of foetal body weight was calculated. The same procedure was carried out for placenta and membranes together. The radioactivity in 5 ml amniotic fluid and 5 ml maternal plasma were counted, each for 100 sec, the latter being counted before and after passing through an ion-exchange resin. After checking against a standard and correcting for background, the percentage concentration of radioiodine per millilitre of amniotic fluid and maternal plasma was estimated. The counts on the samples and standard were obtained by using a Panax Scintillation Counter USC B, fitted with a well-type crystal.

In two patients hysterotomy was carried out at the 8th and 9th weeks of pregnancy. In these cases 20 μCi of radioiodine was administered 12 hr before termination. Since the foetal thyroid gland could not be identified in either case each foetus was homogenized in 3 N-sodium hydroxide solution. The percentage concentration of radioiodine per gram of foetal weight was estimated and did not differ significantly from zero in either case.

In the remaining six patients no radioiodine was administered prior to termination. Histological sections were made from the foetal thyroid glands obtained and strained with haematoxylin and eosin. The foetal age in these cases ranged from 12 to 25 weeks.

Radiation to foetal gonads

Radiation to the foetal gonads is estimated from the five sources listed below. In all cases the dose is referred to an administered activity of 1 μCi.

1. *Gamma-radiation dose from inorganic iodide in maternal and uterine tissues.* We have taken as a model a system in which the initial concentration is the maximum concentration falling off with a half-life of 6 hr. Our results for the concentration of ^{131}I in foetal tissue, amniotic fluid and placenta show high concentration at our earliest measurement 3 hr after injection falling off with a half-life between 4 and 8 hr. Extrapolation of our measurements back to the time of injection gives a spread from 0·001 to 0·004% g, and we have taken 0·0025 as the average.

With these figures the appropriate formula is (Hine & Brownell, 1956)

$$\text{Dose} = 10^{-3}\rho\bar{g}\Gamma C_0\int_0^\infty \exp\left\{-0{\cdot}693\left(\frac{1}{6}+\frac{1}{\tau}\right)t\right\}dt \text{ rad} \quad (t \text{ in hr}),$$

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where $\bar{g}$ body shape factor = 175 for region of foetus,
Γ = 2·18 r/hr/mCi at 1 cm from source, for ^{131}I,
= 11·8 r/hr/mCi at 1 cm from source, for ^{132}I,
ρ = tissue density $\simeq$ 1,
C_0 = $2{\cdot}5 \times 10^{-5}$ μCi/g,
τ = physical half-life $\simeq$ 192 hr for ^{131}I, 2·25 hr for ^{132}I.

2. *Gamma-radiation dose from radioiodine labelled thyroxine.* We assume that the concentration of radioiodine labelled thyroxine increases with a half-period of 3 days and dies away with a half-life of 6 days for ^{131}I.

With these figures the formula is:

$$\text{Dose} = 10^{-3}\rho\bar{g}\Gamma C_0 \int_0^\infty \left\{1 - \exp\left(-0{\cdot}693\frac{t}{3\times 24}\right)\right\}\exp\left(-0{\cdot}693\frac{t}{6\times 24}\right)dt \text{ rad},$$

C_0 is derived from Halnan's value for the maximum concentration of thyroxine in the plasma and assuming that the mean tissue concentration is one-fifth of this.

When the appropriate figures are inserted for ^{132}I the dosage contribution is found to be negligible.

3. *Gamma-radiation from radioiodine in foetal thyroid.* The foetal thyroid concentrates iodine to an increasing extent from the 13th week onwards. The dose to the gonads from this source will therefore be zero before about 13 weeks and will increase as the foetal age increases. We have made a rough estimate of the distance between the foetal gonads and foetal thyroid for a 23-week-old foetus and from this, with a correction for tissue absorption, have calculated the dose received by the gonads.

$$\text{Dose to foetal gonads} = \frac{10^{-3}A_0\Gamma}{d^2}\int_0^\infty \exp\left(-0{\cdot}693\frac{t}{\tau}\right)dt \text{ rad},$$

where A_0 = peak activity in thyroid (mCi),
d = distance from foetal thyroid to foetal gonads (cm),
τ = effective half-life of activity in foetal thyroid (hr),
= 144 hr for ^{131}I,
= 2·25 hr for ^{132}I.

