PRECOCIOUS PUBERTY OF INTRACRANIAL ORIGIN

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Precocious puberty of intracranial origin has been the subject of exhaustive inquiry and numerous theories as to its causative mechanism have been advanced. The pineal region has been most frequently indicted in consideration of the production of this syndrome. Interest in this subject in the present instance was stimulated by a case of undoubted somatic and sexual precocity in which the lesion surgically exposed was an ectopic pineal tumor of the chiasmal region. The pertinent literature on ectopic pineal tumors and also that concerning precocity of intracranial origin has, therefore, been reviewed.

ECTOPIC PINEAL TUMORS

Ectopic pineal tumors have been reported on rare occasions, the most complete review being that of Dorothy Russell in her treatise on the origin of pineal tumors. This writer advanced the theory that the vast majority of pineal tumors are really atypical teratomata. As evidence in support of this thesis, she called attention to the mixed character of the tissues in certain of these tumors, the recognition of "pinealoma" areas in manifest typical and atypical teratomata of the pineal, and their close resemblance to the spheroidal-cell carcinoma of the testis which is generally regarded as an atypical teratoma. She stressed the fact that ectopic pineal tumors, which occupy midline structures, can be more satisfactorily explained if they are considered teratomata.

A review of the literature reveals that 12 cases of ectopic pineal tumors have previously been reported. These cases are tabulated in Table 1. In addition to the tumor listed, Horrax also reported 2 other "pineal tumors" in the chiasmal region. However, it is perhaps best not to consider them as truly ectopic tumors as in one instance a pineal tumor had previously been removed from the usual location and in the other there was direct extension to the chiasm from a pineal tumor. The case reported by the present authors seems almost identical in location to the truly ectopic tumor reported by Horrax.

Globus and Silbert, after a thorough study of the development of the pineal body and of 7 pineal tumors, postulated that these tumors represent autochthonous teratomata. As previously mentioned, Russell considered the lesions to be teratomata. In this connection, it is of interest that the tumor in the case of Horrax was originally thought to be a metastasis from a malignant testicular neoplasm. Ford and Muncie in their original report did not give any definite hypothesis as to the etiology of the tumors, but Ford now believes that they were ectopic pineal tumors. Mackay felt that this
type of tumor developed from anlagen that can produce either ependyma or pineal tissue. Akamatu¹ assumed that the tumor reported by him arose from medullary epithelium germ which differentiated in the direction of the pineal pro-parenchyma and in some way became lost in the infundibular region before the second fetal month.

No case of ectopic pineal tumor previously described has shown any evidence of precocious puberty. The symptoms in each instance were caused by infiltration or compression of neighboring structures by the tumor.

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<tr>
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TABLE 1—continued

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**PREOCIOUS PUBERTY**

Precocious puberty occurring in association with intracranial lesions has been the subject of intensive study since the latter part of the nineteenth century. Attention at first was directed almost exclusively to the pineal body but recently the hypothalamus has been more critically examined. As the tumor here reported is of pineal structure, although of ectopic location, it is pertinent to consider the present status of the pineal body.

The oldest theory concerning the causation of precocious puberty of intracranial origin begins with the premise that the pineal is a gland of internal secretion. Gutzzeit and Ogle first noted the occurrence of precocity with pineal tumors and Frankl-Hochwart emphasized this connection. Marburg in 1908 concluded that the pineal is a gland of internal secretion which inhibits sexual maturation in early life and undergoes involution at time of puberty. This theory stimulated an immense amount of experimental work and even more critical reasoning which produced no incontrovertible facts. Indeed, Krabbe in 1923 stated as follows: "We must point out that the hypothesis that the secretion (of the pineal gland) plays a role in the development of puberty is to date completely without significant evidence. . . . One has very often the impression that the authors' desire to consider the organ incretory in function is greater than their critical judgment regarding their published researches." That the following 18 years produced no further enlightenment is shown by the statement of Martin and Davis in 1941 that "overenthusiasm to disclaim or substantiate a physiologic function for the pineal gland, on the one hand, has been balanced by the attitude of neglect, confusion or evasion, on the other, the net result being a voluminous,
rambling, bewildering and unconvincing literature.” There has been no subsequent work that has definitely clarified this problem. The continued observations of Berblinger, however, are of interest, as this worker has long been interested in the pineal. In 1944 he stated that the pineal is not a true gland and formation of a pineal hormone has never yet been proven. He considered the pineal cells to be nerve cells and preliminary stages of such cells with signs of secretory function and, therefore, classed the cerebral epiphysis as an endocrine organ in a wider sense. It suffices to state that the status of the pineal as a gland of internal secretion remains shrouded in doubt. Therefore, any theory concerning the etiology of precocious puberty that considers hypopinealism or hyperpinealism a factor must remain unproven for the present.

