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## TUMORS OF THE DIENCEPHALON AND PRECOCIOUS PUBERTY

by

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### INTRODUCTION

Since precocious puberty of intracranial origin occurs not only in association with tumors in the diencephalon but also with inflammatory processes in the same region of the brain, many theories as to the causation of precocious puberty have been advanced.

The oldest theory is that the pineal body is a gland of internal secretion. The second and much debated theory is that the type of tumor is important rather than the structure from which it arises. In the third theory, attention has been directed to the location of the pathological process rather than to its histological appearance. However, any of these three theories have not been definitely proven.

Regarding the first theory, that is, in order to know whether the pineal body plays a role in the development of precocious puberty, a series of animal experiments have been made by HANDA, KUROSAWA, TANAKA and KAGEYAMA in our laboratory. These studies showed that precocious puberty might not be produced by the function of the pineal body itself but probably by the secondary dysfunction of the hypothalamus resulting from the lesion in the roof area of the diencephalon. In this paper, in a total of 7 clinical cases of precocious puberty (5 undoubted and 2 suspected) which had accompanied a diencephalic tumor, the histo-pathological study of the diencephalon including the tumor was made.

### I. METHOD

1. The brains of cases 1, 4 and 7 had been fixed in absolute alcohol and those of cases 2, 3, 8 and 9 in 10% formalin. Serial sections were made about  $30\mu$ . in thickness, except in case 2 in which sections were made about  $70\mu$ . due to erroneous chromizing, and stained with hematoxylin-eosin, Nissl stain and myelin stain at the interval of about 1 mm.

2. The thalamic nuclei were classified according to Niimi.

3. As to the description of the hypothalamic nuclei, an atlas written by H. A. RILEY was consulted.

## II. CASES

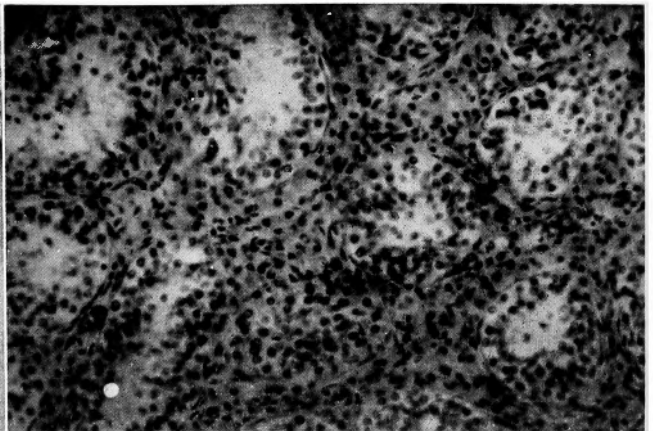
## Group 1. Pineal tumors

**Case 1.** K MORI, a 7-year-old male, was admitted on June 6, 1955.

About 6 years and 5 months of age, the patient began to show a remarkable bodily growth associated with a tendency to become obese. By the age of 6 years and 9 months, his external genitalia became precociously mature with growing of pubic hair giving an appearance of puberty (Fig. 1). Ten days before admission, the patient developed frequent vomiting and headaches followed by generalized convulsion and loss of consciousness. Immediately after admission, a ventricular drainage was performed. He developed hyperthermia and the following day he died of respiratory paralysis. Urinary 17 K.S. value of the patient corresponded to that of a normal male 12 or 13 years of age. In the testicle, remarkable increase in number of the interstitial cells, occurrence of spermatogenesis and spermatozoa in some areas were noted (Fig. 2). There was, however, no evidence of intratesticular tumor in the serial microscopic sections. The hypophysis was of normal size and there was no change in number of parenchyma cells of each type.



**Fig. 1.** Case 1. 7-year-old male.

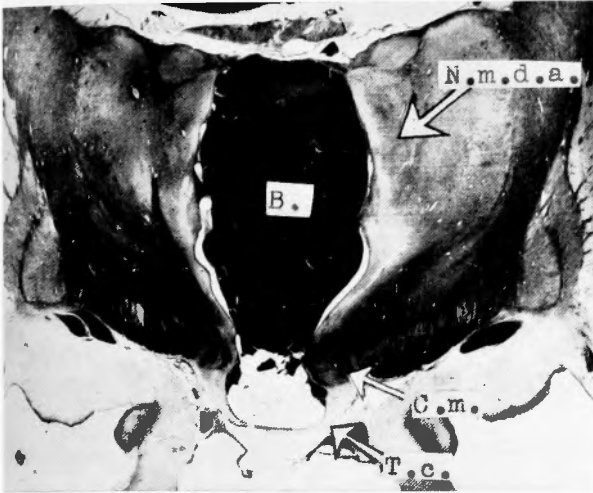


**Fig. 2.** Case 1. Testicle. H-E. stain.  $\times 200$ .

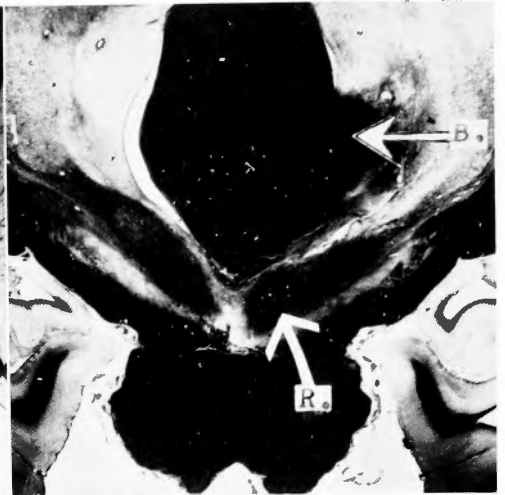
## Autopsy findings of the brain:

## 1) Macroscopic findings (in serial sections)

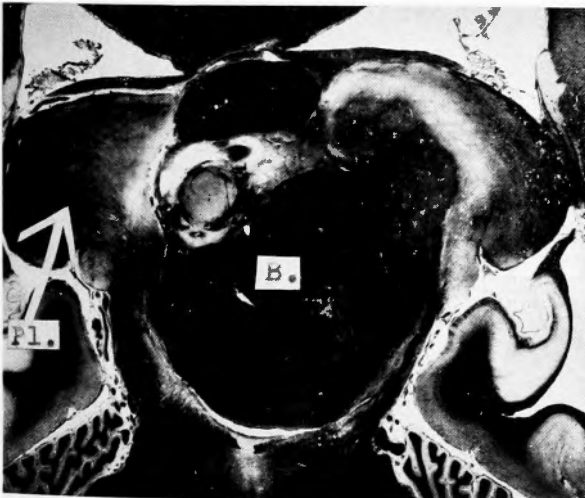
The dilation of the ventricular system, especially the posterior half of the third ventricle and the aqueductus mesencephali, was noted. The third ventricle and the aqueductus mesencephali were filled by a large clotted blood which had extended to the cisterna colliculorum. The pineal body, the corpora quadrigemina and the velum medullare anterius were destroyed and there was a severe mechanical compression at the postero-ventral (mesencephalic) wall of the third ventricle. Besides, the clotted blood described above invaded the left thalamus, more severely in its posterior part. The base of the third ventricle, that is the hypothalamus, was compressed severely, too. The infundibulum was relatively free of damage macro-



**Fig. 3.** Case 1. Frontal section of the diencephalon through the tubero-mammillar region of the hypothalamus. Myelin stain (EHRlich).  
 B. Clotted blood (anterior half) in the third ventricle.  
 C.m. Corpus mammillare.  
 T.c. Tuber cinereum.  
 N.m.d.a. Anterior part of the medial dorsal thalamic nucleus.



**Fig. 4.** Case 1. Frontal section of the diencephalon through the red nucleus. Myelin stain (EHRlich).  
 B. Blood invading into the area of the medial ventral nucleus and the parafascicular nucleus of the left thalamus.  
 R. Red nucleus.



**Fig. 5.** Case 1. Frontal section of the diencephalon through the pulvinar thalami. Myelin stain (EHRlich).  
 B. Blood filling the posterior half of the third ventricle and invading into the medial part of the nucleus pulvinaris.  
 Pl. Pulvinar thalami.



**Fig. 6.** Case 1. Frontal section of the diencephalon through the cisterna colliculorum. Myelin stain (EHRlich).  
 Ci. Cisterna colliculorum which was filled by the blood clot.  
 B. Clotted blood in the aqueductus mesencephali.

scopically but the pars tuberalis hypothalami was remarkably thinned by the compression (Figs. 3, 4, 5 and 6).

## 2) Microscopic finding (in serial sections)

### i) The tumor

There was a dense population of the tumor cells in the pineal region, where a thin capsule surrounded the blood clot. Other parts of the lesion consisted mostly of coagulated blood within which the tumor cells were scattered. The histological structure of the tumor mainly consisted of the following three elements ;

(1) Large round cells similar to the epithelial cells and small round cells similar to the lymphocyte as seen in a usual pinealoma were noted. There was, however, not a mosaic formation as seen in a typical pinealoma but an irregular arrangement of two kinds of cells (Fig. 7).

(2) The area showing teratomatous picture including cysts and other elements was found. The cysts were surrounded by cells similar to those of epidermis and contained hornified substance (Fig. 8).

(3) In a very small area in the coagulated blood which was assumed to be located in the corpora quadrigemina, large cells, the diameter of which might reach to about  $40\ \mu$ ., were found. These cells gathered closely like a stone wall without forming ducts. Each cell had clear cytoplasm and vacuolated, somewhat clear nucleus which was relatively poor in chromation and of which nuclear membrane was thin. The nucleolus was mostly one or two in number, large in size and irregular in shape. This undifferentiated cell was diagnosed as belonging to the cyto-trophoblast type cell (Fig. 9) and this tissue was diagnosed the cytrophoblastoma (DIXON & MOORE).

