EXPERIMENTAL STUDY OF MALE PRECOCIOUS PUBERTY CAUSED BY CHORIONIC GONADOTROPIN

by

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I - INTRODUCTION

For the explanation of the precocious puberty associated with a pineal tumor, the ontogenic theory was advocated by ASKANAZY in 1906. He experienced a case of chorionepitheliomatous teratoma in the pineal region accompanying the precocious puberty and presumed that the precocious puberty might be due to the secretion of the gonadotropin-like substance from the chorionepithelioma. Thereafter, many unfavorable arguments were made, so that this theory has been almost ignored.

In 1957, FUKUSHIMA of our laboratory histologically examined four brain tumors with precocious puberty — three pineal tumors (two of them were evidently teratomas) and a teratoma in the hypophyseal region, and found that the two of the three teratomas contained the chorionepithelioma-like tissue, and the third one contained a cytotrophoblastoma-like tissue. Moreover, in a part of the remaining non-teratomatous pineal tumor, which was for the most part pinealoma, there were adenomatous or canalicular structures, suggesting the possibility of teratoma. Thus, of the four tumors mentioned above, three had the tissue that might produce chorionic gonadotropin and also the remaining one (largely pinealoma) had a possibility to be partly teratoma, so that as far as our cases are concerned, the precocious puberty would possibly be explained by the ontogenic theory, i. e. by the chorionic gonadotropin which was secreted from the chorionepithelioma-like tissue within the teratoma. The most illustrative case will be briefly described in the following.

Boy, 9 years 4 months old, clearly manifestating precocious puberty; the secondary sex characteristics were developed conspicuously (public hair was growing, penis large and glans penis bared).

The boy was 129.5 cm tall and weighed 24 kg, i. e. in normal range.

The gonadotropin in the urine measured with the kaolin adsorption method just before death was found to be considerably increased, the value being 24-48 m. u. u./24 h..

AUTOPSY FINDINGS: - We found a teratoma in the hypophyseal region with a chorionepithelioma-like tissue in a part. In the lung there were multiple metastases of chorionepithelioma. The histological finding of a portion of the main tumor invading the pituitary stalk was similar to a pinealoma, and the hypophysis, being examined by serial sections, was completely replaced by the tumor with no

remaining anterior lobe cell. In the testes LEYDIG cells were hyperplastic but germ cells were atrophic and no spermatozoon was observed. In this case, the amount of gonadotropin in the urine was considerably increased in the absence of pituitary anterior lobe cells, so it could not but be considered that the increased urinary gonadotropin had its origin in the chorionic gonadotropin which had been secreted from the chorionepithelioma-like tissue. Therefore, it can be assumed that in this case the chorionic gonadotropin secreted from the tumor probably induced precocious puberty.

Thus in the present experiments, I administered in the first place a preparation of purified chorionic gonadotropin to immature male rats in a dosis which was roughly estimated from the urinary value of gonadotropin in this case and from the ratio of body weight between man and rat, and in the next place I administered a lyophilized powder of chorionepithelioma in the same way, in order to investigate the experimental production of precocious puberty.

II - METHOD OF EXPERIMENT

1) Experimental animal : - Male rats of the same litter were used; they were weaned three weeks after birth and isolated, and each was fed with the same amount and the same kind of food.

2) a) As for chorionic gonadotropin, Primogonyl, the extract of urine of pregnant women, made by Schering Co., was used.

b) Lyophilized powder of the chorionepithelioma were gained from the tumors in the following two patients.

i) Female, 41 years old.
Clinical diagnosis : - Chorionepithelioma with metastases.
Histological diagnosis : - Hydatid mole.

ii) Female, 16 years old.
Clinical diagonsis : - Teratoma of the ovarium.
Histological diagnosis : - Chorionepithelioma.

From the fresh tumor tissue at the time of autopsy, lyophilized powder was immediately made.

3) Method of Administration : -

a) Every day 30 I. U. of Primogonyl were subcutaneously injected to rats of five days after birth.

b) 10 mg lyophilized powder of chorionepithelioma emulsified in physiologic saline solution was subcutaneously injected three times a week to rats of five days after birth.

As a control for a), physiologic saline solution was injected under similar conditions; as controls for b), lyophilized powder of cancer of the uterus and that of the normal placenta were administered.

Experimental animals were weighed weekly and then sacrificed 4 weeks (33 days after birth) or 8 weeks (61 days after birth) after the beginning of administration, and their sexual and other endocrine organs were weighed and histologically examined.

III - RESULTS OF EXPERIMENT

A. ADMINISTRATION OF PRIMOGONYL

Nineteen male rats of seven litters were divided into two groups, one of which was administered Primogonyl for 4 weeks and the other for 8 weeks respectively.

1) BODY GROWTH: - No difference was found in the lengths of the body and tail in comparison to those in the control groups (Figs. 1 and 2). As regards the increase in body weight, if the rate of increase (the increased body weight divided by the body weight at the commencement of the experiment) was considered, this rate in the 4-week Primogonyl group was 7.45, while that in the control group 7.04, and that in the 8-week Primogonyl group was 18.11, while that of the control group 17.65. Namely in the Primogonyl groups the value was a little high, but when a comparison was made as to the increase in body weight per day, no significant difference was found between the Primogonyl and the control groups (Table 1).

Table 1. Body Weight of Primogonyl Administered Male Rats. (g)

	Litter of Rats	No.	Body Weight				(C-A)	(D-A)	$\left(\frac{C-A}{A}\right)$	$\left(\frac{D-A}{A}\right)$	Body Weight Increase Per Day	
			Before Injection (A)	Injection Period 2 Weeks (B)	4 Weeks (C)	8 Weeks (D)					4-Week Group	8-Week Group
Primogonyl Group	V	29	13.0	35	97		84.0		6.46		3.0	
	VII	36	10.0	29	85		75.0		7.50		2.6	
	IX	37	9.5	28	72		62.5		6.47		2.2	
	XIV	54	12.0	40	98		86.0		7.00		3.0	
	I	92	11.0	33	82		71.0		6.45		2.9	
		3	10.5	29	93	174	82.5	163.5	7.85	15.57	2.9	2.9
	II	4	10.5	31	92	196	81.5	185.5	7.76	17.66	2.9	3.3
		11	7.0	23	61	136	54.0	129.0	7.71	18.42	1.9	2.3
	VI	12	7.5	25	69	156	61.5	148.5	8.20	19.80	2.1	2.6
		33	9.5	43	96	192	86.5	182.5	9.10	19.21	3.0	3.2
	Mean Value		10.0	31.6	84.5	170.8	74.4	165.8	7.45	18.11	2.65	2.86
Control Group	V	30	13.0	36	94		81.0		6.23		2.8	
	VII	38	10.5	33	84		73.5		7.00		2.6	
		39	11.0	32	85		74.0		6.70		2.6	
	IX	55	12.0	40	101		89.0		7.41		3.1	
	XIV	94	11.0	34	78		67.0		6.09		2.3	
	I	6	11.0	33	97	194	86.0	183.0	7.81	16.63	3.0	3.2
		7	10.0	30	83	180	73.0	170.0	7.30	17.00	2.6	3.0
	II	13	7.5	23	64	158	66.5	150.5	7.53	20.06	2.1	2.6
	VI	34	11.5	43	96	206	84.5	194.5	7.34	16.91	3.0	3.4
	Mean Value		10.8	33.7	86.8	184.5	76.0	174.5	7.04	17.65	2.67	3.05

2) SEXUAL DEVELOPMENT: The group to which Primogonyl had been administered for 4 weeks, indicated a more distinct sexual development as compared with the control group (Fig. 1). Namely, in the former, early development of the scrotum and penis were seen and the testes descended into the scrotum in about 16 days after birth. But in the latter descensus testis was not yet completed even 30 days after birth. In the Primogonyl group the testes and especially the accessory sexual organs distinctly increased in weight and size and the glans penis took a U-type (mature type) 29 days after birth, whereas in the control group

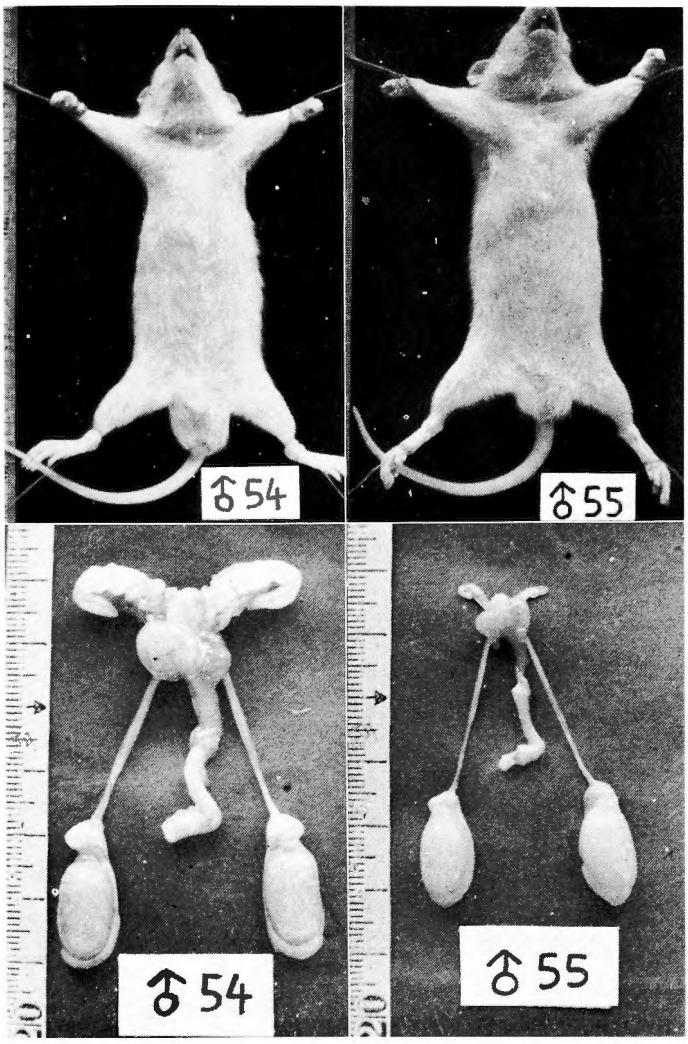


Fig. 1 ♂ 54 Rat No. 54 Male Rat Administered Primogonyl for 4 Weeks (33 Days after Birth).
♂ 55 Rat No. 55 Control Male Rat (33 Days after Birth).

this still showed the type of a V or W (immature type) even 33 days after birth (Table 2).

The weight of the penis in the Primogonyl group was 0.13 g, i. e. the average weight in mature rats and was about 2.4 times as much as that of the control group. The testes were 1.13 g which was a little more than those of the control group, while the epididymides, prostate and seminal vesicles indicated a distinctly early development with an increase of approximately 2 times, 4 times and 19 times respectively in comparison with those of the control group.