A second old and much debated theory as to the causation of precocious puberty states that it is the type of tumor, rather than the structure from which it arises, that is of paramount importance. This theory was first pronounced by Askanazy, who postulated that premature somatic and sexual development is a function of the embryonal tumor tissue, but this conception was later rejected by him. Krabbe later concluded that pineal tumors that are associated with precocious puberty are teratomata producing gonadotropic hormones. Dandy also considered the type of the tumor, i.e. teratoma, to be the important factor in precocity. Berblinger collected 129 cases of pineal tumor from the literature and separated the teratomata from the remaining types of tumor. In 60 per cent of the cases of teratoma there was evidence of precocity whereas only 12½ per cent of the remaining neoplasms were associated with this syndrome. Berblinger, however, rejected the conception of functioning tumor tissue and contended rather that the increased incidence of precocity with teratomata was due to the earlier age at which this tumor manifested itself. As it is known that some teratomata can produce hormones, the work of Russell indicating that most pineal tumors should be considered teratomata gave some added credence to the theory of precocity being caused by pineal tumor. However, the theory remains without proof. It is noteworthy that in only 1 of 13 cases of ectopic pineal tumors has there been evidence of precocious puberty.

Interest in the type of tumors causing precocious puberty, apart from the possibility of their being teratomata, was stimulated by a case reported by Driggs and Spatz in 1939. These authors cited a 2½ year old male child who exhibited marked sexual and somatic precocity and in whom a tumor of the tuber cinereum was found. The individual nuclei of the tuber were intact and the tumor consisted of mature elements similar to the cells of the normal tuber region. It was postulated that the tumor cells actively produced a secretion that was responsible for the precocious puberty. The case of a 22 month old female with marked sexual precocity who showed an almost identical pathological picture was reported by Bronstein, Luhan and Mavrelis in 1942. Cases showing an essentially similar pathology were previously reported by Gross and Le Marquand and Russell. The importance of the
tuber cinereum in the control of genital function is undoubted and will be mentioned later. The theory of hyperfunction of the tuber cinereum or of tumor cells simulating its function cannot be dismissed lightly.

Recent attention to the causation of precocious puberty of intracranial origin has been directed to the location of the pathological process, rather than to its histological appearance. The hypothalamus has been the region indicted and Weinberger and Grant\(^5\) have contended that the syndrome under discussion is a purely hypothalamic or hypothalamic-hypophysial syndrome. These writers concluded that tumors of the posterior hypothalamus destroy some portion of the mechanism that normally serves to control the impulses passing to the pars distalis of the pituitary. This permits the uncontrolled pars distalis to liberate excessive amounts of gonadotropic substances which stimulate the ovaries or testicles into hyperactivity. This gonadal excitation then causes the development of the secondary sexual characteristics. The reader is referred to the excellent article of Weinberger and Grant\(^5\) for a complete presentation of this theory which had previously been advanced in modified form by Berblinger.\(^6\) These authors analyzed 16 cases appearing in the literature of precocious puberty occurring in association with hypothalamic tumors and added 1 of their own. Since the appearance of this article in 1941, 7 similar cases have been added to the literature in addition to the case here reported. These cases are analyzed in Table 2.