Neither the cell of syncytial-trophoblast type nor the tissue of normal pineal body was observed.

### ii) The hypothalamus

Infiltration of the tumor cells was not observed. Petechial hemorrhages which were observed in the subependymal layer of the third ventricle were extended to the preoptic,

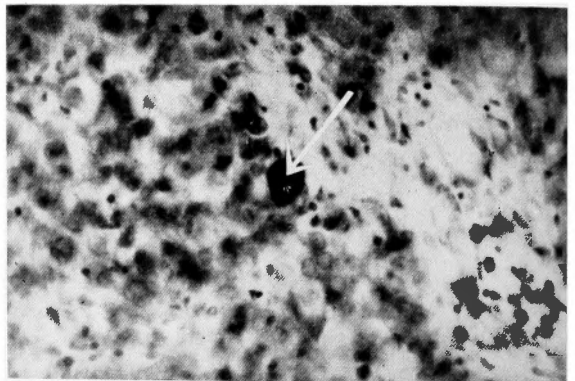


Fig. 7. Case 1. Pinealoma. H.-E. stain.  $\times 400$ . (arrow). Calcification.

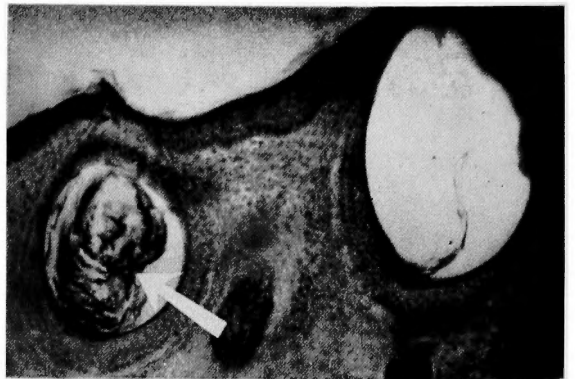


Fig. 8. Case 1. Cysts. H.-E. stain.  $\times 400$ . (arrow). Hornified substance.

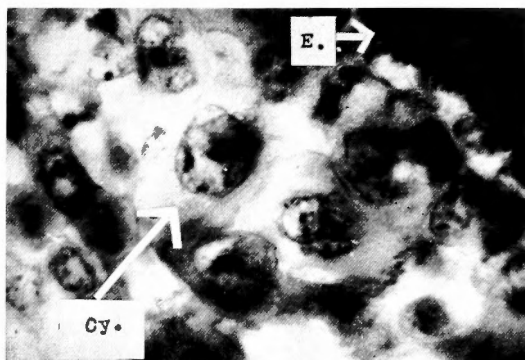
the anterior, the dorsal and the posterior hypothalamic area and the pars tuberalis hypothalami, except for the mammillary body and the area hypothalamica lateralis. This hemorrhage was particularly obvious all over the tuber cinereum, where there were strong changes of nerve cells such as a disappearance of nerve cells in the nuclei laterales tuberis cinerei. And a high grade of degeneration of nerve cells or a decrease in cell number in the nucleus hypothalamicus dorso-medialis et ventro-medialis were observed. Also, both the nucleus paraventricularis and the nucleus hypothalamicus posterior

suffered petechial hemorrhages and were severely changed. Part of the nucleus supra-opticus and the preoptic and the dorsal hypothalamic nucleus showed somewhat degenerative changes, too, and only the mammillary body and the area hypothalamica lateralis seemed to have remained intact.

### iii) The thalamus\*

In the subependymal layer of the third ventricle, there were scattered small hemorrhagic areas and the nucleus reuniens arcuatus was included in the hemorrhagic lesion. Also, the massa intermedia was destroyed and the nucleus reuniens medianus was lost. The hemorrhage in the left thalamus involved the medial, the ventral and the posterior group of the thalamic nuclei, the epithalamus (nucleus habenulae) and the metathalamus (corpus geniculatum mediale et laterale). In the nucleus medialis ventralis or the centre médian (LUVS), the nucleus parafascicularis, the nucleus paramedianus, the pars posterior of the nucleus medialis dorsalis, the medial part of the nucleus pulvinaris and the nucleus habenulae, there was a severe destruction or a disappearance of nerve cells. There was no evidence of the pathological change in the pars anterior of the nucleus medialis dorsalis, the dorsal and the dorso-lateral part of the nucleus laminaris, the anterior part of the nucleus ventralis, the nucleus reticularis, the lateral and the ventral part of the nucleus pulvinaris and the lateral geniculate body. In the anterior and the lateral group of the thalamic nuclei, neither the pathological change of nerve cells nor such a hemorrhagic lesion was observed.

**Case 2.** K. KAWAUCHI, a 11-year and 4-month-old male, was admitted on June 6, 1946. About the age of 11 years and 3 months, he began to complain of frontal



**Fig. 9.** Case 1. Cytotrophoblastoma (DIXON & MOORE).  
H.-E. stain.  $\times 900$ .  
Cy. Cyto-trophoblast type cell.  
E. Erythrocyte.

\* According to the classification by WALKER, the thalamic nuclei regarded to be intact were the nucleus anterodorsalis, anteromedialis and anteroventralis, the nucleus parataenialis medialis et lateralis, the pars anterior of the nucleus medialis dorsalis, the nucleus centralis lateralis, the nucleus ventralis anterior, the nucleus ventralis lateralis, the nucleus submedius, the nucleus medialis ventralis, the nucleus lateralis dorsalis, the nucleus lateralis posterior, the nucleus reticularis, the nucleus pulvinaris lateralis, the nucleus pulvinaris inferior and the lateral geniculate body.

headachs and vomiting, followed by generalized convulsion with sudden loss of consciousness a month later. He was lethargic continuously for 10 days preceding to the admission. The development of his external genitalia was noted to be better than that in average boy of his age (Fig. 10). A ventricular drainage was performed but his condition did not improve and he died 20 days after the operation, on July 21, 1946. The immediate cause of death was possibly intracranial infection.

Autopsy findings of the brain:

1) Macroscopic findings (in serial sections)

There was a generalized enlargement of the ventricles, especially marked in the posterior half of the third ventricle where there was a walnut-sized tumor. The tumor was relatively well circumscribed. The pineal body, the posterior commissure and the corpora quadrigemina were destroyed. The grade of deformity due to the mechanical pressure was highest at the postero-ventral (mesencephalic) wall of the third ventricle, next at the hypothalamus and the lowest at the side wall of the anterior half of the third ventricle (Figs. 11, 12, 13, 14 and 15).

2) Microscopic findings (in serial sections)

i) The tumor

The tumor contained (1) the area where there was a mosaic pattern arrangement of two kinds of cells as usually seen in a typical pinealoma (Fig. 16) and (2) the area where the tumor tissue was rich in tubular structure consisting of cylindrical epithelium, the nuclei of which were displaced to the periphery (Fig. 17).

Also, the area exhibiting a complex histological picture was observed, but its definite diagnosis could not be made because of the thick microscopic sections ( $70\mu$ ) and unsatisfactory stain due to chromizing. No normal pineal tissue was found.

ii) The hypothalamus and the thalamus



Fig. 10. Case 2. 11-year and 4-month-old male.

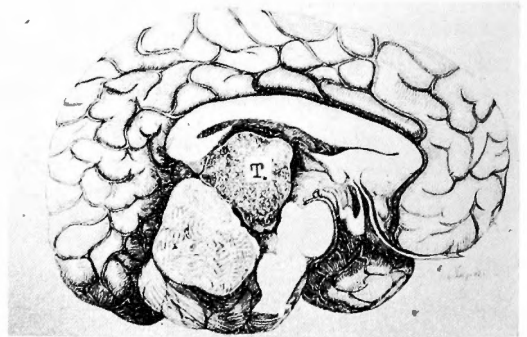
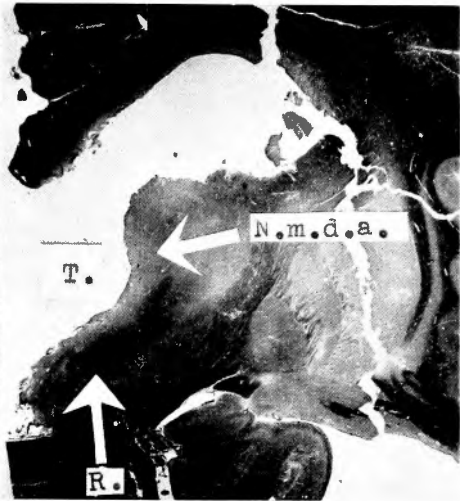


Fig. 11. Case 2. Diagram of the mid-sagittal section of the brain. T. Tumor mass in the pineal region.





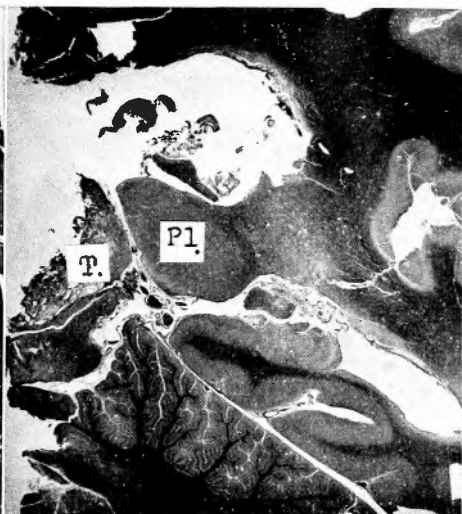
**Fig. 12.** Case 2. Left frontal section of the diencephalon through the pars tuberalis hypothalami. Myelin stain (WEIGERT).  
Tr.op. Tractus opticus.  
T.c. Tuber cinereum.



