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HYPERPLASIA OF THE PINEAL BODY¹

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Few lesions of the pineal body have been observed. Symptoms attributable to abnormalities of the pineal body have been observed only with an increase in its size and in most instances have been due to regional pressure, though in a few instances associated metabolic manifestations have been attributed to this organ.

In man the pineal body, or epiphysis, appears as a single evagination from the hinder part of the roof of the diencephalon. This outgrowth Marburg (1) claims soon branches as a compound gland and becomes invested with a capsule contributed by the choroid plexus; from the choroid plexus penetrating blood vessels carry in connective tissue septa. The pineal body develops rapidly and reaches its greatest growth at the fifth or sixth year. Beginning at about the seventh year, and ending at about the fourteenth year there occur certain well-recognized changes spoken of as involution of the pineal body. After involution is fully established no further changes in its development have been observed.

The adult pineal body possesses a connective-tissue capsule from which septa pass into the substance of the body; these septa branch and join other septa thereby dividing the pineal into multilocular compartments containing the cells of the pineal. This uniform arrangement of islands of pineal cells almost surrounded by septa is the more usual type of pineal; nevertheless it is not exceptional to

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find the stroma broken up into small strands of connective tissue distributed among the cells of the pineal separating individual cells and small groups of cells. In fact the two varieties may be observed in the same pineal.

Krabbe (2) was able to divide the normal pineal into four types in accordance with the arrangement of the connective tissue. To the first group belong those with rather regularly formed islands of cells and rather sparse septa. To the second group belong those in which the septa are enormous in extent being equal to one half the cells of the pineal. To the third group belong those in which the cells of the pineal and the supporting tissue are so confused in arrangement that the picture is quite chaotic. To the fourth group belong those in which the septa are extremely vascular. Each epiphysis may, however, show in different places different conditions and in some places may present the appearance of a transition.

In the pineal body there is a preponderance of fairly large cells; these cells usually have a large oval nucleus, with but little chromatin which is arranged chiefly at the periphery and often contains a nucleolus. There is little cytoplasm. Not infrequently there is found a cell with a divided nucleus. In addition to this type of cell, there is a smaller cell which has all of the characteristics of neuroglial cells. It has a round or oval deeply staining nucleus. The protoplasm is scant and in many instances undistinguishable on account of the intimate relationship to the neuroglial fibers. There are many cells of an intermediate character which prevent a sharp differentiation between the two types of cells described.

Concerning the character of the cells of the pineal body there are different opinions. Krabbe after studying a hundred examples of human pineal of both sexes, of all ages except between the seventh and fourteenth years on account of lack of material, concludes that there are two types of cells; the first, special pineal cells and the second, neuroglial cells. Krabbe believes the cells of the pineal consist of non-neuroglial cells and a small number of neuroglial cells which give off a very large number of fibers which intersect other cells. Jordan (3) as the result of his work upon the sheep believes the entire body, exclusive of the vascular pial trabeculæ and a few white nerve fibers, is composed of more highly differentiated, or neuroglial cells with fibers, and less highly differentiated, or interneuroglial cells of the original ependyma of the third ventricles. He described the neuroglial cells as providing a network of neuroglial fibers in the meshes of which are found the interneuroglial cells. These interneuroglial cells show some variation in size and shape and

sometimes give rise to short neuroglial processes. He concludes that they are all one type of cell.

By involution is designated the changes occurring between the seventh and fourteenth years which are characterized by proliferation of connective tissue, the formation of neuroglial plaques which may at times contain cysts, and the appearance of concretions. The capsule thickens and the septa become widened and relatively conspicuous, particularly where several septa come together. Just how much this change alters the general architecture of the pineal will depend largely upon the primary relationship of the connective tissue to the cells of the pineal. The cells of the pineal lie free in islands between the septa, though Krabbe has emphasized the observation that a few cells may sometimes be caught in the thickening septa and thereby come to lie within them. There occurs a deposition of neuroglia about the blood vessels, so that small masses or plaques are formed. While the formation of plaques is acknowledged as one phase of involution, Marburg recognized this tendency toward neuroglia deposition about the blood vessels even in the newly born.

The presence of cysts within the pineal body was observed by Virchow and other writers of his time. However more recent observers have found small cysts within the pineal body with sufficient regularity to justify the claim that cyst formation is a part of normal involution. The course of development of these cysts has been described at some length by Marburg. He divides cysts in the pineal body into two types according to their pathogenesis. To the first type belong those cysts which are the result of central softening of previously formed neuroglial plaques. To the second type belong those cysts having their origin in a portion of the primary evagination which has become included in the pineal body. These are not particularly infrequent in the normal pineal and as a rule are situated somewhat toward its attachment to the wall of the third ventricle.