The relationship of the hypothalamus to gonadal function has been extensively studied and some conclusions reached. Aschner\(^2\) was the first worker to recognize the importance of the tuber cinereum. Camus and Roussy,\(^1\) and later Bailey and Bremer,\(^4\) produced genital atrophy in dogs by making small lesions in the region of the tuber cinereum. The same results were obtained in rabbits by Bustamante.\(^12\) More recently, Dey\(^18\) abolished the estrous cycles in female guinea pigs by means of destruction of the median eminence alone and concluded that this structure plays an important role in control of the gonadotropic functions of the anterior pituitary. There is thus a mounting body of evidence that the tuber cinereum represents, to some extent at least, a sexual center. The method of operation of this center is a controversial subject. Weisschedel and Spatz\(^5\) contended that gonadotropic substances are formed in the tuber cinereum and produced some supporting experimental evidence but this evidence has been disputed by Richter and Schiler.\(^42\)

The posterior hypothalamic structures and particularly the mammillary bodies have been considered to be of prime importance in precocious puberty by Weinberger and Grant.\(^5\) They reached this conclusion from a study of clinical material and a review of indirect experimental evidence. However, Dey\(^19\) did not abolish the estrous cycle in guinea pigs by lesions in the mammillary bodies and Bustamante\(^12\) likewise noted no genital changes after similar discrete lesions.

An important experiment by Dey\(^19\) indicates the importance of the anterior hypothalamus in the control of genital function. This worker noted
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<th>Evidence of Hypothalamic Involvement</th>
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<tr>
<td>de Lange 1943</td>
<td>Male 10 yrs.</td>
<td>Headache &amp; loss of vision. Marked genital hypertrophy. Tumor removed from sella 2 yrs. before death.</td>
<td>Astrocytoma of chiasmal region extended back to mammillary bodies which were normal.</td>
<td>Normal.</td>
<td>Adrenals and testes normal. No trace of hypophysis found.</td>
<td>Marked emotional disturbances occurring in attacks.</td>
</tr>
<tr>
<td>Herlant, Dubois and Ectors 1945</td>
<td>Male 10 yrs.</td>
<td>Genital hypertrophy. Large body.</td>
<td>Astrocytoma of chiasmal region extending into sella and anterior 3rd ventricle. Extended to mammillary bodies which were compressed.</td>
<td>Normal.</td>
<td>Hypophysis almost completely destroyed. Adrenals normal. Interstitial cells of testicle showed withered appearance. Prostate inactive.</td>
<td>Attacks of unconsciousness followed by somnolence or delirium.</td>
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marked follicular development in the ovaries and extensive hypertrophy of
the external genitalia of guinea pigs following the placing of lesions in the
anterior hypothalamus at the caudal end of the optic chiasm. He suggested
that such a lesion interfered with the liberation of the luteinizing hormone
and this hormonal imbalance produced the changes noted. The significance
of this work is indicated by the fact that 4 of the tumors collected by Wein-
berger and Grant involved mainly the anterior hypothalamus and 3 of the
cases analyzed in Table 2 affected this region.

If, as seems certain, the hypothalamus is intimately concerned with
genital development, the modus operandi of this connection has not been
definitely established. Bustamante concluded that there are nervous con-
nections between the hypothalamus and the genital organs, but this con-
clusion lacks clinical or experimental proof. Certainly such nerves would
have to leave the central nervous system very high as there is no clinical or
experimental evidence of genital change following even high spinal cord
transection. The vast majority of workers in this field have contended that
the hypothalamic influence is mediated by way of the hypophysis. The evi-
dence for this conception has been collected by Brooks and Weinberger and
Grant. The method by which the hypothalamus exerts this influence on the
pituitary is still open to question. The innervation of the anterior lobe of the
hypophysis in the rabbit and rat was studied by Brooks and Gersh, who
found many fibers entering from the neurohypophysis and ending around
gland cells. More recently, Truscott has studied the albino rat and found
nerve fibers of the anterior lobe derived from the infundibular tract, the
hypophysial fasciculi and the small nerves accompanying the blood vessels.
It seems certain that there is a direct innervation of the anterior lobe of the
hypophysis by fibers from the hypothalamus but the importance of such
fibers in the control of the secretion of hormones is still open to conjecture.
Experimental studies have given contradictory results. The recent work of
Markee, Sawyer and Hollinshead on activation of the anterior lobe by
electrical stimulation indicates that the hypothalamic control is probably
hormonal in nature. This concept of hormonal control also agrees with the
history of the patient of Dandy who had regular menses and bore children
after section of the hypophysial stalk. The pathway for transmission of this
hypothetical hormone is also unknown. Green and Harris have thoroughly
studied the portal circulation of the hypophysis and concluded that the
available anatomical evidence suggests that there is a humoral transmis-
sion of stimuli from the median eminence through the portal system of vessels to
the pars distalis of the hypophysis. The case of Dandy in which the infun-
dibular stalk was sectioned would indicate that the transmission must be
more indirect.