**Fig. 13.** Case 2. Left frontal section of the diencephalon through the red nucleus. Myelin stain (WEIGERT).  
R. Red nucleus.  
N.m.d.a. Anterior part of the medial dorsal thalamic nucleus.  
T. Tumor mass in the third ventricle which was artificially fallen off.



**Fig. 14.** Case 2. Left frontal section of the diencephalon through the nucleus habenulae. Myelin stain (WEIGERT).  
T. Tumor mass in the posterior half of the third ventricle.  
N.h. Nucleus habenulae.



**Fig. 15.** Case 2. Left frontal section of the diencephalon through the pulvinar thalami. Myelin stain (WEIGERT).  
T. Tumor mass in the posterior half of the third ventricle.  
Pl. Pulvinar thalami.

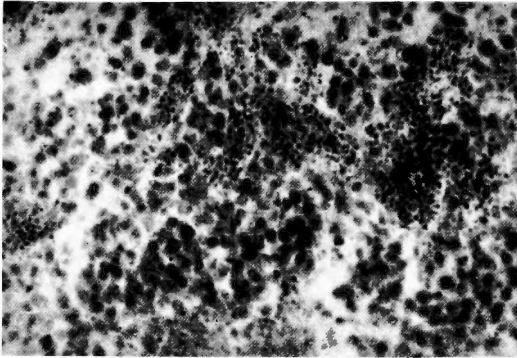


Fig. 16. Case 2. Pinealoma. H.-E. stain.  
×200.



Fig. 17. Case 2. Tubular structure. H.-E. stain.  
×900.

The infiltration of tumor cells was limited to the subependymal layer of the postero-ventral (mesencephalic) wall of the third ventricle and found neither in the hypothalamus nor in the thalamus. Thorough investigation of the degeneration of every nerve cell was almost impossible by chromizing.

**Case 3.** S. TAKEMOTO, a 11-year-old male, was admitted on December 29, 1942.

About the age of 10 years and 3 months, the bodily growth of the patient became prominent with a tendency to become obese and his external genitalia developed to adult form (Fig. 18). At the age of 10 years and 9 months, he began to have frontal headaches, vomiting and staggering of gait. A marked dilation of the anterior half of the third ventricle corresponding to the hypothalamus was noted by the lipiodol ventriculography (Fig. 19). Following the method by Dandy-Brunner (transcallosal pineal approach), intracapsular removal of the tumor in the pineal region was performed. But he died 16 days after the operation, on February 19, 1943, from the complication of pneumonia. The testicle was noted to have increased number of the interstitial cells, spermatogenesis and spermatozoa.

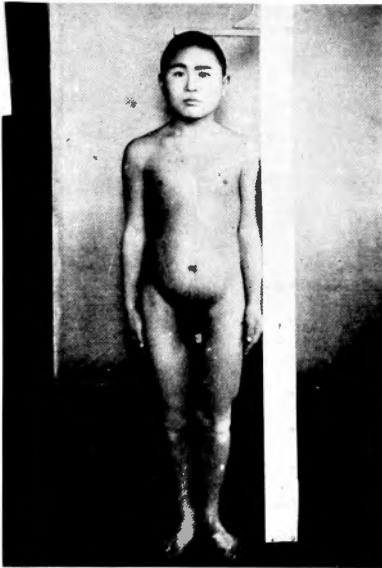


Fig. 18. Case 3. 11-year-old male.

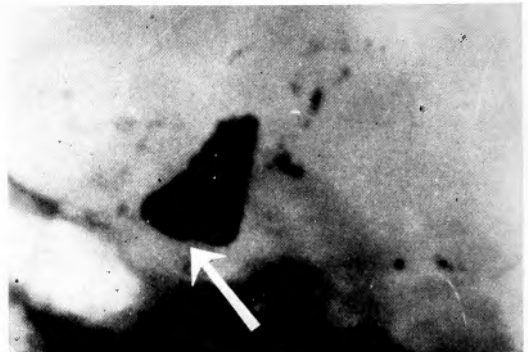


Fig. 19. Case 3. Findings of the lipiodol ventriculography.  
(arrow) Base of the third ventricle.



Autopsy findings of the brain :

1) Macroscopic findings

A walnut-sized tumor was located in the posterior half of the third ventricle. The anterior half of the tumor mass was dark red in color like a blood clot and was quite soft, while the posterior half was harder. The border between the base of the tumor and the corpora quadrigemina was ill-defined but in other places, the tumor mass was circumscribed fairly well and two pea-sized cysts were observed on the cut surface of the tumor mass (Fig. 20). The pineal body and the corpora quadrigemina were considered to be destroyed. Also, atrophy of the thymus and hypertrophy of the lymph-follicles of the tonsil, the colon and the small intestine were observed.

2) Microscopic findings

i) The tumor

The posterior half of the tumor mass consisted mainly of (1) the teratoid structure (epidermis-like tissue, cysts, tubular structure (Fig. 21), cartilagenous tissue (Fig. 22) and smooth muscle tissue etc.) and (2) the pinealoma tissue (Fig. 23) in many places, which did not show a mosaic pattern but a linear arrangement

of large cells with scattered small cells. Moreover, (3) in a corner of the blood clot which occupied most of the anterior half of the tumor mass, the chorionepithelioma tissue was observed (Figs. 24-a and 24-b). Among the cells composing the chorionepithelioma, the cyto-trophoblast type cells were predominant in number, though the syncytial-trophoblast type cells were observed as well. There was no normal tissue of the pineal body.

ii) The hypothalamus and the thalamus

No examination was performed microscopically.

Group 2. Hypothalamic tumors

**Case 4.** Y. OISHI, a 9-year and 4-month-old male, was admitted on March 1, 1956.

About the age of 8 years and 4 months, the patient developed diabetes insipidus. His urinary volume reached 15 liters a day at the peak of the disease and then tapered down.

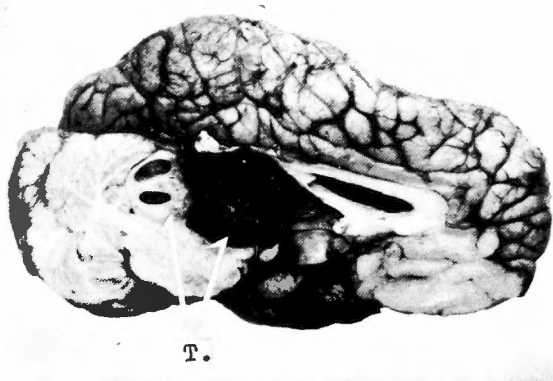


Fig. 20. Case 3. Mid-sagittal section of the brain.

T. Tumor mass in the pineal region.

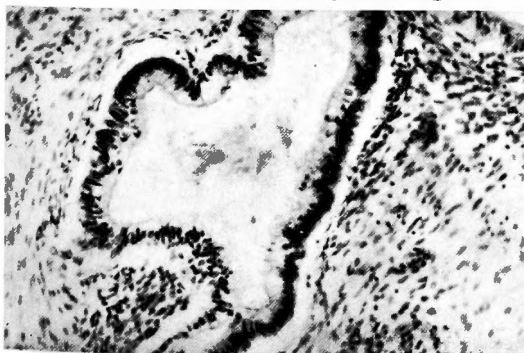


Fig. 21. Case 3. Tubular structure.

H.-E. stain.  $\times 400$ .

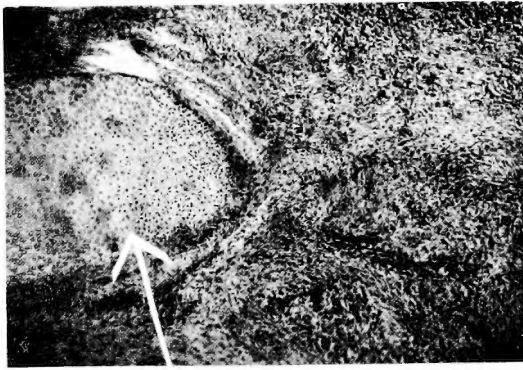


Fig. 22. Case 3. Cartilaginous tissue. (arrow). H.-E. stain.  $\times 100$ .

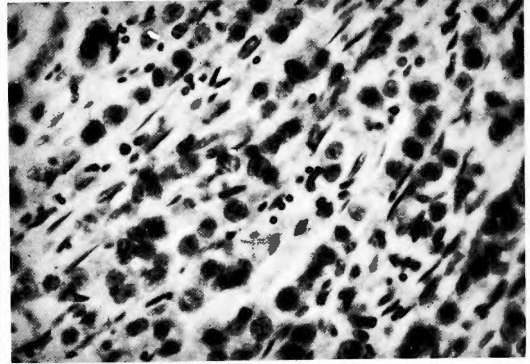
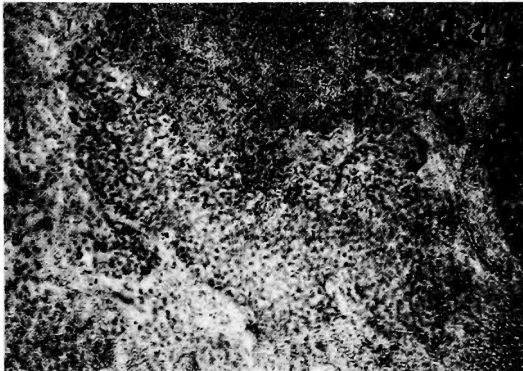


Fig. 23. Case 3. Pinealoma. H.-E. stain.  $\times 400$ .