In the 8-week groups, the penis of the control group also showed the U-type (mature type), but the accessory sexual organs of the Primogonyl group showed much more increases in weight and size (Fig. 2). Yet, as compared with the difference in the 4-week groups, the difference between their weights in the Primo-

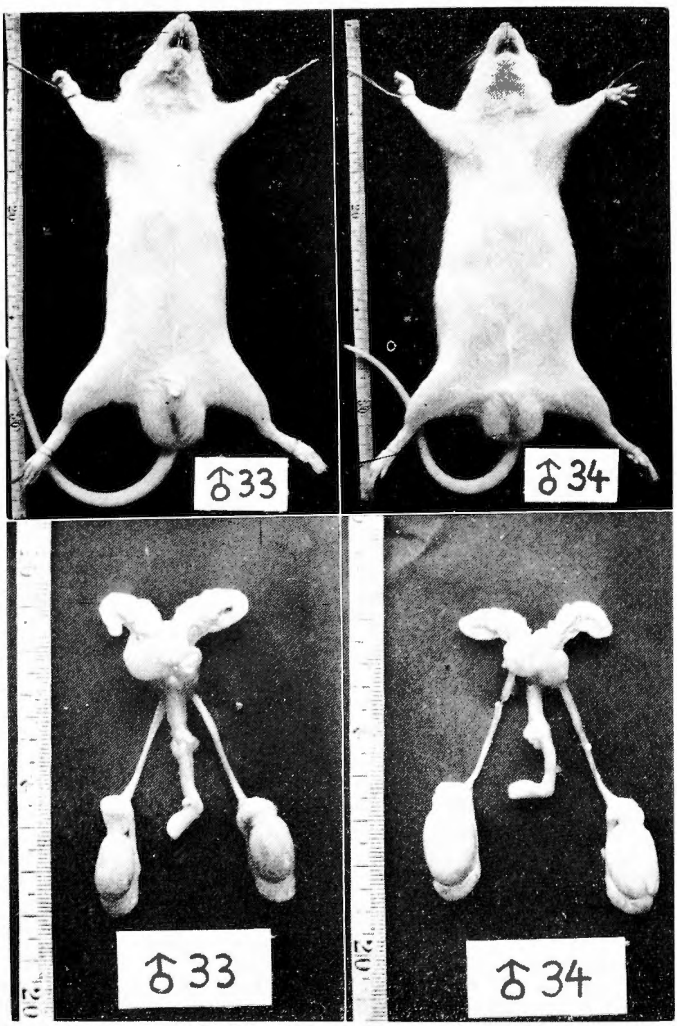


Fig. 2 ♂ 33 Rat No. 33 Male Rat Administered Primogonyl for 8 Weeks (61 Days after Birth).
♂ 34 Rat No. 34 Control Male Rat (61 Days after Birth).

gonyl group and those in the control group was lesser in degree. Namely, the weight of the penis was 0.22 g, i. e. approximately 1.4 times as much as that of the control group, and the weight of the testis was about the same as that of the control group, but the epididymis, prostate and seminal vesicle were approximately 1.4, 2.8 and 3.0 times respectively as heavy as those of the control group (Table 3).

3) The weight of the hypophysis, thyroid gland and adrenal gland of the 4-week (Table 4) and the 8-week Primogonyl (Table 5) group indicated no difference in comparison with those of the control group.

HISTOLOGICAL FINDINGS

1) TESTIS: In the experimental group which was administered Primogonyl for 4 weeks, distinct hyperplasia of LEYDIG cells in the interstitial tissue, and

Table 2. Weights of Sexual Organs and Their Ratio to Body Weight in Male Rats Administered Primogonyl for 4 Weeks.

	Litter of Rats	No.	Body Weight (g)	Type of Penis (Age Day)	Weight (g)					Ratio to Body Weight (g/g×100)				
					Penis	Testes *	Epid.*	Prost.	Sem. Ves.	Penis	Testes	Epid.	Prost.	Sem. Ves.
Primogonyl Group	V	29	97	U (30)	0.127	0.91	0.232	0.552	0.296	0.13	0.93	0.23	0.56	0.30
	VII	36	85	U (29)	0.117	1.30	0.260	0.326	0.420	0.13	1.52	0.30	0.37	0.49
		37	72	U (30)	0.122	1.05	0.200	0.353	0.302	0.16	1.44	0.27	0.34	0.41
	IX	54	98	U (28)	0.165	1.30	0.243	0.510	0.530	0.16	1.32	0.24	0.52	0.54
	XIV	92	82	U (29)	0.121	1.13	0.223	0.412	0.280	0.14	1.36	0.27	0.50	0.34
	Mean Value		86.8	(29)	0.130	1.13	0.232	0.431	0.365	0.14	1.31	0.26	0.45	0.41
Control Group	V	30	94	V (33)	0.077	0.81	0.107	0.147	0.027	0.08	0.86	0.11	0.15	0.02
	VII	38	84	W (33)	0.056	0.85	0.125	0.085	0.019	0.06	1.11	0.13	0.11	0.02
		39	85	W (33)	0.032	0.82	0.107	0.120	0.017	0.03	0.96	0.12	0.14	0.02
	IX	55	101	W (33)	0.052	0.84	0.113	0.081	0.022	0.05	0.83	0.11	0.08	0.02
	XIV	94	78	V (33)	0.051	0.80	0.098	0.074	0.013	0.06	1.02	0.12	0.09	0.01
	Mean Value		88.2		0.053	0.82	0.110	0.101	0.019	0.05	0.95	0.11	0.11	0.018

*···Weight of Bilateral Organs Epid.···Epididymides Prost.···Prostate Sem. Ves.···Seminal Vesicle

Table 3. Weights of Sexual Organs and Their Ratio to Body Weight in Male Rats Administered Primogonyl for 8 Weeks.

	Litter of Rats	No.	Body Weight (g)	Type of Penis (Age Day)	Weight (g)					Ratio to Body Weight (g/g×100)				
					Penis	Testes *	Epid.*	Prost.	Sem. Ves.	Penis	Testes	Epid.	Prost.	Sem. Ves.
Primogonyl Group	I	3	174	U (28)	0.24	1.82	0.64	0.82	1.17	0.13	1.04	0.36	0.47	0.67
		4	196	U (30)	0.31	1.90	0.74	0.73	0.75	0.15	0.96	0.37	0.37	0.38
	II	11	136	U (28)	0.22	1.90	0.66	1.02	1.10	0.16	1.39	0.48	0.75	0.80
		12	156	U (28)	0.20	1.60	0.60	0.74	0.82	0.12	1.02	0.38	0.47	0.52
	VI	33	192	U (30)	0.17	1.80	0.53	0.73	0.92	0.09	0.98	0.47	0.38	0.49
	Mean Value		170.8	(28)	0.22	1.80	0.63	0.80	0.95	0.13	1.07	0.37	0.48	0.57
Control Group	I	6	194	U (40)	0.20	2.00	0.45	0.36	0.25	0.10	1.03	0.23	0.18	0.12
		7	180	U (47)	0.15	1.95	0.42	0.20	0.18	0.08	1.08	0.23	0.11	0.10
	II	13	158	U (52)	0.12	1.66	0.42	0.14	0.20	0.07	1.05	0.27	0.08	0.12
	VI	34	206	U (43)	0.15	2.90	0.48	0.45	0.44	0.07	0.97	0.23	0.21	0.21
	Mean Value		184.5	(45)	0.16	1.90	0.44	0.28	0.26	0.08	1.03	0.24	0.14	0.13

*···Weight of Bilateral Organs Epid.···Epididymides Prost.···Prostate Sem. Ves.···Seminal Vesicle

numerous spermatocytes in the seminiferous tubules were found, but in the control group such changes were not noticed (Fig. 8, A, E). In the 8-week Primogonyl group, though there was no distinct difference in the weight of the testis as compared with that of the control group, distinct hyperplasia of LEYDIG cells was seen in the interstitial tissue. Numerous spermatocytes were noticed in both the Primogonyl and the control group (Fig. 9, A, F).

2) As regards the thyroid gland, adrenal gland and pineal body of the 4-week and 8-week group, there was no difference in weight and in the histological finding to note between the Primogonyl and the control group.

Table 4. Weights of Hypophysis, Thyroids and Suprarenals and Their Ratio to Body Weight in Male Rats Adminlstered Primogonyl for 4 Weeks.

	Litter of Rats	No.	Body Weight (g)	Weight (g)			Ratio to Body Weight (g/g×100)		
				Hypophysis	Thyroids *	Suprarenals *	Hypophysis	Thyroids	Suprarenals
Primogonyl Group	V	29	97	0.0045	0.014	0.021	0.0046	0.014	0.021
	VII	36	85	0.0036	0.012	0.023	0.0042	0.014	0.027
		37	72	0.0042	0.011	0.018	0.0058	0.015	0.025
	IX	54	98	0.0033	0.014	0.019	0.0033	0.014	0.019
	XIV	92	82	0.0029	0.011	0.021	0.0035	0.013	0.025
	Mean Value		86.8	0.0037	0.012	0.021	0.0041	0.014	0.023
Control Group	V	30	94	0.0042	0.019	0.029	0.0044	0.020	0.030
	VII	38	84	0.0040	0.011	0.024	0.0047	0.013	0.027
		39	85	0.0040	0.012	0.023	0.0047	0.014	0.026
	IX	55	101	0.0035	0.013	0.031	0.0034	0.012	0.030
	XIV	94	78	0.0030	0.010	0.022	0.0038	0.012	0.028
	Mean Value		88.2	0.0037	0.013	0.025	0.0042	0.014	0.028

*···Weight of Bilateral Organs

Table 5. Weights of Hypophysis, Thyroids and Suprarenals and Their Ratio to Body Weight in Male Rats Administered Primogonyl for 8 Weeks.

	Litter of Rats	No.	Body Weight (g)	Weight (g)			Raio to Body Weight (g/g×100)		
				Hypophysis	Thyroids *	Suprarenals *	Hypophysis	Thyroids	Suprarenals
Primogonyl Group	I	3	174	0.0072	0.016	0.034	0.0041	0.0091	0.019
		4	196	0.0066	0.015	0.030	0.0033	0.0076	0.015
	II	11	136	0.0044	0.016	0.030	0.0032	0.0117	0.021
		12	156	0.0055	0.014	0.023	0.0035	0.0089	0.014
	VI	33	192	0.0050	0.020	0.026	0.0025	0.0104	0.013
	Mean Value		170.8	0.0057	0.016	0.028	0.0033	0.0095	0.016
Control Group	I	6	194	0.0062	0.015	0.031	0.0031	0.0077	0.015
		7	180	0.0070	0.014	0.026	0.0038	0.0075	0.014
	II	13	158	0.0067	0.022	0.027	0.0042	0.0138	0.018
	VI	34	206	0.0065	0.022	0.036	0.0031	0.0106	0.017
	Mean Value		184.5	0.0066	0.018	0.030	0.0035	0.0099	0.016

*···Weight of Bilateral Organs

B. ADMINISTRATION OF CHORIONEPITHELIOMA LYOPHILIZED POWDER

Forty-six rats of twelve litters were separated into two groups and the lyophilized powders produced from chorionepitheliomas in two patients mentioned above were administered to each experimental group. The tumor i) was used for experimental group I and the tumor ii) for experimental group II.

