TABLE III. Comparison Between Fetal and Maternal Heart on Uptake of C^{14} Digitoxin and its Metabolites in Guinea Pigs.

	Unchanged digitoxin				Metabolites			
	Fetal hearts		Maternal heart		Fetal hearts		Maternal heart	
Animal*	μg/heart	μg/g	μg/heart	μ/g	μg equiv†/ heart	μg equiv/ g	μg equiv/ heart	μg equiv/ g
G.P. 1	N.S.C.‡	—	.03	.01	.06	.46	.23	.09
2	.05	.09	.03	.01	.07	.12	.45	.16
3	.03	.07	.02	.01	.09	.21	.28	.18
4	.02	.03	.02	.01	.05	.06	.19	.10
Avg	.03	.06	.03	.01	.07	.21	.29	.13
Stand. dev.	±.007	±.013	±.004	±.0	±.006	±.09	±.003	±.08

* Animals sacrificed one hr after administration of drug.
† Amount of original drug converted into metabolic products.
‡ No significant counts.

talizing an embryonic heart beyond the therapeutic level.

Summary. 1. Digitoxin, and possibly its metabolic products, crosses the placenta of rats and guinea pigs. 2. Larger amounts of both unchanged digitoxin and its metabolites were found in the fetuses of guinea pigs than in the fetuses of rats. 3. Embryonic tissue may have a marked ability to catabolize the drug, or there may be a selective penetration of the metabolites across the placenta, as noted by its high metabolite-digitoxin ratio. 4. On a tissue weight basis, digitoxin and its metabolites were found in higher concentrations in the embryonic heart than in the maternal heart.

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Factors Influencing Development of Hypophyseal Tumors in Mice After Treatment with Radioactive Iodine.* (19683)

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It has been shown(1) that quantities of radioiodine of approximately 200 μc given to mice destroy, or almost destroy, the thyroid gland. This treatment is followed after an interval of about a year by development of fatal tumors of the pituitary gland. Gonadectomy neither favors nor inhibits the growth of the pituitary tumors(2).

In further exploration of the reasons for the tumorous growth, the following 2 series of experiments were initiated.

When C_{57} mice are fed the Remington "low-iodine" diet for one or 2 weeks before they are given I^{131}, 60% of the radioiodine accumulates in the thyroid gland. With such use of the Remington diet it is possible to produce the same thyroidal destruction with 30 μc of I^{131} as is produced in mice fed normal (Purina chow) diets by 200 μc(2) of I^{131}. The systemic, or "whole-body" radiation in the 2 cases is, however, very different,

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TABLE I. Relationship Between Dose of I^{131}, Dietary Regimen, and Incidence of Late Hypophyseal Tumors.

Group	No. of mice	Pre-I^{131} diet*	Dose of I^{131}, μc	Age at time sacrificed (mo)	Wt of pituitaries—In detail, mg	Wt of pituitaries—Avg, mg	Condition of thyroid gland
1	10	Purina Chow	None	12 –17	.7, .7, .9, .9, .9, 1, 1.2, 1.4, 1.6, 1.7	1.2	Normal
2	5	"	30	12.5–16.5	1.1, 1.3, 1.4, 1.6, 2.8	1.8	Normal or slight medullary fibrosis
3	14	"	200	11.5–16.5	2.6, 6.2, 12.4, 12.9, 17.2, 25.8, 32.6, 37, 52.1, 91.1, 98, 110.4, 116.2	48.9	Complete, or almost complete, destruction
4	9	Low-iodine	30	11 –16	.7, 1, 1, 1.1, 1.1, 1.4, 1.7, 1.8, 3.8	1.5	Complete, or almost complete, destruction
5	12	"	200	11 –16.3	11.2, 11.8, 13.6, 14.3, 14.8, 16.2, 18.6, 24, 36.4, 37.4, 56.2, 110	30.4	Complete destruction

* The low-iodine diet was begun at the age of 44-45 days, and fed for 35 days. The 30 μc or 200 μc doses of I^{131} were inj. subcut. on the tenth day of feeding the special diet.

varying by a factor of about 15 times. For the purposes of this experiment 24 C_{57} strain mice were fed the Remington diet† for 35 days. Radioiodine was given subcutaneously on the 10th day of this period in doses of 30 μc, or 200 μc (Table I). An equal number of mice was given these dosages of I^{131} while on a regimen of Purina Lab Chow.