Figs. 24-a and 24-b. Case 3. Cyto-trophoblast type cells. H.-E. stain. Fig. 24-a.  $\times 50$ .

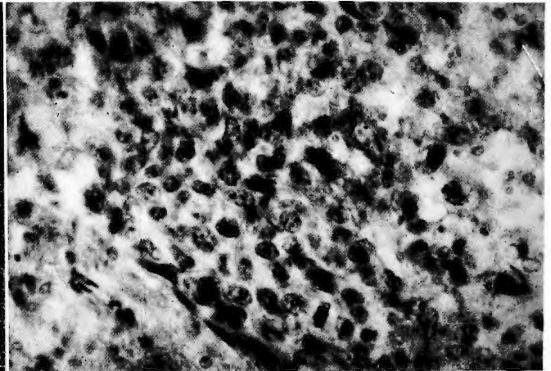


Fig. 24-b.  $\times 400$ .



Fig. 25. Case 4. 9-year and 4-month-old male.



Fig. 26. Case 4. Testicle. H.-E. stain.  $\times 100$ .

And its continuation was about 10 months. About the age of 8 years and 11 months, growing of the pubic hair was noted (Fig. 25). About the age of 9 years and 3 months, he developed headaches, vomiting, ptosis on the right side and double vision. 10 days prior to the admission, immobility of the right eyeball took place with visual disturbance on the same side and he finally died on March 15, 1956 in a condition similar to the Simmonds' symptoms. Although not conspicuous, the interstitial cells of the testicle were increased in number as compared with the average in his age and spermatogenesis and spermatid were noted (Fig. 26). The seminal tubules were enlarged showing hyperplastic changes and the histological picture of the prostate was adenomatous hyperplasia.

Endocrine function tests:

In 2850 c.c. of urine excreted in a day, the gonadotropin was 24 to 48 m.u.u./24 h. using kaolin adsorption method and 17 K. S. value was 0.25 mg/24 h. Urinary excretion of 17 O. H. C. S. following administration of A. C. T. H. was consistent with that in adrenal hypofunction. B. M. R. was very low, being minus 55.9 %.

Autopsy findings of the brain:

1) Macroscopic findings (in serial sections)

In the region of the hypophysis there was a tumor mass which was dark red in color and was hen-egg in size. The hypophysis and n. oculomotorius, n. trigeminus and n. abducens on the right side were embedded in the tumor (Fig. 27-a) and the hypophyseal stalk was thickened three or four times as normal one (Fig. 27-b). By the observation on the serial sections, the ventricles were noted not to be dilated (Figs. 28, 29, 30-a and 30-b) and the size of the pineal body was normal (Fig. 31). Also, generalized enlargement of the lymphnodes and atrophy of the thymus, the thyroid and the adrenal glands were observed. These changes were

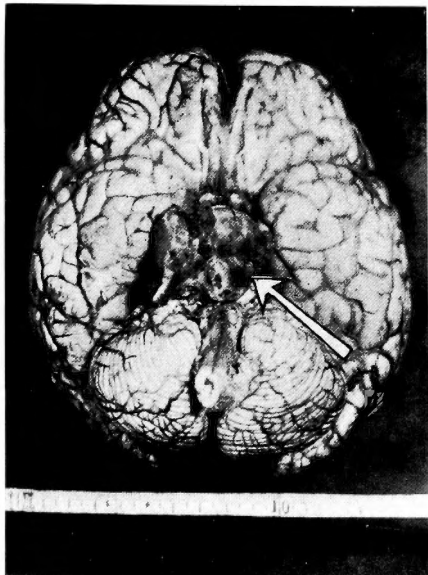
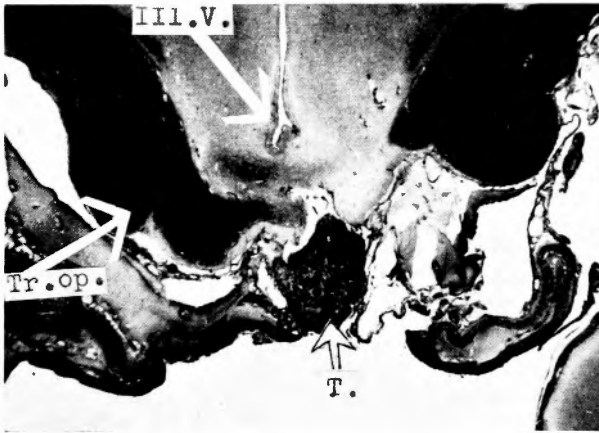


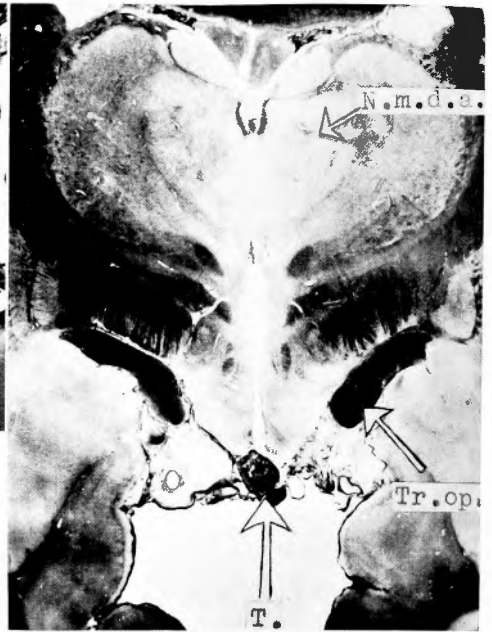
Fig. 27-a. Case 4. Tumor mass in the pituitary region (arrow).



Fig. 27-b. Case 4. Dorsal surface of the same tumor as in Fig. 25-a. (arrow). Hypophyseal stalk.



**Fig. 28.** Case 4. Frontal section of the hypothalamus through the infundibulum. Myelin stain (EHRlich).  
 III. V. Third ventricle.  
 Tr.op. Tractus opticus.  
 T. Infundibulum replaced by the tumor tissue.



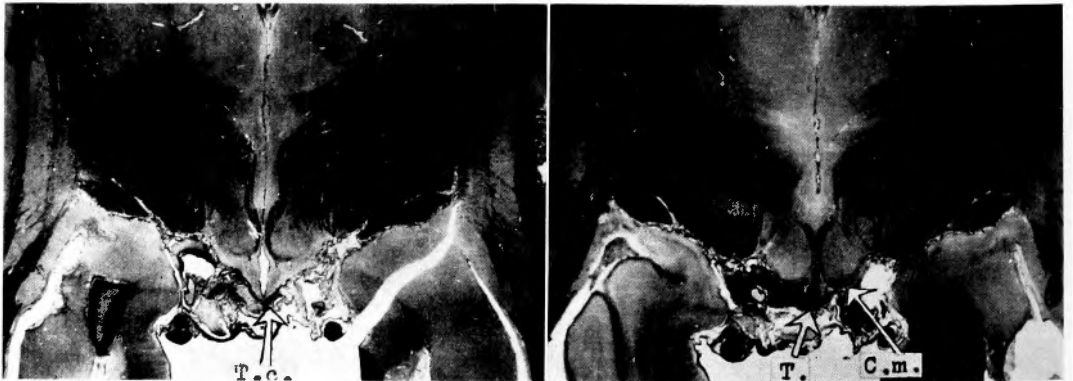
**Fig. 29.** Case 4. Frontal section of the diencephalon through the tubero-infundibular region. Myelin stain (EHRlich).  
 T. Infundibulum replaced by the tumor tissue.  
 Tr.op. Tractus opticus.  
 N.m.d.a. Anterior part of the medial dorsal thalamic nucleus.

confirmed histologically. Also there was a histological evidence of the feminization (hyperplasia) of the breasts.

2) Microscopic findings (in serial sections)

i) The tumor

Most of the tumor mass in the hypophyseal region was hemorrhagic and necrotic except for the following two elements remaining in a small part; (1) The teratomatous tissues composed of epidermal tissue, cartilagenous tissue (Fig. 32), glandular structure made of cylindrical



**Figs. 30-a and 30-b.** Case 4. Frontal section of the hypothalamus through the tubero-mammillar region. Myelin stain (EHRlich).  
 T.c. Tuber cinereum. C.m. Corpus mammillare.  
 T. Tumor tissue in the area of the tuber cinereum.

epithelium (Fig. 33) and other tissues. (2) The small amount of tissue, which was histologically similar to the chorion-epithelioma or the embryonal carcinoma of the testicle. Here, the cytotrophoblast type cells were predominant in number, while the syncytial-trophoblast type cells were also found (Figs. 34 and 35). On the other hand, the hypophyseal stalk was replaced by the pinealoma tissue (Fig. 36) which showed an irregular arrangement of two kinds of cells without forming a mosaic pattern. Moreover, the large cells in the pineal body were generally larger than normal ones, being irregular in size and showing pinealomatous appearance. There was no normal tissue left in either the anterior or the posterior lobe of the hypophysis. In the bilateral lungs, numerous metastatic foci of the chorion-epithelioma were found.

ii) The hypothalamus

The tumor cells in the hypophyseal stalk infiltrated continuously into the tuber cinereum through the attachment of the stalk to the base of the brain. The infiltration was severe all over the tuber cinereum (Fig. 37) and pushing the subependymal layer of the third ventricle upwards at the border between the tuber cinereum and the mammillary body. Among the nuclei in the hypothalamus, those in the tuber cinereum suffered the severest change, such as a disappearance of the



Fig. 31. Case 4. Frontal section of the diencephalon through the pulvinar thalami. Myelin stain (EHRlich). (arrow). Pineal body.