1) BODY GROWTH:- In both the experimental group I and II there was no difference in the lengths of the body and tail as compared with the controls (Figs. 3, 4, 5, 6 and 7). As regards the increase in body weight, i. e. the rate of increase and the increase of weight per day in both the experimental groups I and II, no difference was noticed as compared with those of the control groups

Table 6. Body Weight of Male Rats Administered Lyophilized Chorionepithelioma and Placenta Powder. (g)

	Litter of Rats	No.	Body Weight: Before Injection (A)	Injection Period: 2 Weeks (B)	4 Weeks (C)	8 Weeks (D)	(C-A)	(D-A)	$\left(\frac{C-A}{A}\right)$	$\left(\frac{D-A}{A}\right)$	Body Weight Increase Per Day: 4-Week Group	8-Week Group
Chorionepithelioma Group	XVIII	100	10.0	26	86		76.0		7.60		2.7	
		101	10.0	27	77		67.0		6.70		2.3	
	XX	120	12.0	32	78		66.0		5.50		2.3	
	XXII	130	9.5	28	68		58.5		6.15		2.0	
	XXIII	133	11.0	32	76		65.0		5.90		2.3	
	VIII	45	9.5	30	85	216	75.5	206.5	7.94	21.73	2.6	3.6
	X	59	9.0	26	71	189	62.0	180.0	6.88	20.00	2.2	3.2
		60	10.0	25	63	175	53.0	165.0	5.30	16.50	1.8	2.9
	XII	82	9.5	34	78	168	68.5	158.5	7.21	16.62	2.4	2.8
		83	9.5	32	79	174	69.5	164.5	7.37	17.31	2.4	2.9
	Mean Value		10.0	29.2	76.1	184.4	66.1	174.8	6.65	18.43	2.30	3.08
Placenta Group	XVIII	102	11.0	31	68		57.0		5.18		2.0	
		103	10.0	30	71		61.0		6.10		2.1	
	XX	121	11.0	30	74		63.0		5.72		2.2	
	XXII	131	10.0	29	74		64.0		6.40		2.2	
	VIII	46	9.0	28	70	189	61.0	180.0	6.77	20.00	2.1	3.2
	X	61	9.0	25	72	171	63.0	162.0	6.63	18.00	2.2	2.8
		62	9.5	26	67	183	57.5	173.5	6.06	17.21	2.0	3.0
	XII	84	9.5	32	80	174	70.5	164.5	7.42	17.26	2.5	2.9
		85	10.0	31	72	182	62.0	172.0	6.20	17.20	2.2	3.0
	Mean Value		9.8	29.1	72.0	179.8	62.1	170.4	6.27	17.93	2.16	2.98
Control Group	XVIII	104	9.0	27	79		70.0		7.77		2.5	
	XX	122	11.0	33	82		71.0		6.45		2.5	
	XXIII	134	11.0	29	82		71.0		6.45		2.5	
	XXII	132	10.0	29	68		58.0		5.80		2.0	
	VIII	48	8.5	28	78	192	69.5	183.5	8.17	21.47	2.4	3.2
	X	65	10.0	26	68	186	58.0	176.0	5.80	17.60	2.0	3.1
	XII	88	9.5	35	86	190	76.5	180.5	8.04	19.00	2.7	3.2
	Mean Value		9.8	29.5	77.5	189.3	67.7	180.0	6.92	19.35	2.37	3.16

(Tables 6 and 7). Moreover, it seemed right to assume that a malignant tumor has no effect on body growth, as shown in the Table 8.

2) SEXUAL DEVELOPMENT

Similarly to the previous experiment in which Primogonyl was administered, the administration of the lyophilized powder of the chorionepithelioma brought about an early development of the sexual organs. Namely, in the experimental group I of 4-week administration, there was a distinct difference in the development of the penis, scrotum and the other accessory sexual organs as compared with those of the control group (Fig. 3). In this group the glans penis took the mature U-type in about 34 days after birth while in the control group the U-type of glans penis took place approximately 50 days after birth.

In the group where lyophilized powder of a malignant tumor was administered, no sexual precocity could be noticed.

In the 4-week chorionepithelioma group, the mean value of the weights of the penis was 0.105 g, i. e. approximately 2 times as much as that in the controls,

Table 7. Body Weight of Male Rats Administered Lyophilized Chorionepithelioma Powder. (g)

	Litter of Rats	No.	Body Weight Before Injection (A)	Injection Period 2 Weeks (B)	1 Weeks (C)	8 Weeks (G)	(C-A)	(D-A)	$\left(\frac{C-A}{A}\right)$	$\left(\frac{D-A}{A}\right)$	Body Weight Increase Per Day 4-Week Group	8-Week Group
Chorionepithelioma Group	XXIV	183	10.5	28	76		65.5		6.23		2.3	
	XXX	193	11.5	28	83		71.5		6.21		2.5	
		194	11.0	28	82		71.0		6.45		2.5	
		195	10.0	26	68		58.0		5.30		2.0	
	XXVI	219	10.0	38	78		68.0		6.80		2.4	
	XXVIII	174	9.5	26	75	168	65.5	158.5	6.88	16.78	2.3	2.8
		175	9.0	26	74	164	65.0	155.0	7.22	17.22	2.3	2.7
		176	10.0	27	78	174	68.0	164.0	6.80	16.40	2.4	2.9
	XXIX	184	10.5	28	72	174	61.5	163.5	5.85	15.66	2.1	2.9
	Mean Value		10.2	28.3	76.2	170.0	66.0	160.2	6.41	16.51	2.31	2.82
Control Group	XXIX	186	10.5	27	74		63.5		6.04		2.3	
	XXX	196	11.5	27	72		60.5		5.26		2.2	
		197	11.0	29	80		69.0		6.27		2.4	
	XXVI	220	10.5	40	82		71.5		6.80		2.5	
	XXVIII	177	9.0	26	72	180	63.0	171.0	5.88	19.00	2.3	3.0
		178	9.5	26	70	166	60.5	156.5	6.36	16.47	2.2	2.7
		179	9.0	26	72	163	63.0	154.0	5.88	17.11	2.3	2.7
	XXIX	185	11.0	28	73	180	62.0	169.0	5.63	15.36	2.2	3.0
	Mean Value		10.2	8.6	74.4	172.2	64.1	162.6	6.01	16.98	2.30	2.85

Table 8. Body Weight of Male Rats Administered Lyophilized Chorionepithelioma and Cancer Powder. (g)

	Litter of Rats	No.	Body Weight Before Injection (A)	Injection Period 2 Weeks (B)	1 Weeks (C)	8 Weeks (D)	(C-A)	(D-A)	$\left(\frac{C-A}{A}\right)$	$\left(\frac{D-A}{A}\right)$	Body Weight Increase Per Day 4-Week Group	8-Week Group
Chorionepithelioma Group	VIII	45	9.5	30	85	216	75.5	206.5	7.94	21.73	2.6	3.6
	X	59	9.0	26	71	189	62.0	180.0	6.88	20.00	2.2	3.2
		60	10.0	25	63	175	53.0	165.0	5.30	16.50	1.8	2.9
	Mean Value		9.5	27.0	73.0	193.3	63.4	183.4	6.70	19.41	2.20	3.23
Cancer Group	VIII	47	9.0	28	70	176	61.0	162.0	6.77	18.00	2.1	2.8
	X	63	10.0	26	63	190	53.0	180.0	5.30	18.00	1.8	3.2
		64	10.0	25	62	202	52.0	192 0	5.20	19.20	1.8	3.4
	Mean Value		9.6	26.3	65.0	189.3	55.3	178.0	5.75	18.40	1.90	3.13
Control Group	VIII	48	8.5	28	78	192	69.5	183.5	8.17	21.47	2.4	3.2
	X	65	10.0	26	86	186	58.0	176.0	5.80	17.60	2.0	3.1
	Mean Value		9.2	27.0	73.0	189.0	63.7	179.7	6.98	19.53	2.20	3.15

but as for the testis, it was 0.36 g, i. e. 0.41 times as small as that in the control group, but the accessory sexual organs, namely the epididymis, prostate and seminal vesicle were approximately 1.5 times, 2.8 times and 5.8 times respectively as much as those in the control group (Table 9).

In the 8-week chorionepithelioma group the average weight of the penis was

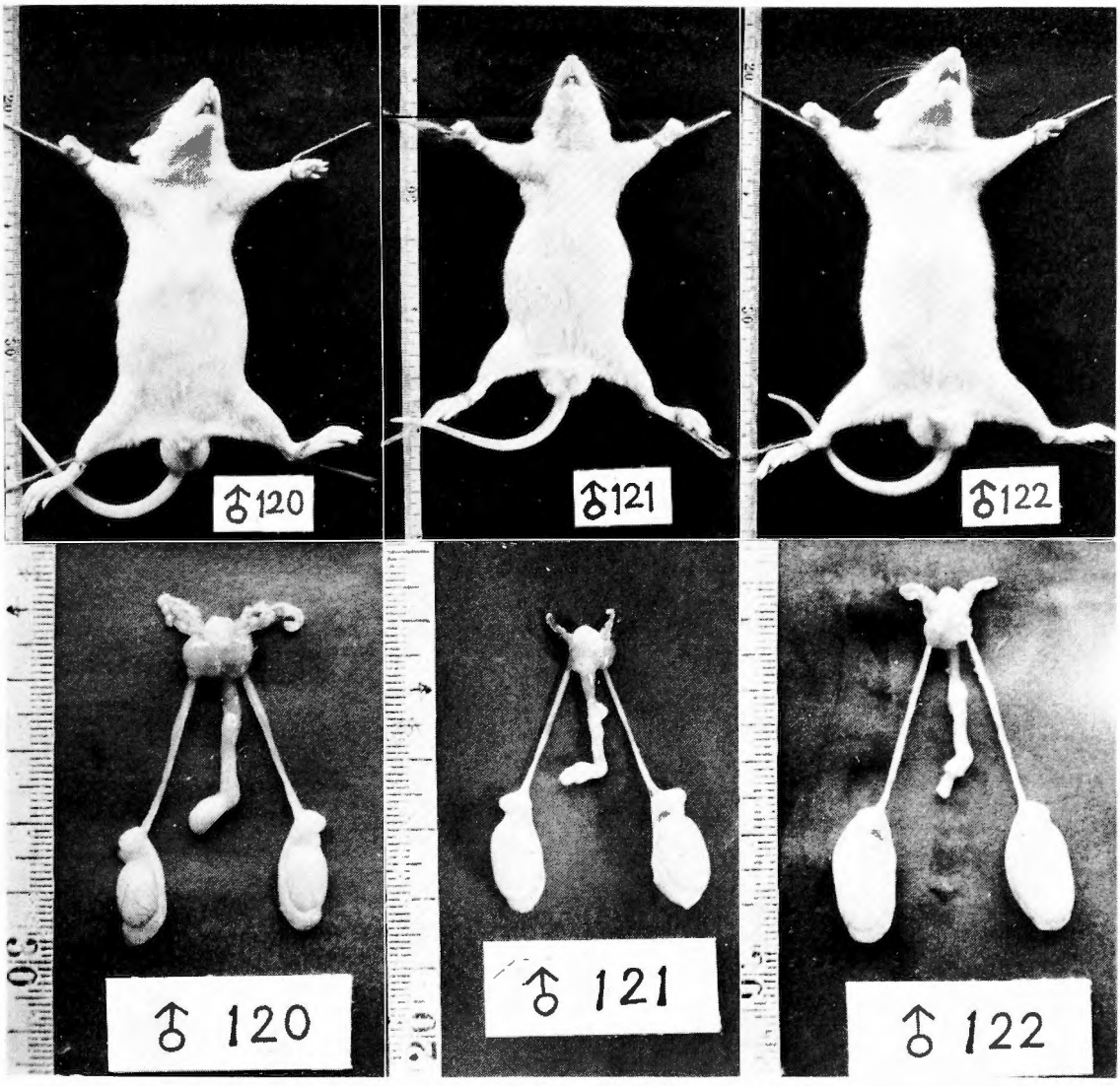


Fig. 3 ♂ 120 Rat No. 120 Male Rat Administered Chorionepithelioma Lyophilized Powder for 4 Weeks (33 Days after Birth).
♂ 121 Rat No. 121 Male Rat Administered Placenta Lyophilized Powder for 4 Weeks (33 Days after (Birth).
♂ 122 Rat No. 122 Control Male Rat (33 Days after Birth).