Actual hormonal secretion by the hypothalamus has not been definitely
proven but it is probable that it does occur. Scharrer and Scharrer have
suggested that the nuclei supraopticus and paraventricularis have glandular
function and cited the following as evidence: (1) The extraordinary appear-
ance of the nuclei in the cells, (2) the rich and specialized vascularization of the region, and (3) the histological pictures from which it is possible to reconstruct the processes of elaboration and discharge of substances other than normal metabolic products. Berblinger has also advanced this conception and reviewed the pertinent literature. The final proof of isolation of an active hypothalamic hormone, however, has not yet been attained.

Anatomical evidence of hyperfunction of the pars distalis of the hypophysis in cases of precocious puberty is also lacking. In the vast majority of cases the hypophysis has been reported as normal. Bronstein, Luhan and Mavrelis noted a possible acidophilic hyperplasia in the case reported by them as a differential cell count revealed 60 per cent acidophiles, 30 per cent basophiles and 10 per cent chromophobes. However, Severinghaus found variations of 23 to 60 per cent acidophiles and 4 to 27 per cent basophiles in normal pituitary glands. Studies in endocrinology have indirectly indicated hyperfunction of the pituitary. In the cases of precocious puberty reported by Gross and Weinberger and Grant, there were large quantities of estrogens and androgens, respectively, in the urine. McKenna, Bronstein and Kiefer have studied a 3 year old male exhibiting precocious puberty in whom sperms were motile and urinary assay revealed excessive gonadotropins. All studies for tumor were negative but it was suggested that there might be hypothalamic involvement. Bronstein had previously reported a 9 year old male with marked sexual precocity in whom there was a marked increase in urinary prolact and androgen, again without evidence of any type of tumor. In the case of undoubted sexual precocity noted by Bronstein, Luhan and Mavrelis, however, the assays for gonadotropins and estrogens were negative. Many other cases of precocious puberty, sometimes even familial in occurrence, have been reported without evidence of hypothalamic involvement or existence of neoplasm anywhere, but the majority of these cases have not been completely studied. These cases may represent examples of the "constitutional precocity of Neurath" although de Lange doubts the existence of true precocity without a definite lesion. Direct evidence of the effect of pituitary hormones is obtained from the observations of Thompson and Heckel who noted definite precocious puberty in young males undergoing treatment for undescended testicles with anterior-pituitary-like substances. However, the experiments of Bustamante indicate that a functioning tuber cinereum is essential for genital development as the administration of pituitary gonadotropic hormone did not protect the experimental animal from the genital atrophy resulting from lesions in the tuber. Weinberger and Grant, and later Papez and Ecker, postulated that an intact hypophysis is essential to the development of precocious puberty but it seems evident that an intact tuber cinereum or tissue functioning like tuber tissue is equally essential.

CASE REPORT

M.B., a boy 14 years of age, was admitted to the Neurosurgical Service of the Medical College of Virginia on July 10, 1946 with the complaints of headache, nausea and vomiting, and loss of vision.
Family History. Father and mother and 7 siblings were entirely normal. Twin brother of patient suffered a cranial injury in infancy and developed mild hydrocephalus. He has shown slight mental retardation but no evidence of precocious puberty.

Past History. Birth reported by mother as being entirely normal and not difficult. Early development normal in every way. Measles and mumps with no sequelae.