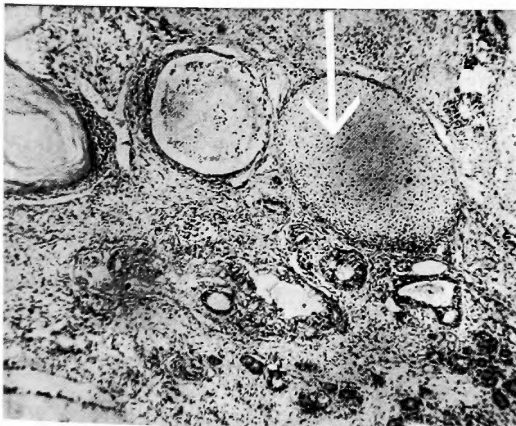


Fig. 32. Case 4. Cartilagenous tissue (arrow). H.-E. stain.  $\times 100$ .

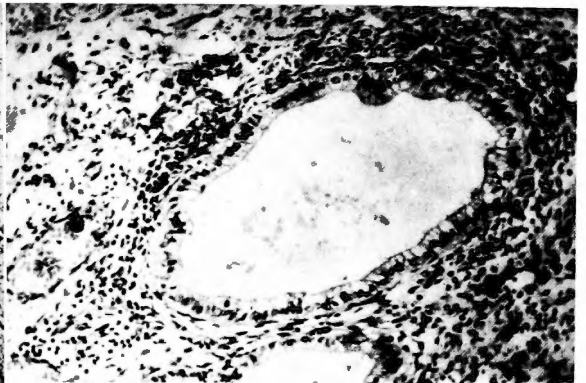


Fig. 33. Case 1. Tubular structure. H.-E. stain.  $\times 400$ .



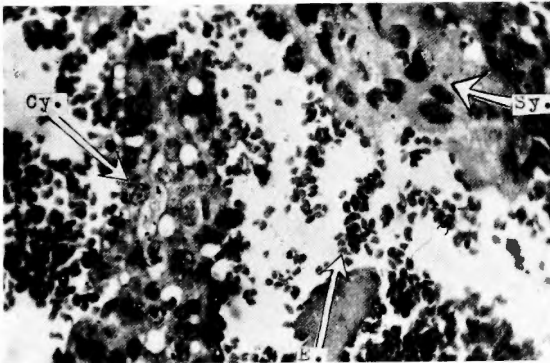


Fig. 34. Case 4. Chorionepithelioma. H.-E. stain.  $\times 400$ .

Cy. Cyto-trophoblast type cell.  
 Sy. Syncytial-trophoblast type cell.  
 E. Erythrocyte.

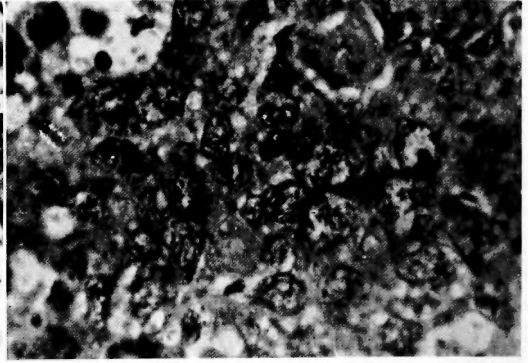


Fig. 35. Case 4. Cyto-trophoblast type cells. H.-E. stain.  $\times 900$ .

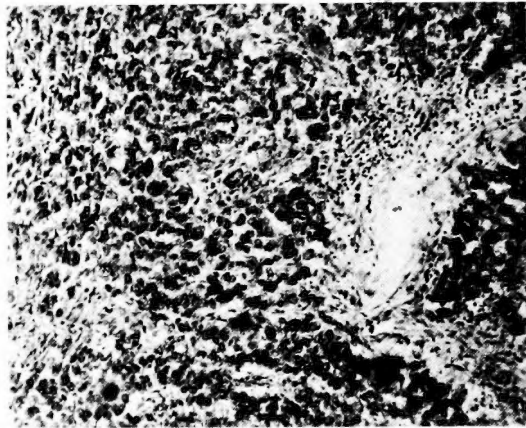


Fig. 36. Case 4. Pinealoma. H.-E. stain.  $\times 200$ .



Fig. 37. Case 4. Tumor cell infiltration in the area of the tuber cinereum. Nissl stain.  $\times 200$ .  
 III.V. Third ventricle.  
 T. Tumor cell infiltration.

nuclei laterales tuberis cinerei. There were a decrease in number and a degeneration of nerve cells in the nucleus hypothalamicus ventro-medialis and the infiltration of tumor cells in an area of the nucleus hypothalamicus dorso-medialis. Also, a slight but definite degeneration and a moderate decrease in number of nerve cells of both the nucleus hypothalamicus posterior and the nucleus paraventricularis were noted. The nuclei which were regarded to be intact were those in the preoptic, the lateral and the dorsal hypothalamic area and the mammillary body.

### iii) The thalamus

No abnormality of every nerve cell was observed microscopically.

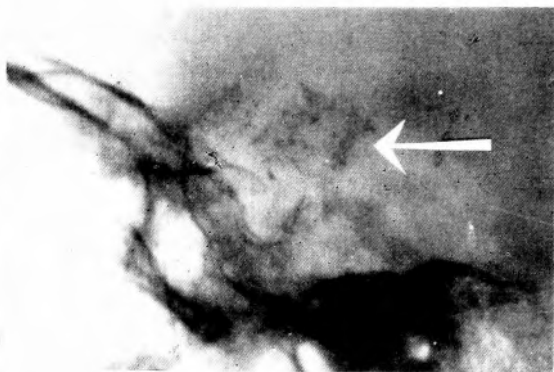
**Case 5.** T. ISHIHARA, a 8-year and 2-month-old female, was admitted on April 4, 1956.

About the age of 5 years, she developed obesity and diabetes insipidus. About the age of 7 years and 2 months, her breast began to become remarkably large (Fig. 38) and about the age of 8 years and a month, she had her menarche. Her urinary 17 K.S. value was 8.82 mg/24 h. She had visual disturbance of the left



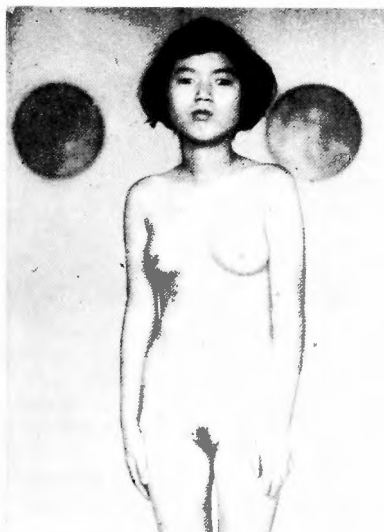


**Fig. 38.** Case 5. 8-year and 2-month-old female.



**Fig. 39.** Case 5. Suprasellar calcification (arrow).

eye and paresis of the left oculomotor and trigeminal nerve. By the ventriculography with lipiodol, the base of the third ventricle was noted high in position and the calcification was observed in the suprasellar region (Fig. 39).



**Fig. 40.** Case 6. 12-year and 3-month-old female.



**Fig. 41.** Case 7. 13-year and 3-month-old female.

These findings suggested the suprasellar tumor, probably the craniopharyngioma. She discharged on April 18, 1956 without the operation.

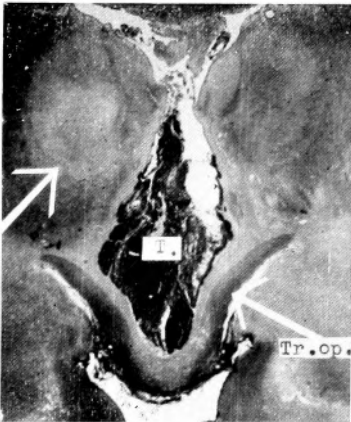
The following two cases belong to the suspected case of precocious puberty. In these cases, there was a marked development of the breast or of the external genitalia, though the patients were more or less older than those in the preceding cases.

**Case 6.** S. KOBAYASHI, a 12-year and 3-month-old female, was admitted on October 29, 1942 and discharged on December 11, 1942.

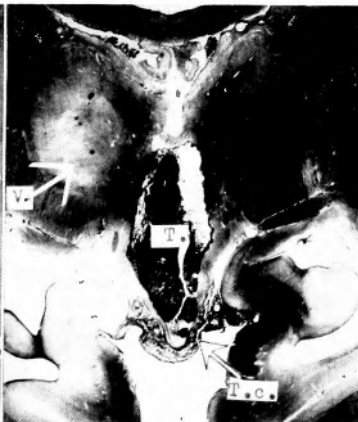
About the age of 10 years, the patient noticed for the first time lowering of the vision which increased its grade as time went on. She had her menarche at the age of 11 years and 11 months. About the age of 12 years and a month, she developed vomiting and then frontal headaches. On admission, her external appearance was similar to that in puberty (Fig. 40). At the operation, an encapsulated and a walnut-sized tumor was found to be located in the region of the optic chiasm. The tumor tissue seemed to have grown in the right optic fasciculus and also down through the right optic canal. Intracapsular removal of the tumor was performed. The histological feature of the tumor was suggestive of the spongioblastoma polare.

