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Influence of 5-Fluorouracil on Thyroid Function.* (32293)

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5-Fluorouracil (5-FU) inhibits fetal growth, growth, liver regeneration, testosterone-induced growth of seminal vesicles, and somatotropin-induced growth of the epiphyseal cartilage(1); however, it increases the adrenal size presumably by stimulating secretion of ACTH(2). Acute experiments indicate that other antimetabolites such as Actinomycin D(3) and Puromycin(4), which interfere with protein synthesis, do not alter thyroidal iodine metabolism. Experiments were designed to determine if treatment with 5-FU, in doses that inhibit the growth of certain transplantable tumors when given for 5 or 10 days, would alter the effects of TSH on thyroid weight or iodine metabolism.

Material and methods. Four groups of male rats (Barkbridge Farms, N.J.) weighing about 150 grams were used. Each group consisted of 5-FU-treated and control animals; the latter differed from the former only in that they did not receive the antimetabolite. Group 1 had free access to laboratory chow and tap water and were injected with 25 mg/kg body weight of 5-FU for 5 days. Group 2 consumed an iodine-deficient diet and distilled water for 21 days and were injected with 5-FU, 25 mg/kg body weight, for the last 5 days of the experimental period. Group 3 were injected with 12.5 mg/kg body weight of 5-FU daily for a 10 day period during which they were given the iodine-deficient diet and distilled water. Group 4 received laboratory chow and tap water and were given 25 mg/kg body weight of 5-FU for five days and 8 U of TSH daily for the last four days, the last dose of each being given 24 hrs before death of the animals.

24 hours prior to sacrifice each animal was injected with one microcurie of I-131. At the time of sacrifice the thyroid glands were dissected and weighed, and the radioactivity was measured in a well counter. The circulating radioactive compounds of the animals in Group 2 (iodine-deficient for 21 days) were identified by radiochromatography using the butanol-ethanol-ammonia system.

Results and discussion. The results are listed in Table I. 5-FU in a dose of 25 mg/kg body weight for 5 days did not significantly alter the thyroid weight or the I-131 accumulation of rats fed either laboratory chow or an iodine-deficient diet for 21 days (Groups 1 and 2); however the I-131 uptake of the 5-FU treated iodine-deficient animals tended to be higher than that of their controls. Results of radiochromatographic analysis of the plasma of the 21 day iodine-deficient animals were the same in the 5-FU treated animals as in the controls. The ratio of radioactivity corresponding to thyroxine to that of inorganic iodide was 4:1, lesser amounts ran

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TABLE I. Changes in Thyroid Weight and I-131 Uptake Induced by 5-Fluorouracil.

No.	Treatment	Thyroid weight		I-131 uptake	
		Absolute	mg/100 g B.W.	Absolute	Per mg thyroid
	Group 1. 5-FU, 25 mg/kg B.W. for 5 days (stock diet)				
15	Control	10.1 ± 2.79*	6.3 ± 1.53	6.9 ± 2.04	0.69
18	5-FU	8.6 ± 2.11	6.1 ± 1.68	5.3 ± 2.05	0.63
	Sign. of diff.	n.s.	n.s.	n.s.	
	Group 2. Iodine def. diet, 21 days; 5-FU, 25 mg/kg B.W. for last 5 days				
12	Control	14.7 ± 4.28	8.7 ± 1.47	32.7 ± 8.59	2.22
14	5-FU	13.9 ± 2.47	8.7 ± 1.14	36.6 ±10.14	2.63
	Sign. of diff.	n.s.	n.s.	n.s.	
	Group 3. Iodine def. diet, 10 days; 5-FU, 12.5 mg/kg B.W. for 10 days				
11	Control	12.6 ± 1.83	8.2 ± 0.919	26.0 ± 5.96	2.05
13	5-FU	10.6 ± 2.04	7.9 ± 1.56	34.1 ± 6.08	3.21
	Sign. of diff.	$p < 0.02$	n.s.	$p < 0.01$	
	Group 4. Stock diet, 5-FU, 25 mg/kg B.W., 5 days; TSH, 8 U for 4 days				
8	TSH	15.3 ± 1.43	9.74 ± 1.87	8.9 ± 2.38	0.587
8	TSH, 5-FU	12.7 ± 3.01	7.51 ± 1.37	14.8 ± 3.43	1.08
	Sign. of diff.	$p < 0.05$	$p < 0.01$	$p < 0.01$	

* Mean and S.D.

with the triiodothyronine marker and none was noted at the stable markers for the iodinated tyrosine. These results reflect the enhanced I-131 uptake and thyroxine secretion induced by iodine deficiency.

Significant effects of 5-FU were noted in the animals treated with 12.5 mg/kg body weight during the ten day period of iodine deficiency and in those treated with TSH for 4 days and 5FU, 25 mg/kg, body weight, for 5 days. In each case the thyroid weight in the 5-FU treated animals was significantly less than in the controls, whereas the I-131 uptake was greater (Groups 3 and 4).

These observations indicate that the antimetabolite interferes with the growth response of the thyroid gland to TSH whereas it enhances the I-131 uptake. Studies using other metabolites such as Actinomycin D(3) and Puromycin(4) demonstrate that these agents, in acute experiments, interfere with TSH-stimulated thyroidal amino acid uptake but do not alter TSH-induced iodine accumulation or thyroxine secretion. These studies also support the concept that the TSH influence on hormone synthesis is not dependent on its growth promoting effect. Our observations support the finding of Dumont *et al*(5) that 5-FU stimulates thyroidal I-131 uptake. The failure of the 5-day course of treatment to alter the response of the thyroid of animals iodine-deficient for 21 days may be a reflection of the more intense TSH stimulation induced by the longer period of iodine deficiency, the increased TSH overcoming the inhibitory effects of the antimetabolite. An escape from the inhibitory effects of 5-FU testosterone-induced stimulation of the seminal vesicles occurs when a large dose of the androgen is used(6).

Summary. Treatment with 5-FU for 5 days inhibits the growth response of the thyroid gland to exogenous TSH and treatment for 10 days inhibits the growth response induced by iodine deficiency. The antimetabolite enhances the I-131 uptake induced by either exogenous or endogenous TSH.

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