HORMONE RELATED TUMORS

EDITED BY
HIROSHI NAGASAWA
KAORU ABE

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Preface

Marked progress has been achieved in these years in research on tumors of hormone target organs, to which recent developments in radioimmunoassay, radioreceptor assay, and immunohistochemical analysis of hormones have contributed a great deal. The importance of research on these tumors is increasing with the growing complexity of our social, mental, and daily lives. This is well reflected by several international symposia on hormones and cancers, most of the results of which are published as proceedings.

However, books which include in one volume original reviews of recent progress in both experimental and clinical research on hormone related tumors are scarce despite the great significance of this subject. This is the reason why we are publishing this book. Articles were prepared by the most active and leading investigators in the world. They include extensive survey and discussion from the endocrinological standpoint of updated publications on the development, progression, characteristics, biology, and theories of diagnosis and therapy of major hormone related tumors.

We believe this book will be of much benefit not only to experimental and clinical researchers in related fields, but also to students and physicians.

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PITUITARY TUMOR

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Experimental Pituitary Tumors

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It has been generally accepted that the anterior pituitary of mammals is made up of five distinct cell types from which ten different hormones are secreted. Although the development of tumors from the respective cell types is accepted theoretically, tumors derived from every cell type have not necessarily been observed, and the response of cells to tumorigenic stimuli is greatly dependent on both the cell type and the species. Experimental studies on pituitary tumors (PT) may contribute toward the exploration of endocrinological problems including the following aspects. i) Functional PT are the suitable models for the comparative study of pathophysiology in PT patients. ii) PT can be utilized as the source for determination of the molecular structure of a given hormone. iii) Induction of PT by deranging the homeostatic balance of the feedback mechanism without any carcinogenic treatment appears to be an excellent model for studying the mechanism of evolution from a hyperplastic to a neoplastic state cell. iv) A transplantable PT should be a good source for a continuous supply of an endogenous hormone in evaluating the role of pituitary hormones in the development and progression of tumors in various target tissues. Unlike other tissues, the pituitary has not been the primary target of any carcinogens except radiation, by which certain

types of PT have been induced probably as a part of its random tumorigenic effect. The PT genes appear to represent the uniqueness of the tumorigenic mechanism in the endocrine system. In this review, we will briefly describe the available data obtained through studies of experimental pituitary tumors, mainly in mice and rats (*22*, *31*).

I. SPONTANEOUS PITUITARY TUMORS

Spontaneous PT have been observed in many species of mammals including humans. In old rats, the frequency of PT seems to be quite high if they are carefully observed. The development of PT is usually not common in rats less than 18 months old, but it increases with age.

A survey by Russfield (*75*) from old literature and our recent observations on the incidence of spontaneous PT in aged rats indicated that there is a great strain difference, ranging from 4 to 94% (Table I); *e.g.*, in Shermann rats only 4% in males (*77*) and 62% in females (*52*); in Wistar rats 12% in males and 68% in females (*90*); in Wistar/Furth (W/Fu) rats 60% in males (*51*) and 27% in females (*53*); and a 94% incidence was noted in male Long-Evans rats (*38*). Sass *et al.* (*76*) recently reported that PT developed in 35.9% of females and 23.8% of males of Fischer (F-344) rats kept throughout their natural lifespan.

Although there have been no standard rules for the diagnosis of PT in an individual report, a pituitary gland weighing more than 19 mg in rats and

TABLE I
Incidence of Spontaneous Pituitary Tumors in Rats

Strain	Male (%)	Female (%)	Observation period (months)	Ref.
Wistar	12	68	24	Wolfe *et al.*, 1938 (*90*)
Yale (Osborne-Mendel)	60	30	20	Saxton and Graham, 1944 (*77*)
Shermann	4	—	24	Saxton and Graham, 1944 (*77*)
W/Fu	—	27	>17	Kim *et al.*, 1960 (*53*)
R (Amsterdam)	—	60	>33	Kwa, 1961 (*57*)
Long-Evans	94	—	24	Griesbach, 1967 (*38*)
Shermann	—	62	>21	Kaunitz *et al.*, 1970 (*52*)
Charles River	48.8	—	>21	Ito *et al.*, 1972 (*51*)
W/Fu	60	—	>21	Ito *et al.*, 1972 (*51*)
F 344	24	36	>22	Sass *et al.*, 1975 (*76*)
ACI/N	6	21	42	Maekawa and Odashima, 1975 (*62*)

TABLE II
Incidence of Spontaneous Pituitary Tumors in Mice

Strain	Male (%)	Female (%)	Age (months)	Ref.
$(O_{20} \times DBAf)F_1$	—	10	Old	Mühlbock, 1951 (*68*)
$(C57 \times A)F_1$	—	8	36	Upton and Furth, 1955 (*84*)
A	0	—	28	Furth *et al.*, 1957 (*19*)
C57L	—	+	28	Furth *et al.*, 1957 (*19*)
NZY	—	25	>12	Bielschowsky *et al.*, 1956 (*4*)
C57BL/6J	0	75	30	Schechter *et al.*, 1979 (*78*)

3 mg in mice have been empirically scored as tumors, in which microtumorous foci can be found by histological examination (*51*). There appears to be no sex preference in the prevalence of spontaneous tumors. In general, the frequency of spontaneous development of PT in rats is higher than in mice. In this review, we will use the nomenclature for PT in conformity with that proposed by Furth *et al.* (*22*). Kim *et al.* (*53*) first described the functional characteristics of spontaneous PT by observing the physiological changes in primary tumor-bearers and by transplantation studies, and concluded that most, if not all, of the tumors are mammo-somatotropic. Kwa *et al.* (*58*) and Ito *et al.* (*51*) later confirmed this by using radioimmunoassay and immunohistochemical staining. Immunocytological and fine structural studies of spontaneous PT have revealed the existence of prolactin cells in the tumors (*56*). In contrast with estrogen-induced PT which are usually fully hormone dependent in the early transplantation passages, spontaneous PT are autonomous even in the original passage (*51*, *53*).