4. *Beta-radiation dose from inorganic iodide.* The time constants and concentrations are the same as for section 1.

$$\therefore \text{Dose} = 1{\cdot}6 \times 10^{-8}\bar{E}_\beta\, 3{\cdot}7 \times 10^4 C_0 \int_0^\infty \exp\left(-0{\cdot}693\frac{t}{\tau}\right)dt \text{ rad},$$

where τ = 6 for ^{131}I = $\frac{2{\cdot}25}{24}$ for ^{132}I,

$\bar{E}_\beta$ = mean β-ray energy (MeV) = 0·187 for ^{131}I = 0·49 for ^{132}I.

5. *Beta-radiation from organically bound radioiodine.* The time-constants and concentrations are the same as for section 2.

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$$\therefore \text{Dose} = 1{\cdot}6\times10^{-8}\bar{E}_\beta\, 3{\cdot}7\times10^{4}C_0\int_0^\infty\left\{1-\exp\left(-0{\cdot}693\frac{t}{3\times24}\right)\right\}\exp\left(-0{\cdot}693\frac{t}{6\times24}\right)dt \text{ rad,}$$

for ^{131}I.

For ^{132}I the dose, with the appropriate decay-constants, is negligible.

Radiation dose to foetal thyroid

The weight and radioiodine concentrations were measured for each foetal thyroid and from this the dose can readily be calculated. The assumption has been made that each thyroid gland can be considered as two spheres set a little apart so that β-radiation from the one has little effect on the other. The dose from γ-radiation has also been neglected as of little importance compared with that from β-radiation. A correction has also been calculated for the finite size of the lobes. In the smallest thyroid measured this correction was about 18%. The correction was negligible for the largest of the foetal thyroids.

The appropriate formula is (Hine & Brownell, 1956),

$$\text{Dose} = \frac{51{\cdot}2\times\bar{E}_\beta\times T_{\text{eff}}\times C_0\times K}{0{\cdot}693}\text{ rad.}$$

where T_{eff} is the effective half-life of the radioiodine in the thyroid (in days),
and K is a factor (<1) depending on gland size,
C_0 = concentration (μCi/g).
C_0 has been assumed to be the initial concentration in thyroid by neglecting the short uptake period.

In the case of ^{132}I the uptake half-period is of the same order as the physical half-life and the above formula is replaced by

$$\text{Dose} = \frac{51{\cdot}2\times\bar{E}_\beta\times T_{\text{eff}}^2\times C_0\times K}{0{\cdot}693\times(T_u+T_{\text{eff}})}$$

where T_u = uptake half-period (days).

RESULTS

A table (*Clin. Sci.* Table 31/5) giving measured and derived data in respect of stage of gestation and foetal thyroid and placental weights has been deposited with the Librarian, Royal Society of Medicine, London, W.1, from whom copies may be obtained.

Correlation of period of gestation with foetal thyroid weight and radioiodine uptake

Fig. 1 shows the relationship between foetal thyroid weight and age in twenty-nine cases and a positive correlation is present (r = 0·716). Foetal thyroid weight thus increases with foetal age over the age range studied.

Fig. 2 shows the percentage uptake of radioiodine per milligram of foetal thyroid in twenty-six cases between 3 and 96 hr after administration of the isotope to the mother plotted against foetal age in weeks; again a positive correlation was found (r = 0·650). Thus the ability of the foetal gland to concentrate iodine increases with gestation. Fig. 2 has two points at 8 and 9 weeks gestation representing the foetal thyroids which did not concentrate radioiodine. It was not until after the 12th week of gestation that measurable amounts of ^{131}I were detected in the gland.