**Case 7.** Y. SHIKANO, a 13-year and 3-month-old male, was admitted on August 29, 1955.

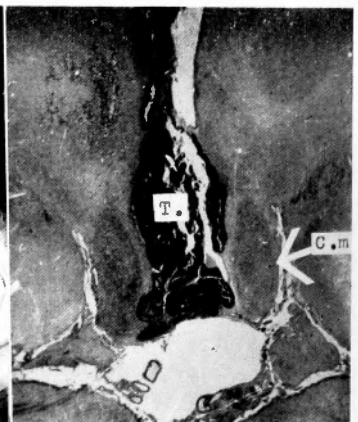
The patient noticed growing of the pubic hair about the age of 12 years and 6 months (Fig. 41). A week prior to the admission, he developed headaches and vomiting of sudden onset. His temperature rose to 38.4°C. and he became lethargic followed by generalized convulsion with unconsciousness. A ventricular drainage was performed immediately after the admission but he died of hyperthermia and respiratory paralysis on the next day of the operation. In the testicle, there was a moderate increase in number of the interstitial cells and spermatozoa were noted in some parts. The hypophysis was normal in size and there was no change in number of parenchyma cells of each type.



**Fig. 42.** Case 7. Frontal section of the diencephalon through the anterior portion of the hypothalamus. Myelin stain (EHRlich).  
I. Tumor mass in the anterior half of the third ventricle.  
Tr.op. Tractus opticus. (arrow). Vascular lesion in the area of the lateral group of the thalamic nuclei.



**Fig. 43.** Case 7. Frontal section of the diencephalon through the tuber cinereum. Myelin stain (EHRlich).  
T. Tumor mass in the anterior half of the third ventricle.  
T.c. Tuber cinereum.  
V. Vascular lesion.



**Fig. 44.** Case 7. Frontal section of the diencephalon through the mammillary body. Myelin stain (EHRlich).  
T. Tumor mass in the third ventricle.  
C.m. Corpus mammillare.

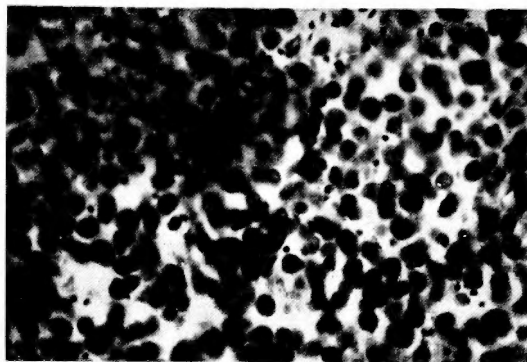
Autopsy findings of the brain :

1) Macroscopic findings (in serial sections)

A ventricular enlargement was noted in the anterior half of the third ventricle which was filled with a tumor mass below the *messa intermedia* (Figs. 42, 43 and 44). The posterior half was not dilated and the size of the pineal body was normal (Fig. 45).



**Fig. 45.** Case 7. Frontal section of the diencephalon through the pulvinar thalami. Myelin stain (EHRlich). (arrow) Pineal body.



**Fig. 46.** Case 7. Pinealoma. H. - E. stain.  $\times 400$ .

2) Microscopic findings (in serial sections)

i) The tumor

The tumor consisted of two kinds of cells mixed together irregularly without forming a mosaic pattern as seen in a usual pinealoma (Fig. 46). And there was no evidence of the existence of teratomatous components by the examination of the serial sections.

ii) The hypothalamus

The infiltration of tumor cells was marked all over the tuber cinereum, where normal tissue was replaced almost entirely by the neoplastic tissue (Fig. 47). Nerve cells in every nucleus of the hypothalamus showed a severe degeneration and a decrease in number or a disappearance due to the hemorrhage, the compression and the tumor cell infiltration. These changes were especially marked in the tuber cinereum.

iii) The thalamus

A diffuse gliosis was found in the thalamus. Also, at the posterior portion,



**Fig. 47.** Case 7. Tumor cell infiltration in the area of the tuber cinereum. Nissl stain.  $\times 200$ .  
T. Tumor mass in the third ventricle.  
t. Tumor cell infiltration in the tuber cinereum.

the left medial and posterior group of the thalamic nuclei and at the anterior portion, the right medial, lateral and midline group of the thalamic nuclei, respectively, showed a localized disappearance of nerve cells. It can not be ruled out that these changes might have been induced by the secondary circulatory disturbance. Nerve cells in the anterior and the ventral group of the thalamic nuclei, the epithalamus (nucleus habenulae) and the metathalamus (corpus geniculatum mediale et laterale) were essentially free of change.

### Group 3. Pineal tumors showing no precocious puberty

**Case 8.** T. MINAMI, a 9-year and 11-month-old male, was admitted on January 14, 1953 and died on February 7, 1953.

About the age of 9 years and 9 months, the patient developed headaches and vomiting. 10 days prior to the admission, he had a generalized convulsion accompanied by unconsciousness.

Autopsy findings of the brain:

#### 1) Macroscopic findings (in serial sections)

The dilatation of the posterior half of the third ventricle was conspicuous, in which the tumor mass was located. The anterior half of the third ventricle, showed a minimal dilation.

The pineal body, the posterior commissure and the corpora quadrigemina were destroyed.

#### 2) Microscopic findings (in serial sections)

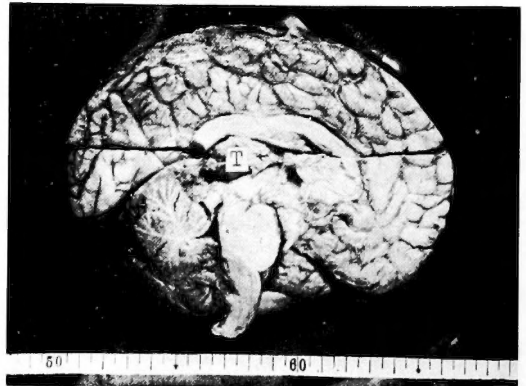
The infiltration of tumor cells was found in the ependymal layer of all ventricles. Also, in the regions of the medial group of the thalamic nuclei, of the epithalamus (nucleus habenulae) and of the medial part of the pulvinar thalami, the massive tumor cell infiltration was observed, which was more marked in the caudal parts of these structures (Figs. 48, 49, 50 and 51).

But in the region of tuber cinereum, tumor cell infiltration or definite change of nerve cells was not observed. The tumor consisted of large and small type of cells as seen in a usual pinealoma

and showed a typical mosaic pattern arrangement (Fig. 52) and had no teratomatous elements. The normal pineal tissue was not observed.

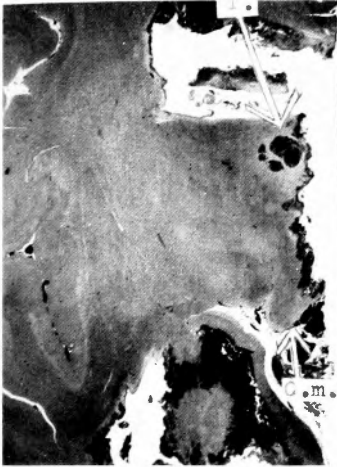
**Case 9.** M. KIMATA, a 9-year and 10-month-old female, was admitted on February 21, 1956.

About 3 months after the operation (total extra-capsular enucleation of a thumb-tip-sized pineal teratoma), she had a recurrence and became lethargic and died in the state of cachexia on April 7, 1956. The hypophysis was normal in size.



**Fig. 48.** Case 8. Mid-sagittal section of the brain.

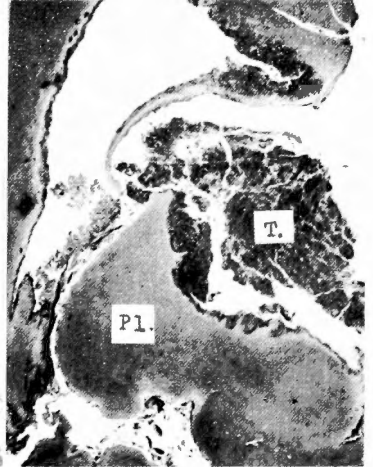
T. Tumor mass in the pineal region.



**Fig. 49.** Case 8. Right frontal section of the diencephalon through the mammillary body. H.-E. stain.  
T. Massive tumor cell infiltration in the area of the anterior part of the medial dorsal thalamic nucleus.  
C.m. Corpus mammillare.



**Fig. 50.** Case 8. Right frontal section of the diencephalon through the red nucleus. H.-E. stain.  
R. Red nucleus.  
T. Tumor in the third ventricle.  
N.h. Habenular nucleus which was infiltrated by the tumor cell.



**Fig. 51.** Case 8. Right frontal section of the diencephalon through the pulvinar thalami. H.-E. stain.  
T. Tumor mass in the posterior half of the third ventricle.  
Pl. Pulvinar thalami.

