Hormone-Secreting Transplantable Neoplasms of the Pituitary Induced by I^{131}.* (19027)

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Among the abnormal growths those of the endocrines and their target organs are the most difficult to characterize. Are the nodules of the adrenal, thyroid, prostate, and pituitary, which are commonly encountered in man and animals, true tumors or mere hyperplasias produced by endocrine overstimulation or dysfunction? Where is the borderline between hyperplasia and neoplasia, and what are the criteria to distinguish between them? Ovaries implanted into the spleens of castrated rats and mice invariably give rise to granulosa cell masses, by virtue of an endocrine disturbance brought about by destruction of gonadal hormones in the liver and secondary stimulation of the pituitary gland (1). Are these nodules true tumors? Stimulated by excessive gonadotropic hormones the granulosa cells grow progressively, but only a few such growths are transplantable to normal hosts. Occasionally, however, they can give rise to malignant growths(2). Gorbman(3) discovered that destruction of the thyroid by I^{131} gives rise to pituitary growths, presumably by overstimulation of the pituitary due to lack of thyroid hormone (TH). Are these growths true neoplasms, or merely hyperplasias? The answer to this question called for transplantation studies. Similarly long continued administration of antithyroid compounds causes the development of chromophobe tumors of the pituitary gland(4).

In our preliminary experiment we fully confirmed Grobman's observations and all mice receiving thyroid destructive doses of I^{131} and living longer than 13 months after such treatment developed pituitary growths (Table I). Mice of both sexes of the C57 strain were given $NaHSO_3$—NaCl solution subcutaneously in volumes of 0.2 cc and containing 200 to 400 μc of carrier free I^{131}. Immediately after injection many animals were lowered in the 100% geometry γ-ray ionization chamber(5) to determine the precise quantity of radioactivity introduced.

The mice were 6 to 10 weeks old when injected with either I^{131} or tumor fragments. Some were obtained through courtesy of Dr. William L. Russell, others from the Jackson Memorial Laboratory, and still others were raised by us. They were fed a standard laboratory diet including purina chow, given *ad libitum*.

The grafts were made into the leg muscle. The animals were kept until death or were killed only *in extremis*, with the exception of a few mice killed in order to study the histogenesis of pituitary growths and related changes. The head was opened under aseptic conditions, and the induced pituitary growths of 14 mice were removed for transplantation. Microscopic nodular, or ill-defined, tumor-like areas appeared in the pituitary 9 months after the I^{131} treatment, and gross tumors after about 10 months. Most mice living longer than 10 months listed in Table I were killed when a marked, usually sudden weight loss ("pituitary cachexia") and listlessness suggested the presence of a pituitary tumor. In the course of 8 months fragments of pituitary growths from 14 mice were implanted in 140 I^{131} pretreated or normal mice. The results of 9 transplantation experiments, the recipients of which lived longer than 6 months, are summarized in Table II. Some were

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TABLE I. Induction of Pituitary Growth by I^{131}.

Survival time after inj., mo.	No. in group	Result of treatment			
		Negative	±*	Pretumor	Tumor
>3	19	19			
3- 8½	31	31			
9- 9¾	4	1		3	
10–11¾	10	2	1	2	5
12–12¾	9	1	1		7
13–13¾	8				8
14–14¾	5		1		4
15–15¾	7				7
16–18¼	6				6

* The presence of a pretumor or tumor in these was probable but could not be fully established.

TABLE II. Summary of Transplantations of Nine I^{131} Induced Pituitary Growths.

		Recipients			
		I^{131} pretreated		Normals	
	Sex	No. grafted	No. +	No. grafted	No. +
Original growth	♀	18	10	59	0
	♂			20	0
Subpassage	♀	9	9	8	0

grafted on I^{131} pretreated or normal mice only, some were grafted on both.

All 3 primary pituitary growths which were grafted in I^{131} pretreated mice proved transplantable, while none of 7 similar (or the same) growths grew in normal mice. The first subpassage attempted succeeded in all 9 I^{131} pretreated mice and in none of the 7 normal mice of the same strain, age and sex. The I^{131} treatment was administered about 3 to 5 weeks prior to the graft so that a sufficient time elapsed for destruction of the thyroid. Indeed, destruction of the thyroid, we believe, created the necessary stimulus for the multiplication of the grafted pituitary cells.