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Uptake of radioiodine by foetal thyroid against injection-termination period

Fig. 3 shows the log percentage uptake of ^{131}I/mg in twenty-nine foetal thyroid glands plotted against the time between injection of ^{131}I into the mother and the termination of

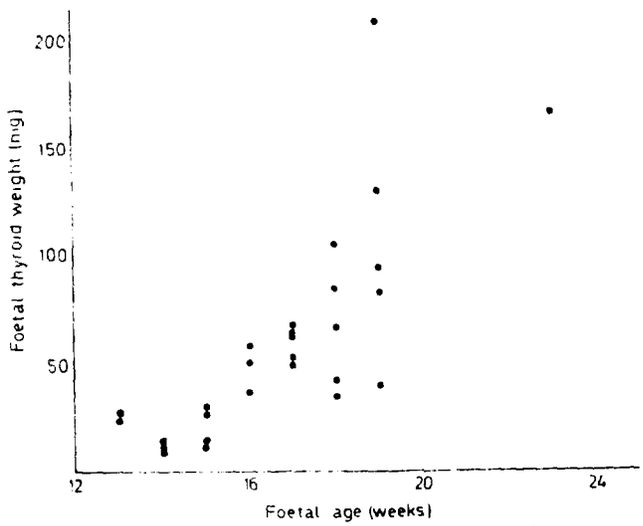

FIG. 1. The correlation of foetal thyroid weight with foetal age in twenty-nine cases.

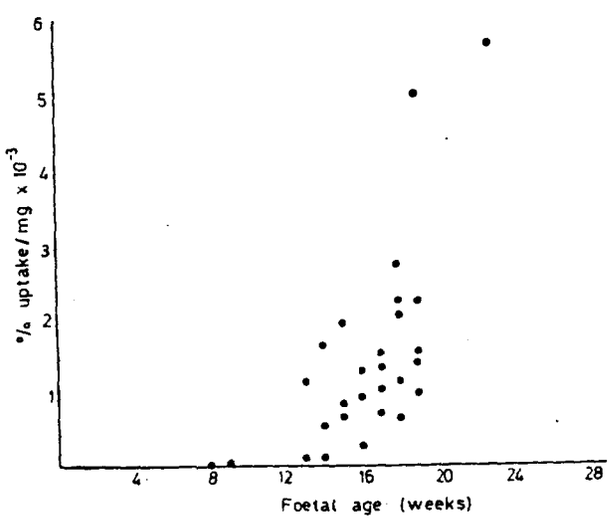

FIG. 2. The uptake of ^{131}I by the foetal thyroid, between 3 and 96 hr after administration of the isotope to the mother, correlated with foetal age in twenty-six cases. $r = 0{\cdot}650$; $P < 0{\cdot}001$.

pregnancy. The figure written beside each point is the foetal age in weeks. It can be seen that the maximum uptake of ^{131}I by the foetal thyroid is reached within approximately 12 hr of injecting the dose. A trend towards discharge of the radioiodine after that time can be seen in the 18- and 19-week-old foetuses while complete discharge was reached within 144 hr in the three foetuses aged 13, 14 and 16 weeks. This trend can also be seen by comparing the

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13- and 14-week values at 12, 48 and 144 hr and also the 16- and 17-week values at 6, 48, 96 and 144 hr.

The minimum and maximum biological half-lives of ^{131}I in the foetal thyroid gland between 13 and 19 weeks gestation was derived from the two slopes which would best fit the data. The estimated range was found to be 16–28 hr.

Radiation doses to foetal gonads and thyroid

The radiation doses (rad) to foetal thyroid and gonads from β- and γ-irradiations were calculated from the data shown in Table 1 and the results are summarized in Table 2.