In a second series of C_{57} female mice (Table II) all were given the pituitary tumor-eliciting dose of 200 μc of I^{131}. Of this group 25 then were given 2 subcutaneous injections per week of 2.5 μg of d-l thyroxine for the duration of their lives. In this same series, 17 mice were implanted subcutaneously 25 days after the I^{131} treatment with 2 complete lobes of thyroid glands from normal mice of the same age (70 days) and strain (C_{57}). In a similar way, 7 mice were implanted with an ovary, 7 with a pituitary, and 9 with an adrenal gland (Table II).

Results and discussion. The data summarized in Table I indicate that radiothyroidectomy *per se* will not lead to production of hypophyseal tumors. The mice whose thyroids were destroyed by 30 μc of I^{131} developed no tumorous pituitaries after periods of more than a year. This does not seem to be due to any inhibitory effect of the low-iodine diet because this diet did not prevent growth of pituitary tumors in mice treated with 200 μc of I^{131}.

In the doses used, thyroxine injections reduced the incidence and size of the pituitary tumors expected to develop after I^{131} treatment (Table II). It might be that higher doses of thyroxine would have been even more effective. This confirms the report of Goldberg and Chaikoff(4), and would seem to support their contention that the abnormal pituitary growth is due to the hypothyroidism resulting from the radiant destruction of the thyroid gland. However, the absence of pituitary tumors in the "30 μc-low iodine diet" group of mice indicates that such an uncomplicated conclusion is not possible.

The most effective agent found in these experiments in prevention of the pituitary tumorous growth was implantation of new thyroid tissue. Only in the few instances in which the implanted thyroids failed to survive were there pituitary tumors (Table II). No such protective action was obtained from implants of pituitary, adrenal, or ovarian tissue. The pituitary transplants completely degen-

† The ingredients for this diet were as follows (expressed as percent by weight): yellow corn meal 73.5%, wheat gluten 19.0%, dry brewer's yeast 5.5%, iodine-free NaCl 1.0%, $CaCO_3$ 1.0%. The NaCl was purified by precipitation from ethyl alcohol according to the procedure suggested by Pinching and Bates(3).

TABLE II. Relationship of Treatment of Mice with Thyroxine or Endocrine Gland Transplants to Development of Hypophyseal Tumors after Injection with I^{131}.* (All mice in this table were injected with 200 μc of I^{131} at 45 to 60 days of age.)

Group	No. of mice	Nature of treatment†	Age at time of sacrifice (mo)	No. of mice in which implant was: Recovered	Not recovered	Wt of pituitaries: In detail, mg	Avg, mg
1	25	Thyroxine inj., 5 μg/wk	9 –10	—	—	1.6, 1.8, 2, 2, 2	1.9
			14 –16.5	—	—	1.8, 2.2, 2.5, 2.8, 2.8, 2.9, 3.2, 3.4, 3.6, 3.6, 3.6, 3.8, 4, 5.6, 9, 9.3, 10, 13.4, 13.9, 28	6.5
2	17	Implant of thyroid, 2 lobes	12.5–16.5		4	6, 66.4, 94.2, 138.3	76.2
				13		.4, .8, .9, 1, 1.6, 1.8, 2, 2.4, 2.6, 2.8, 3.4, 4, 4.8	2.3
3	7	Implant of one ovary	12 –15		1	35.6	33.7
				6		4.5, 10, 11.9, 35.8, 45.6, 92.6	
4	7	Implant of one pituitary	12.5–15.3	7		26.2, 55.4, 70.6, 77.8, 126.2, 153, 157.4	95.2
5	9	Implant of one adrenal	12 –15		1	18	29.7
				8		9.4, 19.4, 22.8, 29.9, 38.1, 39.2, 49, 70.8	

* For additional control data see groups 1 and 3 in Table I.

† Thyroxine inj. were begun directly after the I^{131} inj. The tissue implants all were made 25 days after the I^{131} inj.

erated; the few surviving adrenals contained only a bit of the capsule and small amounts of zona glomerulosa; most of the ovarian transplants were recovered in an involuted condition and they lacked most of their germinal epithelia.

Summary. 1. Radiation thyroidectomy (under specified dietary conditions) with smaller amounts of I^{131} is not followed by pituitary tumors in C_{57} mice. 2. Such radiation thyroidectomy with larger quantities of I^{131} is followed by pituitary tumors. 3. Thyroid implants or adequate thyroxine dosages prevent appearance of the pituitary tumors after suitable I^{131} treatment. 4. Similar implantation of pituitary, ovarian, or adrenal tissue in treated mice does not prevent growth of the tumor. It is concluded that the radiation thyroidectomy is a necessary, but not the sole factor, leading to growth of the pituitary tumor in I^{131}-treated mice. It appears likely that another factor, related to the ionizing radiation itself, may be an influence aggravating or synergizing the thyroidectomy in its tumorigenic action on the pituitary gland of the mouse.

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