Present Illness. At about 9 years of age the patient's mother observed that he seemed stronger than his elder brothers and frequently beat them in fights. This growth continued and his parents noted his thick-set stature. Enlargement of external genitalia and excessive pubic hair were first noted at 10 years of age. At 11 years of age genitalia had developed to the point noted at time of admission.

Eight months before admission, the patient complained of progressive loss of vision, first noted in the left eye. Left frontal headaches began at the same time and gradually became very intense.

For 3 weeks before admission there had been numerous bouts of vomiting and attacks of dizziness.

Physical Examination. Patient showed marked muscular development and thick-set stature. Height, 145 cm. Weight, 42 1/2 kgm. (Fig. 1). There was considerable hair over the entire body and it was most prominent in the pubic region. External genitalia showed com-

![Patient at time of admission. Somatic and sexual growth had been attained at least 2 years previously.](image-url)
complete adult development. Patient persistently refused prostatic examination. Voice was rather deep.

Neurological Examination. There were no sensory changes. Tendon reflexes were hypactive but equal on the two sides. Cranial nerves were intact except for the eyes. Examination of the fundi revealed pallor of the optic discs, most marked on the left side. Vision was OD 20/200, OS 6/400. Patient fixed with the right eye and showed about 20° divergent strabismus in all meridians. Visual fields showed a bitemporal hemianopsia with some constriction of the nasal field of the right eye and marked constriction of the left eye.

Mental status was apparently normal. Patient was intelligent and cooperative. Average daily fluid intake was 1800 cc. and urine output 1500 cc. Temperature was 98°-99°.

Special Examinations. Basal metabolic rate was −35. Glucose tolerance test: fasting—80; ½ hr.—148; 1 hr.—190; 2 hrs.—170; 3 hrs.—138; 4 hrs.—74; 5 hrs.—50. Insulin tolerance test: fasting—73; 2nd specimen—65; 3rd specimen—75; 4th specimen—70. Cholesterol was 220. Calcium was 10. Wassermann was negative. Blood pressure was 110/70. X-ray of the skull revealed slight convolutional atrophy. Sella turcica was 19 mm. in length and 16 mm. in height, with marked thinning of the floor and posterior clinoids (Fig. 2). Intravenous pyelography revealed satisfactory function in both urinary tracts with no evidence of tumor. X-ray of the chest was entirely normal. Examination of the long bones suggested overdevelopment of bone growth with a bone age of at least 18 years.

Operation was postponed early because of a severe upper respiratory infection. On July 24, 1946 ventriculography revealed a defect in the anterior floor of the 3rd ventricle (Figs. 3 and 4). The pineal region was well filled and normal. Right frontal craniotomy was performed immediately under avertin anesthesia supplemented by endotracheal ether. When the chiasmal
region was exposed, a greyish-brown tumor was seen to obliterate most of the normal structures. This tumor either arose in the sella turcica or extended into this structure. The chiasm could not be visualized until a large amount of the very tough tumor had been removed. The right optic nerve was freed of tumor and a large mass was also removed from the sella turcica. Some tumor tissue completely surrounded the left anterior cerebral and the anterior communicating artery and could not be removed. There was no evidence of any invasion of cerebral tissue.

Microscopic Study. "Sections of the tumor disclose a mixture of three types of cells in rather bizarre irregular pattern. The three types are: (1) cuboidal cells with abundant clear cytoplasm and a reticular nucleus, round or oval in shape, which occur in small solid groups, (2) small cells like lymphocytes with relatively pale-staining nuclei, scattered in irregular groups, and (3) tissue appearing like glial tissue. The pattern is rather irregular. Diagnosis: Pinealoma" (Figs. 5 and 6).

Postoperative Course. There was a partial right 3rd nerve paralysis. Convalescence was otherwise uneventful. The patient was given 2000 r. hours of roentgen therapy from Aug. 8 to Aug. 16, 1946 and was discharged on Aug. 17, 1946. Vision had improved markedly while in the hospital.