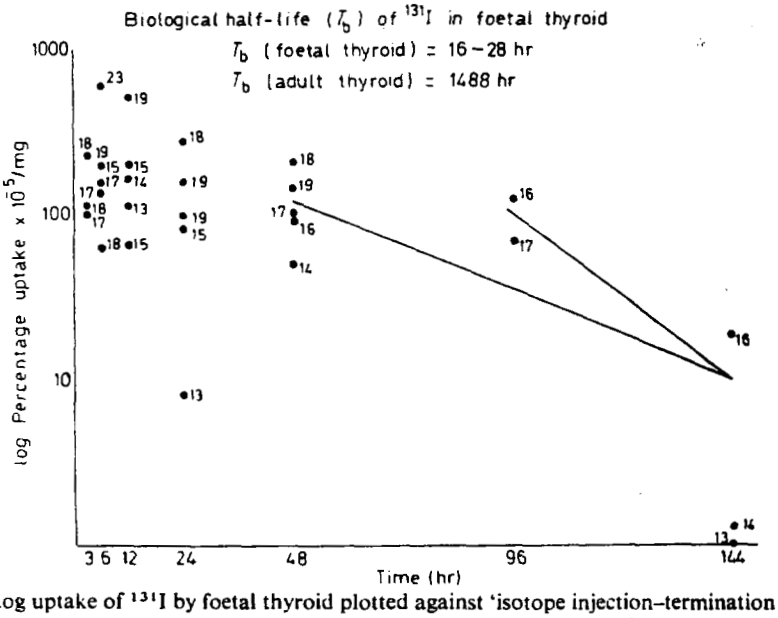

FIG. 3. Log uptake of ^{131}I by foetal thyroid plotted against 'isotope injection–termination period' to derive estimates of minimum and maximum biological half-lives of ^{131}I in the foetal gland, 16 and 28 hr respectively. Compare with adult value of 1488 hr. The foetal age in weeks is shown beside each point.

Concentration of ^{131}I in maternal blood, amniotic fluid, thyroidectomized foetus, placenta an membranes

Fig. 4 shows the concentration of ^{131}I in these fluids and tissues plotted against the isotop injection–termination period and since each point represents the mean of the values shown i Table 2 it is a composite picture of the distribution of radioactivity between the 13th and 24t week of gestation. It shows that the concentrations of ^{131}I in extrathyroidal foetal tissue amniotic fluid and placenta are highest 3 hr after injecting the dose and fall off with a hal life between 4 and 8 hr.

Histology

The histological appearances of the thyroids from six foetuses between 12 and 25 week gestation showed a structural gradation between the poor development of the follicles, tightl packed cells, scanty colloid, and poor vascularity of the youngest to that of well-forme follicles, much colloid and rich vascularity, comparable to the adult thyroid, in the oldest.

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DISCUSSION

has been shown by a number of workers that the thyroid gland of the human foetus begins) trap iodine about the 12th week of gestation (Chapman *et al.*, 1948; Hodges *et al.*, 1955) nd the present study confirms this view. The data of these workers, obtained from a relatively

TABLE 1. Concentration of radioiodine in foetal thyroid and foetal environment as a percentage of a dose given o the mother at 3, 6, 12, 24, 48, 96 and 144 hr before termination of pregnancy (foetal age in weeks shown in parentheses)