0.181 g, i. e. rather large in comparison with that of the controls, but the testis was 0.63 times as small as that of the controls. The epididymis was also rather small, but the prostate and the seminal vesicle were 2.3 times and 1.9 times larger respectively, the differences being not so remarkable (Table 10).

The result of experimental group II was about the same as that of experimental group I, but the difference in comparison with the controls was more prominent (Figs. 6 and 7), the glans penis took U-type about 30 days after birth, i. e. more quickly than approximate 43 days after birth in the controls.

In regard to weights of the sexual organs, the penis of the 4-week chorion-

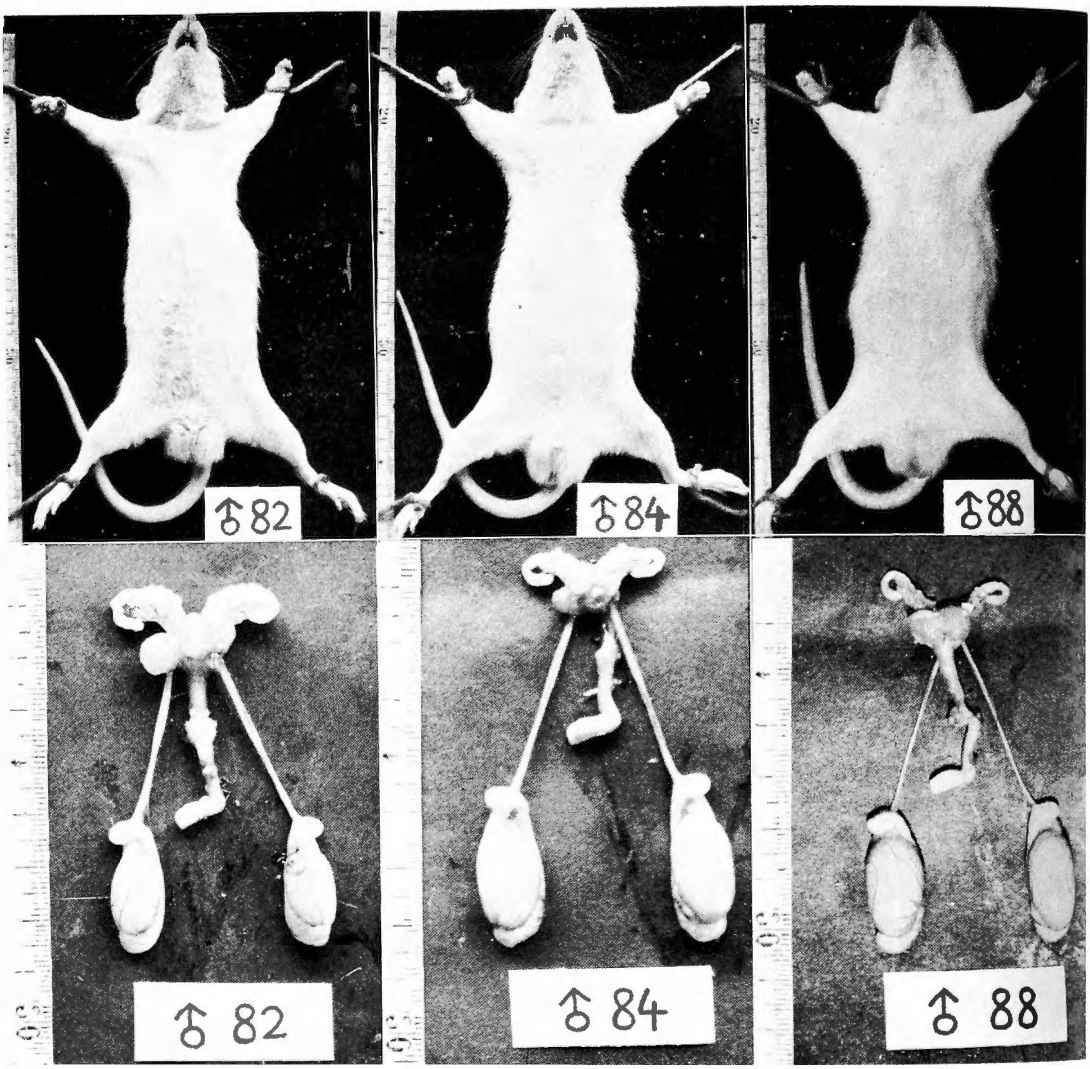


Fig. 4 ♂ 82 Rat No. 82 Male Rat Administered Chorionepithelioma Lyophilized Powder for 8 Weeks (61 Days after Birth).
♂ 84 Rat No. 84 Male Rat Administered Placenta Lyophilized Powder for 8 Weeks (61 Days after Birth).
♂ 88 Rat No. 88 Control Male Rat (61 Days after Birth).

epithelioma group was 0.115 g, i. e. approximately 2.3 times larger than that of the controls, the testis was 0.36 g, i. e. about 0.48 times smaller, but the epididymis, prostate and seminal vesicle were approximately 1.5 times, 3.8 times and 5.6 times respectively larger than those of the controls, the differences being remarkable (Table 11).

In the 8-week chorionepithelioma groups, the penis weighed 0.185g i. e. larger than that of the controls, whereas the testis was approximately 0.54 times smaller than that of the controls, but the prostate and seminal vesicle were approximately 3 times larger than those of the controls (Table 12).

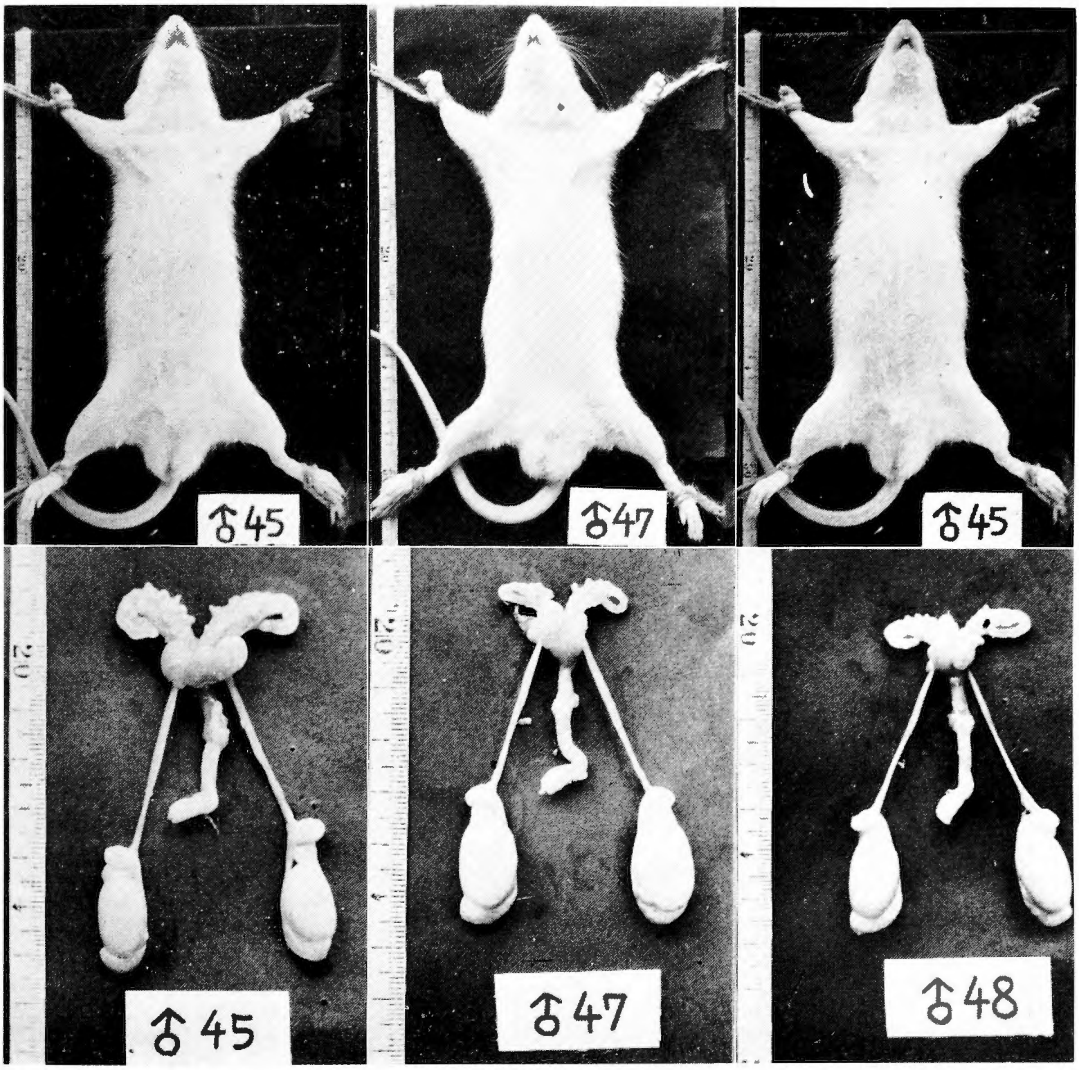


Fig. 5 ♂ 45 Rat No. 45 Male Rat Administered Chorionepithelioma Lyophilized Powder for 8 Weeks (61 Days after Birth).
♂ 47 Rat No. 47 Male Rat Administered Cancer Powder for 8 Weeks (61 Days after Birth).
♂ 48 Rat No. 48 Control Male Rat (61 Days after Birth).

Thus, a decrease in weight of the testis was seen in the rats administered lyophilized powder of chorionepithelioma, and similar decrease was also found, though to a lesser degree, in rats administered lyophilized powder of the placenta. But with the use of lyophilized powder of a malignant tumor such a decrease could not be observed. Therefore, it is supposed that this change is caused by the influence of the chorionic tissue.

Moreover. it was found that the administration of lyophilized powder of a malignant tumor caused no variation in the weight of the accessory sexual organs (Table 13).

Table 9. Weights of Sexual Organs and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma and Placenta Lyophilized Powder for 4 Weeks.