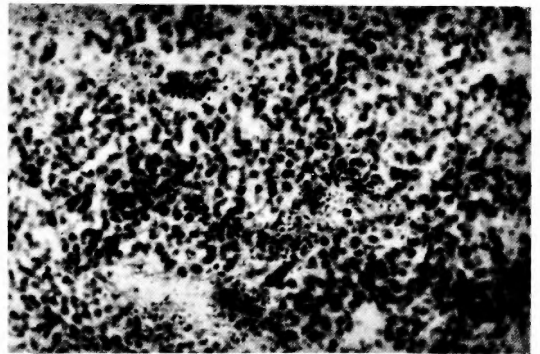
#### Autopsy findings of the brain :

##### 1) Macroscopic findings

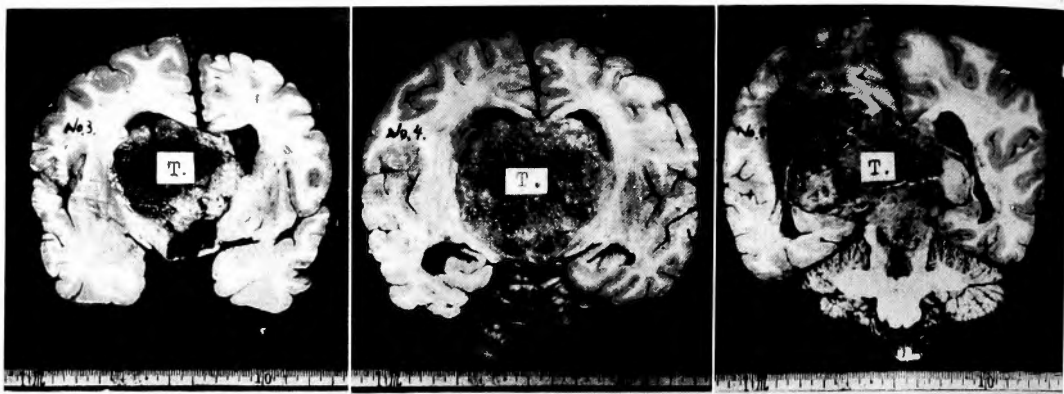
A large recurrent tumor mass was found in the third ventricle, infiltrating and destroying the surrounding tissue. Due to the compression of the tumor, the thalamus, the hypothalamus and the midbrain had become flat in configuration. Two or three small finger tip-sized cysts were observed on the cut surface of the tumor (Figs. 53-a, 53-b and 53-c). Metastatic foci were observed in the lateral ventricle, in the aqueductus mesencephali and in the subarachnoideal space.

##### 2) Microscopic findings of the tumor (in serial sections)

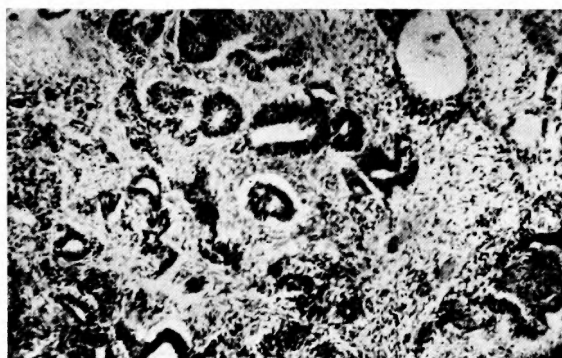
By the examination of the serial sections, the tumor tissue was found to have complex structures including cartilagenous tissue, tubular structure (Fig. 54) and other teratomatous elements. In addition, the characteristic features of the tumor tissue were as follows ; (1) Two kinds of cells as seen in a typical pinealoma made an irregular arrangement and the small cells were very scarce in number (Fig. 55). (2) A group of cells with strong cytological atypism were observed. In each cell, the vesicular nucleus with a thin nuclear membrane had a moderate amount of chromatin and a large and irregular shaped nucleolus. These cells formed mostly



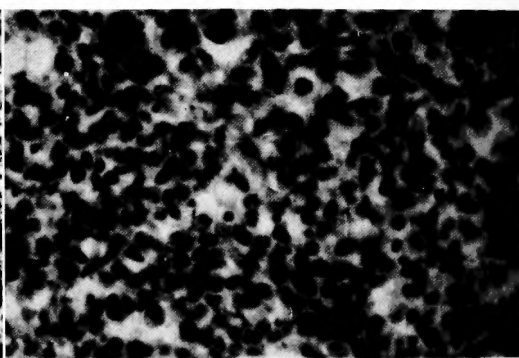
**Fig. 52.** Case 8. Pinealoma. H.-E. stain.  
× 200.



**Figs. 53-a, 53-b and 53-c.** Case 9. Frontal section through the hypothalamus, the red nucleus and the pulvinar thalami, respectively. T. Recurrent tumor mass.



**Fig. 54.** Case 9. Tubular structure. H.-E. stain.  $\times 200$ .



**Fig. 55.** Case 9. Pinealoma.  $\times 200$ .

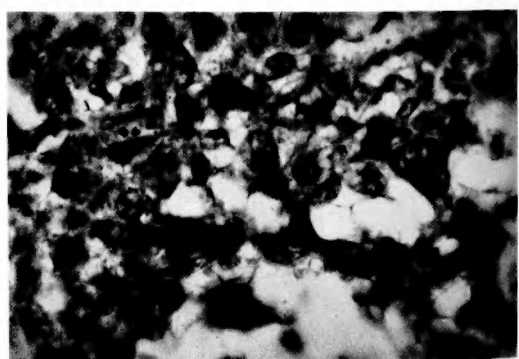
glandular and partly solid structures. This group of cells was diagnosed as the embryonal carcinoma (Fig. 56) but not the cytotrophoblastoma (DIXON and MOORE).

### III. Summary and Discussion

#### 1. Site of the lesion

##### 1) Hypothalamus

Among all the cases presented in this paper, cases 1 and 4 are those of teratomas with precocious puberty originating from the pineal region and from the hypophysis, respectively. Changes were found in both cases by the examination of the serial sections in the hypothalamus, or more specifically in the pars tuberalis hypothalami. The degenerative



**Fig. 56.** Case 9. Embryonal carcinoma. H.-E. stain.  $\times 900$ .



changes in the latter seemed to be due to the pressure by the secondary internal hydrocephalus in case 1 and the direct tumor cell infiltration in case 4, respectively. In case 7, the tumor seems to have originated from the hypothalamus and the histological change in the area of the tuber cinereum is exactly the same as that in case 4 (Figs. 37 and 47). Cases 2 and 3 are those of teratomas which originated from the pineal region, i. e. the same place as that in case 1. In case 2, the severest damage was found at the postero-ventral (mesencephalic) wall of the third ventricle resulting from the mechanical pressure by the tumor and less severe changes were seen in the hypothalamus. Although the serial sections were not made in case 3, the histological change in the hypothalamus in this case seems to be not much different if any from those in case 1, because not only the site of origin but also the nature and the location of the tumor and the clinical course are similar to each other. Since the tumors in cases 5 and 6 originated from the suprasellar region and the region of the optic chiasm, respectively, changes resulting from the direct pressure of the tumor from below may be in the hypothalamus, though both cases were not autopsied. In these kinds of tumors, the anterior hypothalamus usually suffers the greatest change but not infrequently the posterior hypothalamus is severely involved by the posterior extension of the tumor. Thus the exact location in the hypothalamus of the lesion in these cases (Cases 5 and 6) is uncertain. Among the control cases, in which the patients had tumors of the pineal origin not complicated by precocious puberty, the postero-ventral (mesencephalic) wall of the third ventricle in case 8 was severely changed but the hypothalamus was relatively free of damages from the mechanical compression and from the tumor cell infiltration, a fact which could not of course be considered to be characteristic of non precocious puberty cases. In this regard, the tumor (case 8) did not much differ from the tumors in the cases with precocious puberty, only the tumor in this case was highly malignant in view of presence of dissemination metastases. In case 9, there was a high grade of pathological change by a rapid enlargement of the recurrent tumor not only in the hypothalamus but also in all the surrounding tissue of the third ventricle. But in this case, it may be unsuitable to discuss a possible or impossible relationship between the changes in the hypothalamus and the manifestation of precocious puberty because of too large and extensive destructions in the whole diencephalon during a short period of time. Thus cases 8 and 9 are both not good for control study. It seems, however, not unlikely that the cases complicated by precocious puberty might have in common the changes in the hypothalamus, especially in the region of the tuber cinereum, wherever the original site of the tumor may be. If so, chronic injury of the hypothalamus might play some role in the manifestation of precocious puberty. Cases, in which precocious puberty considered to have occurred due to a tumor in the pineal region, have severe changes not only in the pineal region but also in the hypothalamus as claimed by BAILEY and BREMER (1921), BING, GLOBUS, and SIMON (1938) and others. And aside from the cases presented in this paper, many other cases, in which precocious puberty occurred with pathological changes of only the hypothalamus and without those of

the pineal body, have been reported by SCHMALZ (1925), HORRAX and BAILEY (1928) and others. WEINBERGER and GRANT (1941) claimed that the cause of precocious puberty was the injury of the posterior region of the hypothalamus and that the injury of the anterior region caused a reverse change i. e. an atrophy of the sexual organs.

BAUER (1954) pointed out a severe destruction of the anterior region of the hypothalamus (tubero-infundibular region) in many cases (the craniopharyngioma) complicated by an atrophy of the sexual organs when he statistically studied 60 cases of mainly the hypothalamic tumors. From these observations it seems possible that changes of the hypothalamus (especially in the tuber cinereum) in some particular condition play a role in the manifestation of precocious puberty. Moreover, the cases with precocious puberty which were associated with either only a small and localized change of the tuber cinereum (congenital hyperplastic malformation) or an inflammatory disease of the diencephalon or those which were associated with only a hydrocephalus, as reported by DRIGGS and SPATZ (1938), MEYER (1948), SECKEL (1949) and others, seem to give a reason for incriminating the "site of the lesion" to be the cause of precocious puberty and for regarding the hypothalamus to be important in this respect. With regard to the particular localization in the hypothalamus responsible for the manifestation of precocious puberty, there have been some animal experiments but the data presented vary, though no change is observed of the lateral hypothalamic area or of the nuclei in the mammillary body in either case 1 or case 4, inspite of the claim by BURSCHER (1938) that the latter is responsible for precocious puberty.