Time before termination of pregnancy (hr)	Foetal thyroid (% uptake/mg) ($\times 10^3$)	Inorganic iodine in maternal blood (% of dose/ml) ($\times 10^3$)	Organic iodine in maternal blood (% of dose/ml) ($\times 10^3$)	Placenta (% of dose/g) ($\times 10^3$)	Foetal body (% of dose/g) ($\times 10^3$)	Amniotic fluid (% of dose/ml) ($\times 10^3$)
3	1·00 (17)	16·80 (17)	0·00 (17)	9·00 (17)	0·84 (17)	6·30 (17)
	1·10 (18)	1·80 (18)	0·00 (18)	6·60 (18)	0·92 (18)	0·50 (18)
	2·20 (18)	1·30 (18)	0·00 (18)	7·00 (18)	0·79 (18)	0·75 (18)
	2·20 (19)			0·90 (19)	0·98 (19)	1·10 (19)
6	1·90 (15)	0·90 (15)	0·00 (15)	0·40 (15)	0·90 (15)	0·30 (15)
	1·50 (17)	0·80 (17)	0·00 (17)	0·50 (17)	0·70 (17)	0·70 (17)
	1·30 (17)	1·30 (17)	0·00 (17)	0·70 (17)	0·70 (17)	0·90 (17)
	0·60 (18)	0·50 (18)	0·00 (18)	0·30 (18)	0·24 (18)	0·40 (18)
	5·70 (23)	1·00 (23)	0·00 (23)	5·00 (23)	5·60 (23)	1·00 (23)
12	1·10 (13)	0·18 (13)	0·00 (13)	0·20 (13)	0·12 (13)	0·43 (15*)
	1·90 (15*)	0·19 (15*)	0·00 (15*)	0·19 (15*)	0·13 (15*)	0·33 (17)
	0·64 (15*)	0·00 (19)	0·00 (19)	0·28 (15*)	0·12 (15*)	0·50 (19)
	1·60 (14)			0·20 (17)	0·30 (17)	
	5·00 (19)			0·16 (19)	0·20 (19)	
24	0·08 (13)	0·10 (13)	0·00 (13)	0·06 (13)	0·00 (13)	0·16 (13)
	0·80 (15)	0·13 (15)	0·00 (15)	0·00 (15)	0·17 (15)	0·10 (15)
	2·70 (18)	0·04 (18)	0·07 (18)	0·14 (18)	0·40 (18)	0·40 (18)
	1·50 (19)	0·02 (19)	0·05 (19)	0·00 (19)	0·00 (19)	0·40 (19)
	0·96 (19)	0·00 (19)	0·00 (19)	0·03 (19)	0·13 (19)	0·70 (19)
48	0·50 (14)	0·02 (14)	0·18 (14)	0·00 (14)	0·40 (14)	0·13 (14)
	0·90 (16)	0·06 (16)	0·08 (16)	0·08 (16)	0·21 (16)	0·09 (16)
	1·00 (17)	0·00 (17)	0·04 (17)	0·06 (17)	0·14 (17)	0·05 (17)
	2·00 (18)	0·00 (18)	0·34 (18)	0·12 (18)	0·24 (18)	0·06 (18)
	1·40 (19)	0·03 (19)	0·11 (19)	0·07 (19)	0·44 (19)	0·03 (19)
96	1·20 (16)	0·14 (16)	0·08 (16)	0·00 (16)	0·12 (16)	– (16)
	0·67 (17)	0·04 (17)	0·16 (17)	0·00 (17)	0·34 (17)	0·00 (17)
144	0·00 (13)	0·06 (13)	0·31 (13)	0·00 (13)	0·00 (13)	– (13)
	0·03 (14)	0·24 (14)	0·30 (14)	0·00 (14)	0·00 (14)	0·00 (14)
	0·18 (16)	0·00 (16)	0·03 (16)	0·00 (16)	0·08 (16)	0·05 (16)

* Twins.

small number of cases, also suggested that the capacity of the foetal gland to concentrate iodine increased as gestation progressed and this deduction has also been amply confirmed in the present study. The increasing efficiency of iodine trapping with foetal age has also been demonstrated in the macaque monkey by Pickering & Kontaxis (1961). The increase in the

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iodine trapping capacity of the human foetal gland may be explained on the basis of the structural differentiation which occurs, resulting in larger numbers of well-formed acini and an increase in both colloid and vascularity. This structural differentiation has also been demonstrated by Shepherd, Anderson & Anderson (1964). Alternatively there may be an

TABLE 2. Radiation doses to foetal thyroid and gonads

	Dose (rad) to foetal thyroid		Dose (rad) to foetal gonads	
	γ	β	γ	β
From 5 μCi ^{131}I	0	0–4·15	0·00055 –0·00070	0·00060
From 5 μCi ^{132}I	0	0–0·345	0·00060 –0·00070	0·00013
From natural radiation/year (U.N. Committee, 1957)	0·07–0·17			