	Litter No. of Rats	No.	Body Weight (g)	Type of Penis (Age Day)	Weight (g) Penis	Testes *	Epid.*	Prost.	Sem. Ves.	Ratio to Body Weight (g/g×100) Penis	Testes	Epid.	Prost.	Sem. Ves.
Chorionepithelioma Group	XVIII	100	86	U(32)	0.095	0.41	0.148	0.185	0.069	0.11	0.47	0.17	0.21	0.08
		101	77	U(33)	0.105	0.37	0.157	0.237	0.065	0.13	0.48	0.20	0.30	0.08
	XX	120	78	U(33)	0.102	0.35	0.130	0.147	0.075	0.13	0.44	0.16	0.18	0.09
	XXII	130	68	W(33)	0.096	0.34	0.145	0.241	0.114	0.14	0.50	0.21	0.35	0.16
	XXIII	133	76	U(31)	0.131	0.34	0.186	0.190	0.112	0.17	0.44	0.24	0.24	0.14
	Mean Value		77.0		0.105	0.36	0.153	0.200	0.087	0.13	0.46	0.19	0.25	0.11
Placenta Group	XVIII	102	68	V(33)	0.041	0.54	0.075	0.072	0.012	0.06	0.79	0.11	0.10	0.02
		103	71	V(33)	0.041	0.43	0.069	0.039	0.009	0.05	0.60	0.09	0.05	0.01
	XX	121	74	V(33)	0.047	0.64	0.095	0.071	0.010	0.06	0.86	0.12	0.09	0.01
	XXII	131	74	V(33)	0.042	0.57	0.081	0.081	0.014	0.05	0.77	0.11	0.11	0.01
	Mean Value		71.7		0.042	0.54	0.080	0.065	0.011	0.05	0.75	0.10	0.08	0.012
Control Group	XVIII	104	79	W(33)	0.068	0.92	0.125	0.073	0.019	0.08	1.16	0.15	0.09	0.02
	XX	122	82	V(33)	0.047	0.94	0.095	0.045	0.017	0.05	1.14	0.11	0.05	0.02
	XXII	132	68	V(33)	0.041	0.76	0.083	0.076	0.014	0.06	1.11	0.10	0.11	0.02
	XXIII	134	82	V(33)	0.056	0.83	0.097	0.085	0.014	0.06	1.01	0.11	0.10	0.01
	Mean Value		77.7		0.053	0.86	0.100	0.069	0.016	0.06	1.10	0.11	0.08	0.017

*…Weight of Bilateral Organs

Epid.…Epididymides Prost.…Prostate
Sem. Ves.…Seminal Vesicle

Table 10. Weights of Sexual Organs and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma and Placenta Lyophilized Powder for 8 Weeks.

	Litter of Rats	No.	Body Weight (g)	Type of Penis (Age Day)	Weight (g) Penis	Testes *	Epid.*	Prost.	Sem. Ves.	Ratio to Body Weight (g/g×100) Penis	Testes	Epid.	Prost.	Sem. Ves.
Chorionepithelioma Group	VIII	45	216	U(29)	0.205	1.67	0.46	0.64	0.72	0.09	0.75	0.21	0.29	0.33
	X	59	189	U(33)	0.181	1.39	0.36	0.54	0.30	0.09	0.72	0.19	0.28	0.15
		60	175	U(37)	0.171	1.32	0.34	0.53	0.30	0.09	0.75	0.19	0.30	0.17
	VII	82	168	U(37)	0.172	1.36	0.42	0.57	0.51	0.10	0.80	0.25	0.33	0.30
		83	174	U(35)	0.180	1.21	0.41	0.54	0.52	0.10	0.69	0.23	0.30	0.29
	Mean Value		184.4	(34)	0.181	1.39	0.39	0.56	0.47	0.09	0.74	0.21	0.30	0.24
Placenta Group	VIII	46	189	U(52)	0.142	1.72	0.32	0.19	0.11	0.07	0.91	0.18	0.10	0.05
	X	61	171	U(54)	0.138	1.81	0.42	0.28	0.19	0.08	1.05	0.24	0.16	0.11
		62	183	U(51)	0.135	1.67	0.42	0.27	0.20	0.07	0.91	0.22	0.14	0.10
	VII	84	174	U(47)	0.136	2.07	0.42	0.31	0.17	0.07	1.77	0.24	0.17	0.09
		85	182	U(51)	0.144	1.95	0.38	0.29	0.19	0.07	1.07	0.20	0.15	0.10
	Mean Value		179.8	(51)	0.139	1.84	0.39	0.26	0.17	0.07	1.14	0.21	0.14	0.09
Control Group	VIII	48	192	U(47)	0.165	2.12	0.42	0.29	0.30	0.08	1.10	0.21	0.15	0.15
	X	65	186	U(18)	0.150	2.49	0.43	0.25	0.27	0.08	1.33	0.23	0.13	0.14
	VII	88	190	U(50)	0.154	2.42	0.49	0.19	0.17	0.08	1.27	0.25	0.10	0.08
	Mean Value		189.3	(48)	0.156	2.34	0.44	0.24	0.24	0.08	1.23	0.23	0.12	0.12

*…Weight of Bilateral Organs

Epid.…Epididymides Prost.…Prostate
Sem. Ves.…Seminal Vesicle

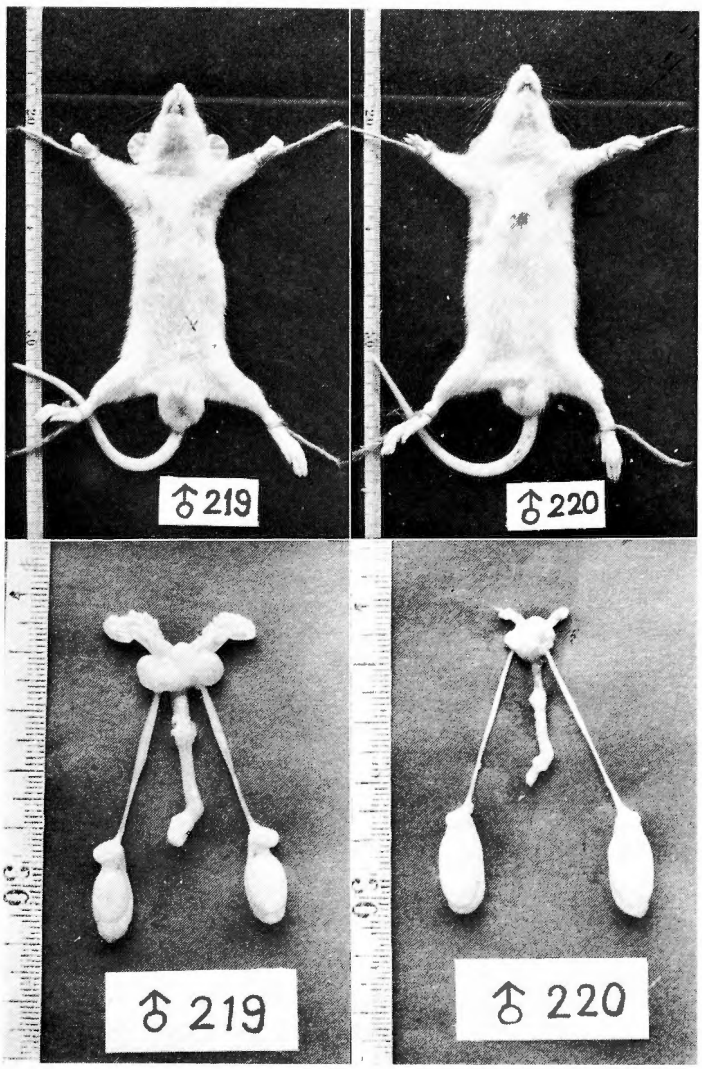


Fig. 6 ♂219 Rat No. 219 Male Rat Administered Chorionepithelioma Lyophilized Powder for 4 Weeks (33 Days after Birth).
♂220 Rat No. 220 Control Male Rat (33 Days after Birth).

3) In both experimental groups I and II, no change was noticed in the weight of the hypophysis, thyroid gland and adrenal gland as compared with the control group (Tables 14, 15, 16, 17 and 18).

HISTOLOGICAL FINDINGS

1) TESTIS: - In the 4-week chorionepithelioma group of the experimental group I hyperplasia of the LEYDIG cells was noticed, but less remarkably than that taking place in Primogonyl administered rats. Germinal cells were more atrophic than the control group and no spermatozoon was found (Fig. 8, C).

In the 8-week chorionepithelioma group, LEYDIG cells hyperplasia was much more distinct, but germinal cells did not differ from those of the control group.

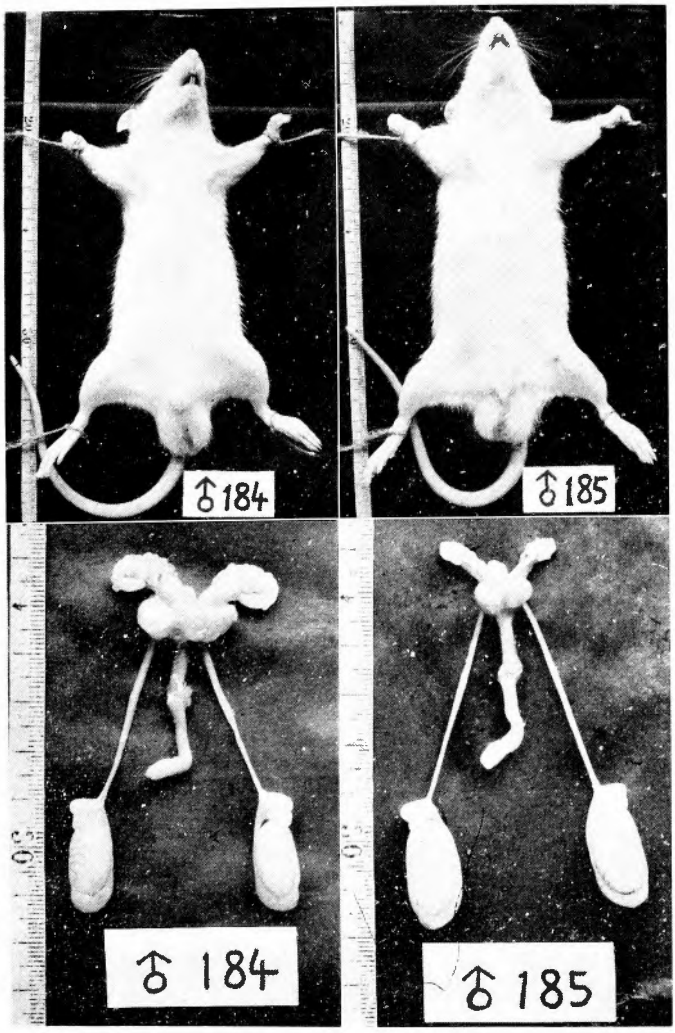


Fig. 7 ♂ 184 Rat No. 184 Male Rat Administered Chorionepithelioma Lyophilized Powder for 8 Weeks (61 Days after Birth).
♂ 185 Rat No. 185 Control Male Rat (61 Days after Birth).