Follow-up Studies. A 2nd course of roentgen therapy was given in November, 1946. Patient was readmitted on Feb. 5, 1947 for further therapy. Since discharge he had continued to drink large quantities of water. Otherwise he was living a normal life. Vision was OD 20/70 and OS 8/200. There was a continuing paresis of the right 3rd nerve. Basal metabolic rate was 0. Glucose tolerance test showed a fasting sugar of 96 and after 30 minutes the value was 152. Fluid intake ranged from 1620 to 3300 cc. and output varied from 1300 to 4030 cc. Patient was discharged on Feb. 18, 1947. He has received regular courses of roentgen therapy as an outpatient. He was last seen on Feb. 4, 1948. General condition has remained excellent and he now raises chickens on his parents' farm. Unfortunately, endocrinologic studies could not be obtained at any time.
FIG. 5. Low power magnification of tumor illustrating typical pineal structure.

FIG. 6. High power magnification of tumor (same section as in Fig. 5).
SUMMARY AND CONCLUSIONS

The case here reported brings to 13 the number of reported instances of ectopic pineal tumors. The occurrence of such tumors is more readily understood if the premise of Russell that "pinealomas" are usually teratomas is accepted, but such a premise cannot yet be completely accepted. In no other case of ectopic pineal tumor has sexual or somatic precocity been noted. The hypothesis that the precocity in this case was caused by actively secreting tumor tissue is an attractive one but is not thought to be correct. It is postulated that the precocity was the result of hypothalamic involvement, either stimulating or destructive by pressure.

The exact functional status of the pineal body remains unknown and there are no incontrovertible facts concerning this region. Almost every statement regarding the function of the pineal has produced valid objections. Its very structure has produced heated controversy. In the case here reported it seems most probable that the pineal region was not in any way involved.

There is a mounting body of evidence indicating the importance of the hypothalamus in the regulation of endocrine function. It is possible that this regulation is effected by means of the hypophysis and thus this "master gland" is relegated from its eminence as a controller to the subordinate position of an effector. It is more probable that the hypothalamus exerts its influence in other ways in addition to its hypophysial influence.

The tuber cinereum has steadily grown in stature as a center for regulation of sexual function. Much of this regulatory function may be mediated by means of the hypophysis but direct nervous or hormonal influence on the gonads probably occurs. It has become increasingly evident from a review of experimental work that a functioning tuber is necessary for normal genital development. This premise has been most strikingly supported by Bustamante who could not, by means of pituitary gonadotropic extract, protect animals from the genital atrophy resulting from discrete lesions in the tuber cinereum. In the presence of an intact tuber, however, the administration of such an extract will produce precocity in some instances. This conception of an essential role for the tuber cinereum may explain the occasional failure of substitution therapy following removal of pituitary tumors as the tuber region undoubtedly is injured in many surgical procedures in the hypophysial regions.

In reported cases of precocious puberty, the tuber cinereum has undoubtedly been involved by tumor but it is possible that this region was stimulated to hyperfunction before it was destroyed. It is also worthy of note that some of these tumors strongly resemble normal tuber tissue and may produce precocity by the equivalent of an overactive tuber cinereum. This possibility was emphasized by Schachter, who stated that "a hyperplastic neoformation, or even any agent capable of exaggerating the function of the tuber, would bring about the syndrome of macrogenitosomia praecox." The probability of hypothalamic neurosecretion is being explored more thoroughly. It is postulated here that the tuber cinereum does not actually secrete gonadotropic hormones but that it does exert an essential sensitizing or activating
influence upon the gonads and pituitary, by either nervous or, more probably, hormonal contact.

Ablation experiments apparently do not hold the key to the unfolding of the problem of precocious puberty of intracranial origin as in no recorded instance has a destructive lesion produced this syndrome. The closest resemblance to such precocity was noted following the destructive lesions of the anterior hypothalamus produced by Dey.18

Future endocrinological studies will undoubtedly yield more evidence as to the causation of precocious puberty. For the present it seems essential to regard this interesting syndrome as being produced by a multiglandular dysfunction. The cause of such dysfunction often appears to be in the tuber cinereum. A stimulation of hypothalamic function seems to be more logical than a destruction of inhibiting influences.

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