The pathogenesis of spontaneous PT has been little known. It is supposed that various estrogenic stimuli in females and an increased secretion of estrogen by conversion of androgen to estrogen in aged males are responsible for the high frequency of spontaneous PT in rats.

Spontaneous PT in mice have been extensively reviewed by Kwa (*57*) and Liebelt (*59*). The frequency of spontaneous PT in various mouse strains is tabulated in Table II. An exceptionally high incidence (75%) was reported in female C57BL/6J mice, but the incidence is nil in males (*78*).

In contrast with rat tumors, information on the functional characteristics of spontaneous PT in mice is rather scanty. The majority of tumors in mice have been described histologically as chromophobic, but many are now considered to be functionally mammotropic.

II. INDUCTION AND PATHOGENESIS OF PITUITARY TUMORS

In 1936, several groups of investigators first announced the successful induction of PT in mice and rats by prolonged administration of estrogens (*5*, *11*, *34*, *63*, *65*, *72*, *97*). These reports were then followed by the induction of PT in rodents by various other means such as exposing the animals to whole-body or partial-body X-irradiation (*26*, *83*, *86*, *93*), abrogating the thyroidal function (*3*, *12*, *13*, *15*, *16*, *36*, *67*, *94*), and ectopic grafting of pituitary glands (*33*, *43*, *60*, *69*).

It has been claimed by some investigators that neonatal gonadectomy is also effective in inducing PT, but the reproducibility has been rather poor. Valid procedures for induction of PT in mice and rats are listed in Table III.

The majority of PT induced by these procedures are functional and capable of hormone production. PT thus induced have been classified basically into the following four types according to the qualities of hormones produced (*22*). i) Mammotropic tumor (MtT) that secretes mammotropic hormone (MtH, prolactin); the functional activity of MtT is often accompanied by somatotropic and sometimes also by adrenocorticotropic activities. ii) Thyrotropic tumor (TtT) that secretes thyrotropic hormone (TtH). iii) Adreno-

TABLE III
Experimental Induction of Functional Pituitary Tumors in Mice and Rats

Tumor type and principal hormone	Variant and accompanying effect	Inducing agent or procedure	Species
MtT	MStT	a) Estrogen	a) Mouse, rat
Prolactin	StH	b) Radiation	b) Mouse, rat
	MSAtT	c) Pituitary isograft	c) Mouse, rat
	StH+ACTH		
TtT	GtT	a) Radiothyroidectomy (^{131}I)	a) Mouse
TtH (TSH)	GtH	b) Surgical thyroidectomy	b) Mouse
		c) Propylthiouracil	c) Mouse
		d) ^{131}I+X-rays	d) Rat
AtT		Radiation	Mouse
ACTH			
GtT		Gonadectomy?	Rat
GtH			

tropic tumor (AtT) that secretes adrenocorticotropic hormone (ACTH). iv) Gonadotropic tumor (GtT) that secretes gonadotropic hormone (GtH).

The growth of PT induced by administration of estrogen or by derangement of the hormonal balance are usually dependent on or responsive to the hormones involved, while that of PT induced by radiation or developing spontaneously are autonomous (hormone independent); they grow equally regardless of the hormonal status of the host (*23*, *93*).

1. Mammotropic Tumor (MtT) and the Variants

MtT is a tumorous growth of acidophils of the anterior pituitary. The majority of spontaneously developing PT in rodents are of this type, as described in the previous section, and can readily be induced by various means in mice and rats (*22*, *31*). MtT is a morphologically chromophobic or acidophilic adenomas. Since tumor-bearing animals show a proliferation of the mammary gland with milk secretion, these tumors were initially designated as MtT. Later, it was demonstrated, by hormone assay and secondary changes in tumor-bearers, especially in animals bearing transplanted MtT, that many of these types of tumors also secrete somatotropic hormone (StH) and, occasionally, also adrenotropic hormone (AtH) concomitantly with prolactin. Thus, it is logical to call them mammo-somatotropic tumors (MStT) or mammo-somato-adrenotropic tumors (MSAtT). In MtT-bearing males, the somatotropic effect is more prominent as compared with that in females in which the prolactin effects are conspicuous.

1) MtT induction

a) Administration of estrogens MtT can readily be induced in mice and rats with a high frequency by prolonged administration of natural estrogens such as estrone, estradiol, and estriol, and of synthesized estrogen, diethylstilbestrol (DES). Strain differences in susceptibility to estrogen-induced PT genesis in mice has been reported. MtT could be induced in about 50% of young female $(C57L \times A/He)F_1$ mice with a latency of 45–100 weeks, by administering a cholesterol pellet containing 0.05–0.1 mg of DES, renewed at a 3-month interval starting at 8–10 weeks of age (*93*).

In rats, MtT can be induced with higher frequency than in mice. It was observed in our laboratory that chronic administration of a cholesterol pellet containing 5 mg of DES results in the development of MtT in 100% of female ACI/N rats and about 80% of Sprague-Dawley and W/Fu rats within 50 weeks. The induction of MtT at a high rate in female Fischer (F-344) rats by a similar DES treatment has also been reported (*23*).

b) Isografts of pituitary gland Mühlbock and Boot (*69*) first introduced the