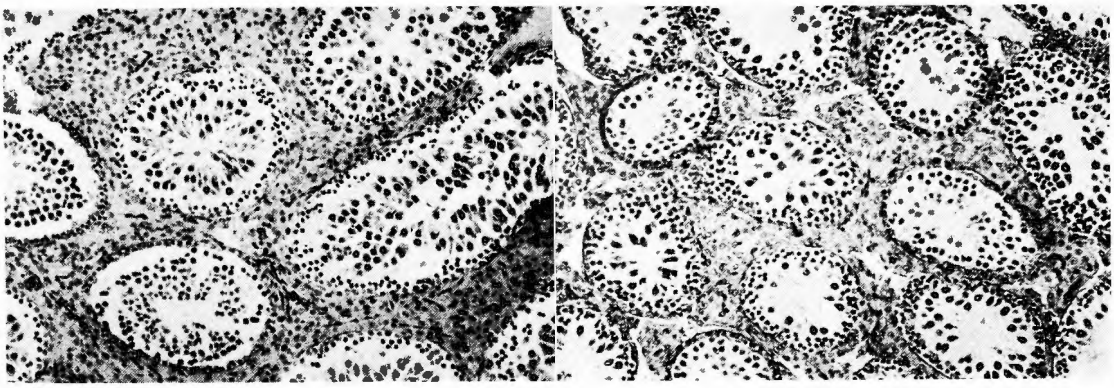
Many spermatozoa were noticed in both groups (Fig. 9, C).

By the administration of the lyophilized powder of the placenta or of a malignant tumor, no marked change took place in the LEYDIG cells and germinal cells (Fig. 8, D and Fig. 9. D).

Experimental group II. The changes in weights of the sexual organs were more prominent than those of experimental group I, and histological examination revealed that hyperplasia of the LEYDIG cells were more distinct than that in experimental group I. As was expected atrophy of germinal cells was found in the 4-week chorionepithelioma group and no spermatozoon was found in seminiferous tubules (Fig. 8, B).

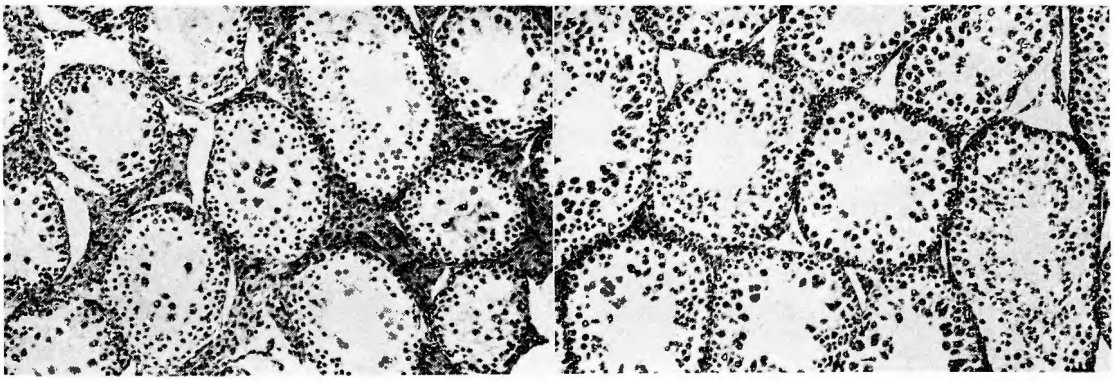
In the 8-week chorionepithelioma group, spermatozoa were found similarly to

Fig. 8 The testis in Rats Administered Primogonyl and Lyophilized Chorionepithelioma and Placenta Powder for 4 Weeks and Control Rats (33 Days after Birth). Hematoxylin-Eosin Stain ×150



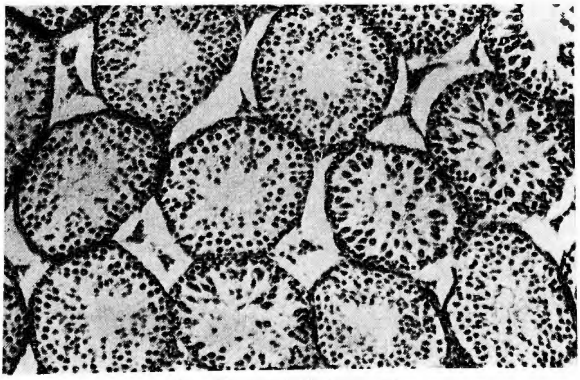
A. Primogonyl Administered Rat No. 54.

B. Chorionepithelioma Lyophilized Powder Administered Rat No. 219.



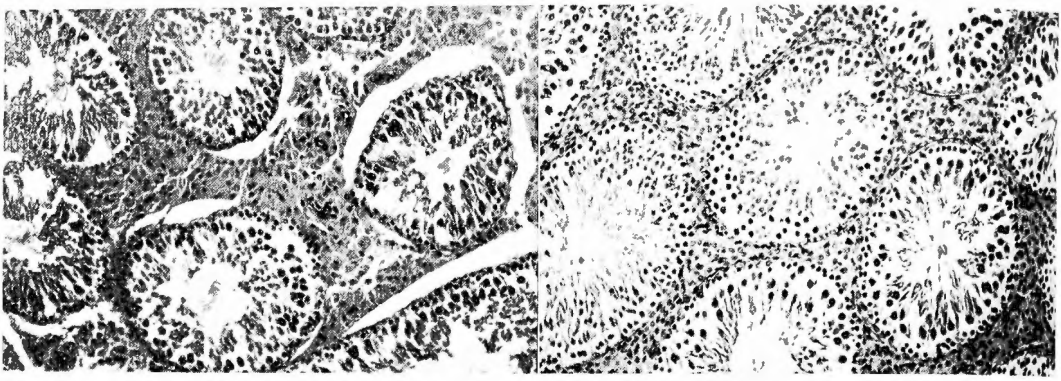
C. Chorionepithelioma Lyophilized Powder Administered Rat No. 120.

D. Placenta Lyophilized Powder Administered Rat No. 121.



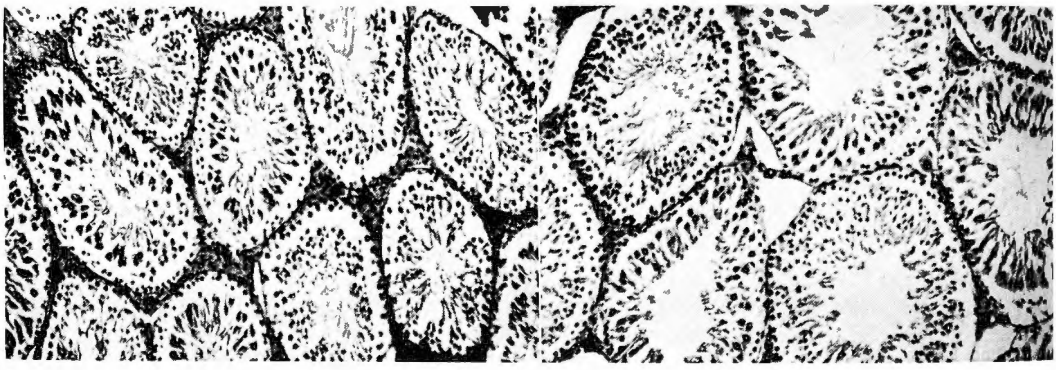
E. Control Rat No. 55.

Fig. 9 The testis in Rats Administered Primogonyl and Lyophilized Chorionepithelioma, Placenta and Cancer for 8 Weeks and Control Rats (61 Days after Birth). Hematoxylin-Eosin Stain ×150



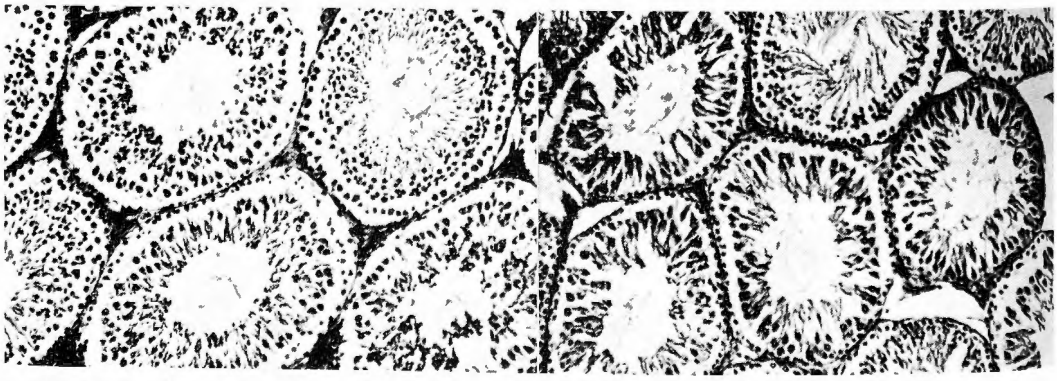
A. Primogonyl Administered Rat No. 33.

B. Chorionepithelioma Lyophilized Powder Administered Rat No. 184.



C. Chorionepithelioma Lyophilized Ppwder Aaministered Rat No. 82.

D. Placenta Lyophilized Powder Administered Rat No. 84.



E. Cancer Lyophilized Powder Administered Rat No. 47.

F. Control Rat No. 34.

Table 11. Weights of Sexual Organs and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma Lyophilized Powder for 4 Weeks.

	Litter of Rats	No.	Body Weight (g)	Type of Penis (Age Day)	Weight (g)					Ratio to Body Weight (g/g×100)				
					Penis	Testes *	Epid.*	Prost.	Sem. Ves.	Penis	Testes	Epid.	Prost.	Sem. Ves.
Chorionepithelioma Group	XXIX	183	76	U(31)	0.115	0.36	0.150	0.310	0.134	0.15	0.47	0.19	0.44	0.17
	XXX	193	83	U(31)	0.108	0.46	0.150	0.196	0.082	0.13	0.55	0.18	0.23	0.09
		194	82	U(30)	0.112	0.43	0.164	0.241	0.086	0.13	0.52	0.20	0.29	0.10
		195	68	W(33)	0.103	0.26	0.134	0.219	0.086	0.15	0.38	0.19	0.32	0.12
	XXXI	219	78	U(29)	0.138	0.38	0.165	0.313	0.178	0.17	0.48	0.21	0.40	0.22
	Mean Value		77.4		0.115	0.37	0.152	0.216	0.112	0.14	0.48	0.19	0.33	0.14
Control Group	XXIX	186	74	W(33)	0.048	0.76	0.077	0.057	0.021	0.06	1.02	0.10	0.07	0.02
	XXX	196	72	V(33)	0.057	0.76	0.101	0.076	0.021	0.07	1.05	0.14	0.10	0.02
		197	80	V(33)	0.046	0.73	0.098	0.052	0.019	0.05	0.91	0.12	0.06	0.02
	XXXI	220	82	W(33)	0.049	0.81	0.114	0.087	0.022	0.05	0.98	0.13	0.10	0.02
	Mean Value		77.0		0.050	0.76	0.097	0.067	0.020	0.05	0.99	0.12	0.08	0.02

*···Weight of Bilateral Organs Epid.···Epididymides Prost.···Prostate Sem. Ves.···Seminal Vesicle

Table 12. Weights of Sexual Organs and Their Ratio to Body Weight in Male Rats Asministered Chorionepithelioma Lyophilized Powder for 8 Weeks.