The tumors grafted in the thigh appeared after about 2 to 3 months. They were firm, grey, "healthy" growths with little or no gross necrosis. There was a conspicuous stimulation of uteri in all tumor-bearing female mice. The ovaries of mice bearing grafted tumors invariably assumed the appearance of those receiving gonadal pituitary hormones or urine from pregnant women, while those bearing primary pituitary growths were atrophic and filled with lutein cells, as those of X-rayed mice. This difference is probably due to the age of the hosts; the former being young, the latter old with atrophic ovaries devoid of ova and normal follicles, non-responsive to pituitary gonadotrophins. This finding is indicative of discharge of large quantities of gonadotropins by the grafted tumors.

It can be assumed that thyrotropic hormones (TSH) are also produced by the neoplastic cells, but the very condition that made the growth of these tumors possible (destruction of the thyroid) made it impossible to observe the morphologic evidence of the presence of TSH. Bioassays are in progress. The changes preceding the development of these pituitary tumors will be more fully described. All tumors are chromophobes and appear to be derived from either basophils or chromophobes.

Comments. These transplantation experiments indicate that maintenance of growth of these pituitary tumors depends on destruction of the thyroid gland and lack of TH. If this is true, injection of TH will prevent the development of pituitary tumors. Patients with thyroid carcinoma heavily treated with I^{131} usually receive thyroid hormones when the signs and symptoms of myxedema are advanced. Therefore, patients so treated are not expected to develop pituitary neoplasms.

The morphologic features of the neoplastic pituitary cells are similar in different animals: all are "chromophobes," and all tumors invariably secrete gonadotropic hormones as indicated by the appearance of uteri and ovaries of tumor-bearing hosts. Presumably, all secrete also TSH and it seems probable that

the same cell manufactures both hormones. Accordingly, one would expect that if hyperplasia of these cells is brought about by a gonadal imbalance, the stimulated cells will also discharge thyrotropic hormones in excess. We are not familiar with clinical experience indicating that this is true.

If one cell produces different hormones, how is the specificity of stimulation maintained? If the induction of these pituitary growths is caused by destruction of the thyroid, would thyroidectomy also incite the development of such neoplasms? Will these conditioned neoplasms change into unconditioned neoplasms in the course of transplantation or in some hosts bearing them, as do the hyperplastic granulosa cell mass induced by the Biskind procedure(2)? Neoplastic cells are abnormal cells which frequently have a characteristically larger or smaller concentration of enzymes than their normal precursors. Will a similar dissociation occur with hormone secreting cells when they turn neoplastic? On basis of experience with liver tumors, it can be anticipated that some pituitary tumors may discharge one hormone only. Could such a dissociation be induced, or a selective depression of secretion of one hormone be brought about? It is possible, though not likely, that hosts whose thyroid had been destroyed by I^{131} are also susceptible to other neoplasms to which they are normally resistant. There are many different experiments which can be designed to answer these questions. It seems that a follow-up of Gorbman's discovery might yield new basic information concerning both the physiology of the pituitary and control of some neoplasms.

Summary. (1) Pituitary growths induced by thyroid destructive doses of I^{131} are readily transplantable in mice whose thyroid glands had been similarly destroyed, but not in normal mice. (2) These growths discharge gonadotropic hormones which in turn stimulate the production of gonadal hormones. Discharge of thyrotropic hormones by these tumors is assumed but remains to be demonstrated. (3) On the basis of observations made it is postulated that (a) the growths of the pituitary induced by thyroid destroying quantities of I^{131} are conditioned neoplasms formed by cells which are driven to proliferation through the stimulus created by the absence of TH; (b) the same chromophobe pituitary cell can discharge both gonadotropic and thyrotropic hormones.

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Glucose-Utilization in Hepatectomized Dogs.* (19028)

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In experiments here reported the rate of disappearance (or utilization) of sugar from the blood in hepatectomized dogs was studied immediately after operation, by determinations of the blood-sugar levels at intervals before and after the intravenous injection of glucose solution. In eviscerated dogs Soskin and Mirsky(1) observed that the rate of disappearance of blood-sugar, expressed in percentage of initial concentrations, was constant before and after intravenous injections of glucose. Comparing the behavior of eviscerated dogs and hepatectomized dogs, DeDuve(2) estimated the rate of utilization of glucose from amounts of intravenously in-

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