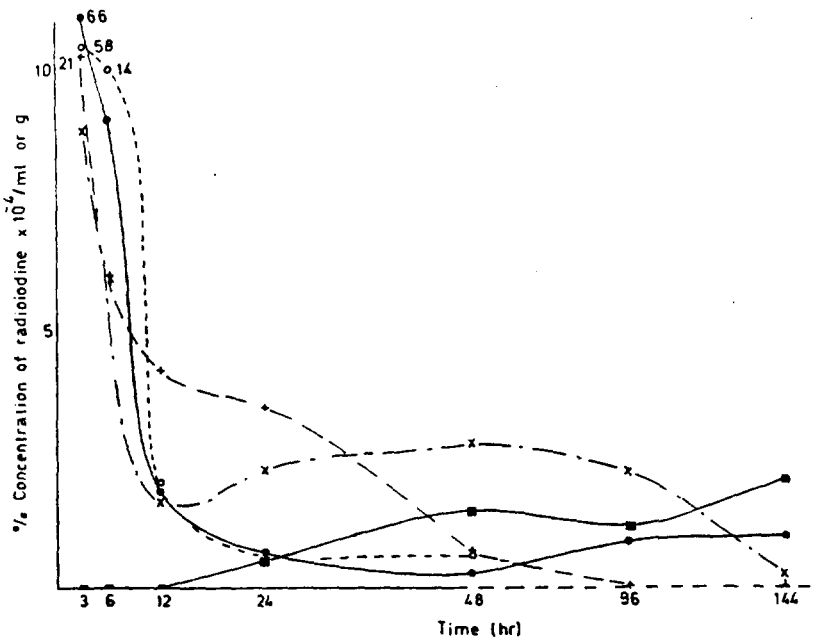

FIG. 4. The concentration of ^{131}I in various extra-thyroidal foetal and maternal fluids and tissues plotted against 'isotope injection–termination period'. ●, Maternal blood (inorganic ^{131}I); ■, maternal blood (organic ^{131}I); +, amniotic fluid; ○, placenta; ×, thyroidectomized foetus.

intrinsic increase in the capacity of the individual acinar cells to trap iodine. It is not inconceivable that both structural and metabolic development may progress together.

The difficulties inherent in an adequate study of the functional activity of the human foetal thyroid other than iodine trapping, are well demonstrated in the present study. Because of our ignorance of the time when maximum uptake of radioiodine would be reached and of the

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rate at which the isotope would be discharged it was necessary to have a large number of 'injection–termination' intervals. Furthermore, because of the nature of the clinical material, the disadvantage of the varying and uncontrolled foetal ages had to be accepted. In spite of the limitations of this type of data it is clear that the foetal thyroid gland metabolizes iodine in a very different manner to the adult gland over the foetal age range observed. Apparently radioiodine is discharged from the foetal gland with a *maximum* biological half-life of 28 hr compared to the adult value of 1488 hr (Rotblat & Owen, 1954). The three observations made in the 144-hr group are critical to this estimate. This small number of key observations must be viewed against the considerable problems in this type of investigation. However, the general hypothesis that radioiodine is discharged more rapidly by the foetal thyroid than by the adult gland gains some support from the trends shown in cases of comparable gestation at different 'injection–termination' times.

It is possible that our finding of a rapid discharge of radioiodine from the thyroid glands of the foetuses studied might indicate a progressive development of the mechanism for thyroid hormone synthesis as suggested by the results of Costa *et al.* (1965). The iodine released might be inorganic or incorporated in thyroid hormone precursors. An alternative explanation of the rapid rate of discharge of iodine might be that the rate of thyroxine excretion is higher than in the adult. Yet another possibility is that the progressive increase of colloid (and thus storage capacity for thyroid hormone) with foetal age could result in a loss of iodinated protein in the younger human foetus.

Doubts concerning the metabolism of radioiodine by the foetal gland do not affect the calculation of irradiation doses to foetal thyroid and gonads derived from the data obtained in this study and it is interesting to compare these dosage estimates with those of Halnan (1958). Halnan quotes the results of Chapman *et al.* (1948) who found uptake of radioiodine to be absent before 14 weeks and then to vary from 0·08%/g at 14 weeks to 4·8%/g at 32 weeks, with an uptake half-period of 3 hr. We have found uptake to be observable from 13 weeks onward; the measured concentrations varied from 0 (before 13 weeks) to 5·7%/g, and the uptake half-period was estimated to be between 2 and 6 hr. These figures are in satisfactory agreement with Chapman's and it might therefore be anticipated that Halnan's dosage figures would agree with ours. But Halnan, in his calculations, uses the physical half-lives of ^{131}I and ^{132}I as equivalent to the effective half-life of radioiodine in the thyroid. While this is admissible in the adult thyroid our results show a very rapid discharge of radioiodine from the foetal thyroid and the dosage calculations must take this into account. This makes little difference in the case of ^{132}I which has a very short physical half-life and in fact our results for ^{132}I are in good agreement with Halnan's. In the case of ^{131}I, however, the effect of the rapid discharge from the foetal thyroid has a large effect on the dosage calculations and the result is that Halnan's estimate of dose is much greater than ours. The difference in the values taken for the effective half-life of radioiodine in the foetal thyroid makes Halnan's calculated values for ^{131}I about seven times our calculated dosage values (after making allowance for the different peak concentration of the radioiodine in the foetal thyroid).

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