	Litter of Rats	No.	Body Weight (g)	Type of Penis (Age Day)	Weight (g)					Ratio to Body Weight (g/g×100)				
					Penis	Testes *	Epid.*	Prost.	Sem. Ves.	Penis	Testes	Epid.	Prost.	Sem. Ves.
Chorionepithelioma Group	XXVIII	174	168	U(30)	0.187	1.02	0.37	0.61	0.62	0.11	0.60	0.22	0.36	0.36
		175	164	U(31)	0.188	1.08	0.33	0.76	0.69	0.11	0.65	0.20	0.45	0.41
		176	174	U(30)	0.183	1.01	0.34	0.70	0.68	0.10	0.58	0.19	0.40	0.39
	XXIX	184	174	U(30)	0.182	1.32	0.36	0.64	0.67	0.10	0.75	0.20	0.36	0.38
	Mean Value		170.0	(30)	0.185	1.10	0.35	0.67	0.66	0.10	0.64	0.20	0.39	0.38
Control Group	XXVIII	177	180	U(44)	0.155	1.96	0.41	0.28	0.23	0.08	1.08	0.28	0.15	0.12
		178	166	U(42)	0.152	1.97	0.38	0.17	0.27	0.09	1.18	0.22	0.10	0.15
		179	163	U(45)	0.150	2.07	0.37	0.24	0.23	0.09	1.26	0.22	0.14	0.15
	XXIX	185	189	U(55)	0.153	2.18	0.38	0.19	0.18	0.08	1.21	0.21	0.10	0.10
	Mean Value		172.2	(43)	0.152	2.04	0.38	0.22	0.22	0.08	1.18	0.23	0.12	0.12

*···Weight of Bilateral Organs Epid.···Epididymides Prost.···Prostate Sem. Ves.···Seminal Vesicle

the control group, but LEYDIG cells hyperplasia was more distinct than in the control group (Fig. 9, B).

2) In regard to the thyroid gland, adrenal gland and pineal body, no marked change was found in both experimental group I and II.

C. COMMENT

In summarizing the results obtained in our experiments, it can be said that by administering Primogonyl and lyophilized powder of chorionepithelioma to immature male rats, though early somatic development did not occur, early development of the sexual organs was noticed. Namely, by the period when rats normally

Table 13. Weights of Sexual Organs and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma and Cancer Lyophilized Powder for 8 Weeks.

	Litter of Rats	No.	Body Weight (g)	Type of Penis (Age Day)	Weight (g) Penis	Testes *	Epid.*	Prost.	Sem. Ves.	Ratio to Body Weight (g/g×100) Penis	Testes	Epid.	Prost.	Sem. Ves.
Chorionepithelioma Group	VIII	45	216	U(29)	0.205	1.67	0.46	0.64	0.72	0.09	0.75	0.21	0.29	0.33
	X	59	189	U(33)	0.181	1.39	0.36	0.54	0.30	0.09	0.72	0.19	0.28	0.15
		60	175	U(37)	0.171	1.32	0.34	0.53	0.30	0.09	0.75	0.19	0.30	0.17
	Mean Value		193.3	(33)	0.185	1.46	0.38	0.57	0.44	0.09	0.74	0.19	0.29	0.21
Cancer Group	VIII	47	176	U(50)	0.148	1.93	0.38	0.29	0.17	0.08	1.09	0.21	0.16	0.09
	X	63	190	U(48)	0.141	2.33	0.41	0.27	0.18	0.07	1.27	0.21	0.14	0.09
		64	202	U(50)	0.149	2.31	0.15	0.26	0.21	0.07	1.14	0.22	0.12	0.10
	Mean Value		189.3	(49)	0.146	2.19	0.41	0.27	0.18	0.07	1.16	0.21	0.14	0.09
Control Group	VIII	48	192	U(47)	0.165	2.12	0.42	0.29	0.30	0.08	1.10	0.21	0.15	0.15
	X	65	186	U(48)	0.150	2.49	0.43	0.25	0.27	0.08	1.33	0.23	0.13	0.14
	Mean Value		189.0	(47)	0.157	2.30	0.42	0.27	0.28	0.08	1.21	0.22	0.14	0.14

*…Weight of Bilateral Organs　Epid.…Epididymides　Prost.…Prostate　Sem. Ves.…Seminal Vesicle

Table 14. Weights of Hypophysis, Thyroids and Suprarenals and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma and Placenta Lyophilized Powder for 4 Weeks.

	Litter of Rats	No.	Body Weight (g)	Weight (g) Hypophysis	Thyroids*	Suprarenals *	Ratio to Body Weight (g/g×100) Hypophysis	Thyroids	Suprarenals
Chorionepithelioma Group	XVIII	100	86	0.0042	0.013	0.023	0.0048	0.015	0.026
		101	77	0.0027	0.012	0.022	0.0035	0.015	0.028
	XX	120	78	0.0035	0.013	0.022	0.0044	0.016	0.028
	XXII	130	68	0.0032	0.011	0.018	0.0046	0.016	0.026
	XXIII	133	76	0.0036	0.011	0.018	0.0047	0.014	0.023
	Mean Value		77.0	0.0034	0.012	0.020	0.0044	0.015	0.026
Placenta Group	XVIII	102	68	0.0025	0.010	0.021	0.0036	0.014	0.030
		103	71	0.0028	0.011	0.021	0.0039	0.013	0.029
	XX	121	74	0.0037	0.010	0.018	0.0050	0.013	0.024
	XXII	131	74	0.0035	0.010	0.024	0.0047	0.013	0.032
	Mean Value		71.7	0.0031	0.010	0.021	0.0043	0.013	0.028
Control Group	XVIII	104	79	0.0042	0.012	0.027	0.0053	0.015	0.034
	XX	122	82	0.0041	0.012	0.023	0.0050	0.014	0.028
	XXII	132	68	0.0036	0.009	0.022	0.0052	0.013	0.032
	XXIII	134	82	0.0039	0.009	0.023	0.0047	0.010	0.027
	Mean Value		77.7	0.0039	0.010	0.023	0.0050	0.013	0.030

*…Weight of Bilateral Organs

Table 15. Weights of Hypophysis, Thyroids and Suprarenals and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma and Placenta Lyophilized Powder for 8 Weeks.

	Litter of Rat	No.	Body Weight (g)	Weight (g)			Ratio to Body Weight (g/g×100)		
				Hypophsis	Thyroids*	Suprarenals*	Hypophysis	Thyroids	Suprarenals
Chorionepithelioma Group	VIII	45	216	0.0072	0.031	0.042	0.0033	0.014	0.018
	X	59	189	0.0062	0.021	0.039	0.0032	0.011	0.020
		60	175	0.0065	0.022	0.030	0.0037	0.012	0.017
	XII	82	168	0.0067	0.021	0.030	0.0039	0.012	0.018
		83	174	0.0069	0.025	0.033	0.0039	0.014	0.018
	Mean Value		184.4	0.0067	0.024	0.034	0.0036	0.012	0.018
Placenta Group	VIII	46	189	0.0060	0.020	0.041	0.0031	0.010	0.021
	X	61	171	0.0077	0.021	0.034	0.0045	0.012	0.019
		62	183	0.0073	0.031	0.029	0.0039	0.016	0.015
	XII	84	174	0.0059	0.021	0.038	0.0033	0.012	0.021
		85	182	0.0068	0.019	0.036	0.0037	0.010	0.019
	Mean Value		179.8	0.0067	0.022	0.035	0.0037	0.012	0.019
Control Group	VIII	48	192	0.0070	0.024	0.040	0.0036	0.012	0.020
	X	65	186	0.0067	0.025	0.037	0.0036	0.013	0.019
	XII	88	190	0.0074	0.024	0.039	0.0038	0.012	0.020
	Mean Value		189.3	0.0070	0.024	0.038	0.0036	0.012	0.019

*...Weight of Bilateral Organs

Table 16. Weights of Hypophysis, Thyroids and Suprarenals and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma and Cancer Lyophilized Powder for 8 Weeks.

	Litter of Rat	No.	Body Weight (g)	Weight (g)			Ratio to Body Weight (g/g×100)		
				Hypophysis	Thyroids*	Suprarenals*	Hypophysis	Thyroids	Suprarenals
Chorionepithelioma Group	VIII	45	216	0.0072	0.031	0.042	0.0033	0.014	0.018
	X	59	189	0.0062	0.021	0.039	0.0032	0.011	0.020
		60	175	0.0065	0.022	0.030	0.0037	0.012	0.017
	Mean Value		193.3	0.0066	0.024	0.037	0.0034	0.012	0.018
Cancer Group	VIII	47	176	0.0073	0.018	0.042	0.0041	0.010	0.023
	X	63	190	0.0057	0.025	0.033	0.0030	0.013	0.017
		64	202	0.0063	0.031	0.033	0.0031	0.015	0.016
	Mean Value		189.3	0.0064	0.024	0.036	0.0034	0.012	0.018
Control Group	VIII	48	192	0.0070	0.024	0.040	0.0036	0.012	0.020
	X	65	186	0.0067	0.025	0.037	0.0036	0.013	0.019
	Mean Value		189.0	0.0068	0.024	0.038	0.0036	0.012	0.019

*...Weight of Bilateral Organs

enter puberty, i. e. approximately 30 days after birth, the accessory sexual organs of these rats reached a fully ripe state similar to those of mature rats. Primogonyl gave the most remarkable effect on the early maturation of the accessory sexual

Table 17. Weights of Hypophysis, Tyroids and Suprarenals and Their Ratio to Body Weight in Male Rats Adminlstered Chorionepithelioma Lyophilized Powder for 4 Weeks.

	Litter No. of Rat	Body Weight (g)	Weight (g)			Ratio to Body Weight (g/g×100)		
			Hypophysis	Thyroids *	Suprarenals *	Hypophysis	Thyroids	Suprarenals
Chorionepithelioma Group	XXIX	183	0.0039	0.0092	0.014	0.0051	0.012	0.018
	XXX	193	0.0036	0.0096	0.016	0.0043	0.011	0.019
		191	0.0039	0.0080	0.017	0.0046	0.009	0.020
		195	0.0034	0.0095	0.016	0.0050	0.013	0.023
	XXXI	219	0.0034	0.0090	0.016	0.0043	0.011	0.020
	Mean Value	77.4	0.0036	0.0090	0.015	0.0046	0.011	0.020
Control Group	XXIX	186	0.0042	0.0085	0.016	0.0056	0.011	0.021
	XXX	196	0.0034	0.0080	0.019	0.0047	0.011	0.025
		197	0.0039	0.0100	0.020	0.0048	0.012	0.025
	XXXI	220	0.0037	0.0100	0.017	0.0045	0.012	0.020
	Mean Value	77.0	0.0038	0.0091	0.018	0.0049	0.011	0.022

*…Weight of Bilateral Organs

Table 18. Weights of Hyoophysis, Thyroids and Suprarenals and Their Ratio to Body Weight in Male Rats Administered Chorionepithelioma Lyophilized Powder for 8 Weeks.