## 2) The thalamus

HANDA (1953) and KUROSAWA (1955) in our laboratory stated on the basis of their experiments in male chickens and female rats, respectively, that the destruction of the thalamic nuclei surrounding the upper part of the third ventricle such as the nucleus habenulae medialis, the anterior part of the nucleus medialis dorsalis and the nucleus internus superior caused a marked retardation of the somatosexual growth and that it seemed to occur due to the secondary dysfunction of the hypothalamus through the nervous connection from the afore-mentioned thalamic nuclei to the hypothalamus. No pathological change was observed of the anterior part of the nucleus medialis dorsalis or of the nucleus habenulae in case 1 or 7, respectively. The area around the anterior part of the nucleus medialis dorsalis in case 2 was only slightly compressed without deformity and free of tumor cell infiltration. The afore-mentioned nuclei are absolutely free of damage in case 4. In the control cases i. e. cases 8 and 9, these nuclei were severely changed by the heavy compression and the massive tumor cell infiltration. Namely, either of these nuclei shows no change in the cases complicated by precocious puberty while it shows severe damage in the control cases not complicated by precocious puberty. From these observations it seems that the possible relationship between the intactness of the particular thalamic nuclei and the occurrence of precocious puberty cannot be ignored.

## 3) The midbrain

Only in cases of the group 1, i. e. those of a tumor in the pineal region, the changes of the midbrain are seen in common and in severe degree. Nerve fibres entering the hypothalamus from the substantia grisea centralis mesencephali are known to pass through a part of the dorsal longitudinal lemniscus (SCHÜTZ) and through the crus mammillare etc. Nothing definite could be, however, said about the possible relationship between pathological change of the midbrain and precocious puberty.

## 2. Nature of the tumor

### 1) Nature of the tumor and precocious puberty

Among the cases complicated by definite precocious puberty (cases 1, 2 and 3 in the group 1 and cases 4 and 5 in the group 2), every case in the group 1 had a tumor which belonged to the teratoma, of the presumable origin in the pineal region. The tumors of cases 1, 2, 3 and 4 were all the teratoma containing a tissue of the pinealoma somewhere within the tumor. Moreover, the cyto-trophoblast type cells were observed in very small areas in the hemorrhagic tumor tissue in these cases, except in case 2, in which such cells were not found with certainty. Precocious puberty had been considered, hazily, to be associated with the pinealoma (GUTZEIT, 1896) until many workers demonstrated that the tumors in the pineal region associated with precocious puberty were almost all teratomas (KRABBE, 1923; BING, GLOBUS and SIMON, 1938; RUSSELL and SACKS 1943; KITAY, 1954). This observation suggests that there is another point of view in regard with the cause of precocious puberty differing from that of attaching importance to the "site of the lesion". In studying the teratomas in relation with precocious puberty, its microscopic feature seems to be more important than its macroscopic one. It is a well known fact that the chorionepithelioma secretes a large quantity of the chorionic gonadotropin and the secretion is generally thought to be due mainly to the activity of the cyto-trophoblast rather than that of the syncytial-trophoblast. Either the pure seminoma or the embryonal carcinoma is considered to contribute nothing to the secretion. The fact that the rate of positivity for the Friedman's test is high in cases of the seminoma or the embryonal carcinoma is explained by the possible hiding of the cytotrophoblastoma (DIXON and MOORE) or of the chorionepithelioma. ASKANAZY, long time ago (1906 and 1920), presented his "ontogene Theorie" in relation with precocious puberty paying attention to the secretory activity owed by the immature tissue of the teratomas. After that, cases of the teratomas in the pineal region having the chorionepithelioma tissue were reported by WIRTH (1929), Fasold (1931), D. S. RUSSELL (1944), W. O. RUSSELL (1944), DAVIDOFF (1944), N. B. FRIEDMANN (1947), H. ZONDEK (1953) and others. The patients reported by these authors were all males before puberty and were complicated by precocious puberty. LAIPPLY (1945) reported a 13-year-old boy who developed the chorionepithelioma originating from the mediastinum and whose testicle showed a marked increase in number of the interstitial cells. YOSHIKAWA, in our laboratory, observed a marked increase in number of the interstitial cells of the testicle of rats and early development of their secondary sexual characteristics following the injection to them of the luteinizing hormone

and of the mused chorionepithelioma substance. Thus, it is likely that the manifestation of precocious puberty, at least, in these teratomatous tumors in the pineal region is due largely to the secretion of the gonadotropin from the immature tumor cells, i. e. the cyto-trophoblast which hide in the teratomatous tissue.

## 2) Precocious puberty and the sex

The fact that there has yet been no report of pineal tumor with precocious puberty in female seems to be explained from nature of the tumor. In cases 1, 3, 4 and 7, except for case 2 in which the pinealoma contained in the teratoma showed a typical mosaic pattern, the pinealomas in the teratomas showed an irregular arrangement of two kinds of cells and belonged mostly to the pinealoma of ordinary two cell type (RINGERTZ et al.), though in some areas, the seminoma-like structure was seen with a small number of the small cells. Since the pinealomas of this kind are seen more often in males than in females according to RINGERTZ et al., it would not be unreasonable to assume that the pinealomas of this kind included in the teratomatous tissue are seen much more often in males than in females. (There is, however, no sexual difference both in the undifferentiated pinealoma and in the pinealoma of adult type without small cells). Thus the difference of the incidence of precocious puberty between both sexes might be explained on the basis of nature of the tumor.

## 3. The clinical course

In cases 1 and 3, in which the tumor is considered to have originated from the pineal region, the patients developed hypothalamic symptoms such as diabetes insipidus, adiposity etc. simultaneously with the manifestation of precocious puberty and much more earlier than the manifestation of serious symptoms due to increased intracranial pressure. Precocious puberty is assumed to be the first clinical manifestation in case 2 which took a rapid clinical course. It took rather long extent of time, namely 12 and 9 months in cases 4 and 7, respectively, in both of which, the tumor is considered to have originated from the hypothalamus, from the time of the manifestation of hypothalamic symptoms and of precocious puberty to that of the death of the patients. It is needless to mention about the protracted course in cases 5 and 6 in which the patients are still living. From these observations, a relationship between the pathological changes of the diencephalon and the development of precocious puberty will be contemplated as follows; In cases of the group 1, the changes of the hypothalamus in early stage of gradually increasing hydrocephalus and in cases of the group 2, the early changes of the hypothalamus about the time when there was still only a minor grade of the tumor cell infiltration or of mechanical compression, might be more important than the changes at the later period when there was a complete destruction. Thus, an irritation might be more important than a destruction in the manifestation of precocious puberty. Also, concerning the nature of the tumor, a question would be raised as to the fact that the chorionepithelioma, which usually grows very rapidly, takes a rather long course in cases under discussion. From the fact that marked terminal increase of the urinary chorionic gonadotropin in case 4 did not go with increase of the interstitial

cells of the testicle and of the 17 K.S. value, it can be assumed that the changes seen in the penis, the pubic hair and the prostate might be remnants of precocious puberty which had developed early in the course of the disease. Also, in the same case, it is assumed that the function of anterior lobe of the hypophysis was preserved until late in the course of the disease because diabetes insipidus persisted for a long time. Consequently, it would be possible that precocious puberty in case 4 might be related in some way to the intactness of the anterior hypophysis. On the other hand, there can be many possibilities of the course or of the final outcome of the chorionepithelioma, for instance unusually long course, spontaneous healing etc. (PRYM 1927), so that the existence or non-existence of this tumor could not be argued on the basis of the long or short duration of the disease.

#### IV. Conclusion

1) The region which was damaged frequently and more or less severely in the cases with precocious puberty seemed to be the hypothalamus, especially the tuber cinereum.

It might be considered, therefore, that the tuber cinereum would be damaged very slowly (supposedly irritated) by the tumor cell infiltration or as a result of the hydrocephalus in cases of precocious puberty.

2) The relative intactness of the anterior part of the medial dorsal thalamic nucleus or the habenular nucleus might have something to do with the production of precocious puberty.

3) In three cases with tumors arising from the pineal region and in a case of tumor in the pituitary region, which were all associated with precocious puberty, the tumors proved to be the teratomas mixed with tissues of the pinealoma. It might be possible that precocious puberty occurs by the secretion of the gonadotropin by the dormant cytrophoblastoma hiding in these teratomatous tumors.

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\* Written in Japanese.

## 和文抄録

### 間脳部腫瘍と Precocious Puberty

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Precocious puberty を合併した7例の間脳部腫瘍症例に就て、視床、視床下部及び腫瘍の、主として、連続標本による病理組織学的検索を行い、次の結論を得た。

1) Precocious puberty を合併した症例で、視床下部、特に灰白隆起部、の腫瘍細胞浸潤或いは脳水腫による圧迫萎縮を認めたが、この部分の極めて緩慢なる損傷 (恐らく刺戟状態) が、Precocious puberty の発現に関係があるかも知れない。

2) 特定の視床核、即ち前背内側核或いは手綱核、

の非損傷状態と Precocious puberty との関係をも、無視する事は出来ないようである。

3) Precocious puberty を合併した3例の松果体部腫瘍及び1例の下垂体部腫瘍は、いずれも Pinealoma の組織像の部分を含む奇形腫であった。かかる奇形腫中に潜在する未熟な腫瘍組織 (Cytotrophoblastoma) の Chorionic gonadotropin 分泌能が、Precocious puberty に関係する可能性も充分考えられる。