	Litter No. of Rat	Body Weight (g)	Weight (g)			Ratio to Body Weight (g/g×100)		
			Hypophysis	Thyroids *	Suprarenals *	Hypophysis	Thyroids	Suprarenals
Chorionepithelioma Group	XXVIII	171	0.0048	0.015	0.025	0.0028	0.0094	0.015
		175	0.0052	0.015	0.024	0.0031	0.0091	0.014
		176	0.0046	0.016	0.024	0.0026	0.0091	0.013
	XXIX	181	0.0061	0.017	0.028	0.0030	0.0097	0.016
	Mean Value	170.0	0.0041	0.015	0.025	0.0028	0.0093	0.014
Control Group	XXVIII	177	0.0048	0.017	0.027	0.0026	0.0094	0.015
		178	0.0041	0.014	0.026	0.0024	0.0084	0.015
		179	0.0054	0.015	0.024	0.0033	0.0092	0.014
	XXIX	185	0.0066	0.018	0.030	0.0036	0.0100	0.016
	Mean Value	172.2	0.0052	0.016	0.026	0.0029	0.0092	0.015

*…Weight of Bilateral Organs

organs. A clear sexual precocity was also produced with lyophilized powder of hydatid mole or chorionepithelioma. It is believed that actually these sexual precocities were brought about by chorionic gonadotropin which is thought to be secreted from the chorionic tissue. It is well known that chorionic gonadotropin (interstitial-cell-stimulating hormone) causes hyperplasia of LEYDIG cells, and allows the LEYDIG cells to secrete a large amount of androgen, resulting in an early appearance of the secondary sexual characteristics.

IV DISCUSSION

Precocious puberty accompanying a diencephalic tumor has been considered by

most investigators to take place through the stimulation or destruction by the tumor of the higher sexual center in the hypothalamus (WEINBERGER-GRANT 1941), though this theory lacks a definite evidence. But according to FUKUSHIMA in our laboratory, three out of four cases of diencephalic tumor associated with the precocious puberty were teratomas and the chorionepithelioma-like tissue was found within the tissue of these teratomas. In one of them, it seemed quite provable from the increased gonadotropin value in the urine, that precocious puberty took place due to chorionic gonadotropin secreted from the tumor tissue.

LAIPPLY (1945) reported a case of the chorionepitheliomatous teratoma in the mediastinum of a 13-year-old boy showing sexual precocity and hyperplasia of LEYDIG cells. RHODEN (1944) found precocious sexual and somatic development in a 9-month-old boy with a presacral teratoma. Besides these, there are several reports of precocious puberty due to the teratoma containing chorionepithelioma tous tissue which originated in the testis or the ovarium (SACHII 1895, FASOLD 1931). Therefore, in the case of intracranial teratoma too, it may be reasonable to assume that precocious puberty may result from the chorionic gonadotropin secreted from chorionepithelioma-like tissue within the teratoma.

In one of the cases reported by FUKUSHIMA the hypophysis was almost completely destroyed, and therefore the gonadotropin, that had increased in the urine could only be considered as having been originated from the chorionepithelioma-like tissue in both the intracranial tumor and its metastases. The gonadotropin value in the urine of this case was sufficient to cause early development of the secondary sexual characteristics. Though in this case the body length was in normal range and no spermatogenesis was noticed in the testis, there were hyperplasia of LEYDIG cells and early development of the distinct secondary sexual characteristics, i. e. the changes corresponding to those in my experimental animals. Therefore, in this case, there is good reason to believe that precocious puberty associated with intracranial teratoma would have been caused by chorionic gonadotropin from the tumor.

As the term macrogenitosomia praecox (PELLIZI) implies, many cases of precocious puberty reported in the literature were not only accompanied by sexual precocity but also by overgrowth of the body. Out of nineteens cases in the literature of the pineal tumor accompanied by precocious puberty, in which the full description of the somatic development (body length and body weight) was given, eleven cases showed the distinct somatic overgrowth and the remaining eight cases were at the upper limit of the normal growth. Besides, according to the literature, in many cases of pineal tumor accompanying precocious puberty, the testis was larger and spermatogenesis appeared earlier than normal.

In my experiment, though the early development of the accessory sexual organs and of the secondary sexual characteristics took place in almost the same way as in the case of precocious puberty in humans, no precocious somatic growth could be observed, and besides, the administration of lyophilized powder of chorionepithelioma caused the decrease in the testicular weight with the tendency to atrophy

of germinal cells. Though the accompaniment of precocious somatic growth is common in cases of human precocious puberty due to pineal tumor, the somatic precocity does not seem to be essential for precocious puberty by following reasons.

1) In the animal experiments reported in the literature on the effect of chorionic gonadotropin, early development of the sexual organs, especially of the accessory sexual organs was recognized in all cases, but body development, though it was seldom described satisfactorily, seems, as in my experiments, to have not been excessive (Boeters 1930, Smith 1934). But in the case of clinical use of chorionic gonadotropin for the treatment of patients with the retention of the testis, somewhat (Thompson 1938) or great (Ichikawa 1956) acceleration of body growth was found simultaneously with early development of the sexual organs. Moreover, in cases of human teratoma or chorionepithelioma of the ovarium, or of interstitial cell tumor of the testis, somatic precocity was noticed in addition to abnormal growth of the sexual organs, especially of their accessories (Harris 1917, Costin 1948, Staubnitz 1953). Thus it seems that there may be some differences between men and animals in the acceleration of body development during the period of puberty (whether it is naturally or artificially induced).

2) The second reason is that chorionepithelioma has the ability to secrete various kinds of hormone other than chorionic gonadotropin, and the proportion of those hormons differs in each chorionepithelioma. In all cases of precocious puberty, early appearance of the secondary sexual characteristics is an indispensable phenomenon but early body development is not always present, and, if it is, varies in degree case by case. Therefore, a possibility can also be supposed that early development of the body depends on the character of the hormone secreted by such tumors.

Next is the problem pertaining to the testis. The increase in the weight of testis and the appearance of spermatozoa are not so characteristic of precocious puberty as the early appearance of the secondary sexual characteristics.

According to the results of my experiment, after the administration of Primogonyl for 4 weeks, spermatozoa appeared which were not observed in the control group, whereas after 8-week administration of Primogonyl spermatozoa were found in both groups in a nearly epual amount. Of the groups to which lyophilized powder of chorionepithelioma was administered, atrophy of germinal cells was noticed in the 4-week group, whereas in the 8-week group germinal cells were found to have returned to normal. But when the amount of powder was decreased, it was difficult for germinal cells to come to atrophy. Thus it can be assumed that histological change of the seminiferous tubules depends upon the amount of powder and the length of period of administration. Therefore, also in this regard, I cannot believe that there is an essential difference between human precocious puberty accompanied by pineal tumor and that of my experimental animals.

However, it seems impossible to explain all cases of cerebral type of precocious puberty from the standpoint of the ontogenic theory, because there are cases of precocious puberty caused by glioma, encephalitis and other non-neoplastic lesions.

Yet, the majority of cases (approximately 3/4) of precocious puberty accom-

panied by pineal tumor are the cases of teratoma (KRABBE1923, HORAX and BAILEY 1925, KITAY 1954), and also in Japan, eight out of eleven cases were reported to be due to teratoma. Besides, according to RUSSELL (1944), pinealoma is all atypical teratoma. Moreover, an elaborate histological examination of teratomas revealed, at times, that they contained chorionepitheliomatous tissue in a part and such tumors, if they developed prior to puberty, gave rise to precocious puberty (WIRTH 1929, D. S. RUSSELL 1944, W. O. RUSSELL 1945, ZONDECK 1953).

Also, from the fact that the majority of cases of cerebral type of precocious puberty are accompanied by pineal tumor and that almost all such patients are males, the development of precocious puberty seems to be easier to understand from the standpoint of the ontogenic theory than from that of the hypothalamic theory. Besides, it has been known that an overwhelming number of cases of extragenital teratoma, especially those of intracranial teratoma have been observed in males. In considering these evidences together with the results of my experiments, I believe the old ontogenic theory should be taken into consideration once again, even though it seems unlikely that all cerebral types of precocious puberty can be explained according to this theory.

SUMMARY

1) By the administration of a large amount of chorionic gonadotropin (Primogonyl and lyophilized powder of chorionepithelioma) to immature male rats, distinct sexual precocity took place, though accompaniment of early somatic development could not be noticed.

2) It is possible that the precocious puberty occurring in cases of diencephalic tumor may be caused by the gonadotropin secreted from the tumor.

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和文抄録

絨毛性 Gonadotropin による雄性 Pubertas praecox の実験的研究

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松果体腫瘍に伴うPubertas Praecox の発生原因に関して Askanazy (1906) は，腫瘍組織に含れる絨毛上皮腫様組織よりの性腺刺戟ホルモン様物質分泌を考えて Ontogene Theorie を提唱した．併しその後この説に対する多くの反論が現れ現在では殆ど省みられなくなつた．

然るに我々の教室の福島は京大第Ⅰ外科に於ける Pubertas praecox を併発した脳腫瘍4例——松果体腫瘍3例（内奇形腫2例）下垂体部奇形腫1例——を詳細に組織学的検索を行い，奇形腫3例中2例に絨毛上皮腫様組織，1例には Cytotrophoblastoma 様組織を認めた．更に他の1例では大部分Pinealoma組織であるのに一部に腺様構造を認め，これも奇形腫である可能性があつた．即ち我々の教室例4例中3例は絨毛性 Gonadotropin を出し得る組織を有して居り他の1例にも同様の事が考えられた．中でも下垂体奇形腫の1例では下垂体は殆ど完全に破壊され前葉細胞は全く認められなかつたのに尿中 Gonadotropin 値は著明に増加して居た．

従つてこの Gonadotropin 値の増加は腫瘍組織に含れる絨毛上皮腫によることは明らかであり，この症例に於ける Pubertas praecox は絨毛性 Gonadotropin によつて発現したと考えられ，他の2例にも同様の事が想像された．これらの事実より Ontogene Theorie を再検討する必要があると考えて絨毛性Gonadotropin と Pubertas praecox との関係について動物実験を行つた．

実験動物は同腹の幼若雄ラッテを使用し絨毛性 Gonadotropin としては Primogonyl (Schering Co.) 及び2例の絨毛上皮腫組織よりつくつた凍結乾燥粉末を生後5日目より前者は1日30 r.u. 毎日皮下注射，後者は1日 10mg 週3回皮下注射を行い，1週毎に体重を測定し，投与4週間（生後33日）投与8週間（生後61日）で屠殺，性器重量及び内分泌臓器の組織学的検査を行つた．

実験結果は Primogonyl 及び絨毛上皮腫凍結乾燥粉末によつて身体早期発育（身長，体重の増加）は来さなかつたが，第二次性徴の早期発現，副性器の著明な早期発育を認めた．即ち雄ラッテが思春期に達すると考えられる生後30日前後で副性器は成熟ラッテに相当する発育を来した．睾丸では重量は却つて減少したが Leydig 細胞の著明な増殖あり，Primogonyl 投与では精子形成の早期発現を認めた．

以上の結果より，間脳部腫瘍による Pubertas praecox は間脳部障害によるもの以外に，腫瘍組織より分泌される Gonadotropin による可能性が相当濃厚なものと考える．