The neuroglial plaques, already alluded to, have their origin in the vicinity of penetrating blood vessels. As the deposition of neuroglia along the blood vessels increases in extent and density, it manifests the tendency to contract and finally strangulate the vessel, whereby the nutrition to a particular part is entirely cut off with the result of subsequent liquefaction of the more central constituents. These cysts appear in section usually as round, oval or elliptical, though it is not uncommon for them to be irregular, their shape depending somewhat upon the plane through which they are cut.

The second type of cyst formation in the pineal body is not a

part of involution, although a brief description may serve to differentiate these cysts from the cysts of softened neuroglial plaques. They are usually lined with ependymal cells which may at times become flattened and resemble endothelial cells. Not infrequently these cells are in part absent. Where wholly absent the remaining cyst may become indistinguishable from those resulting from softened neuroglia. While this confusion might arise concerning their origin, it is evident that the nature of the fluid content is strikingly different, representing on the one hand dissolved tissue and on the other hand cerebrospinal fluid.

Furthermore, certain homogeneous acidophile bodies make their appearance with involution. They are usually round or oval, not infrequently appear to be laminated and at times have a scalloped border. They have often been designated as colloid or amyloid bodies. It is not uncommon for them to become infiltrated with calcium salts giving rise to the so-called brain sand in the pineal. These bodies occur among the cells and sometimes in the septa. According to Krabbe pigment, which he designated lipochrome, is found in the pineal cells, free in the connective tissue and in the cells with divided nuclei. Fat has been found in the septa.

By using Van Gieson's or Mallory's connective tissue stain the capsule and septa take a distinctly lighter stain than that of the adjoining meninges; where the septa are the thickest the collagen fibers are more deeply stained, but in the middle of such places at times the fibers have disappeared, the structure is lost and a finely granular material which remains takes a slightly basic stain. Krabbe designates this material myxomatrix.

No medullated nerve fibers have been demonstrated in the normal pineal body. I have employed Kulschitzky's modification of Weigert's stain for myelin sheath.

In the two following cases lesions of the pineal body have been observed. The changes have been in part similar to those occurring with involution and have caused tumor-like enlargement of the pineal body.

CASE I.—The patient, a man, thirty-three years old, was admitted to the Barnes Hospital a few hours before his death.

He complained of swelling of his feet and ankles, shortness of breath, a colicky feeling and coughing upon exertion. These symptoms have occurred at intervals for the past four years. The patient has always been well until the onset of his present illness. He is married and has two healthy children. His mother died at the age of 45 years with dropsy.

Physical examination shows that the patient was well nourished

and well developed. There was no abnormality of the genitals. Pericardial impulse was visible and there was a wide area of cardiac dullness. The patient was much cyanosed.

It is of interest that the urine reduced Fehling's solution. The urine was of a light brown color, turbid, acid and contained a trace of albumen, a few white blood cells and epithelial cells. There was no opportunity to make other tests for sugar and a quantitative analysis of the urine.

Autopsy.—The body is that of a fairly well-nourished white male adult. The skin, especially over the head, is cyanotic. The scrotum is edematous and there is moderate edema about the ankles.

The pericardium is distended by about 250 c.c. of straw-colored clear fluid. The heart weighs 635 grams and is enormous in size and the auricular appendages are distended and erect. The heart is soft and flabby. The auricles communicate by an opening about 3.5 cm. in diameter; the interauricular septum is represented by a crescentic fold above and anteriorly. The auriculo-ventricular valves are represented by two characteristic openings about 4 and 4.5 cm., guarded by enlarged leaflets which hold water introduced through the aorta and the pulmonary artery. The mitral leaflets are thickened at their distal borders. The ventricular chambers, especially the right, are enormously enlarged. The aorta is small, measuring 1.9 cm. in diameter, while the pulmonary artery measures 3.5 cm. The pulmonary arteries contain patches of intimal thickening which in places have undergone atheromatous change. The right auricular appendage contains a small thrombus.

The right lung is bound above by old adhesions to the chest wall. Below the apex externally there is an area of consolidation about 2 cm. across. At the hilum are found two caseous and calcified lymph nodes. In the left lung along the anterior border of the lower lobe is a small area from which pus-like fluid can be pressed. A triangular portion of the lower anterior part of the lower lobe is collapsed and firm. At the external border is a cheesy nodule about 1 cm. across.

The liver weighs 1,455 grams. The surface is yellowish brown and on section the centers of the lobules are red and the peripheries are yellow.

The spleen weighs 245 grams. The capsule is opaque and thickened. Small white pearl-like bodies are plentiful on the cut section.

The right kidney weighs 150 grams and the left 155 grams. Removal of the capsule leaves a smooth dark red surface. The organ is firm and the cut surface is a dark reddish brown color.

The suprarenals are studded with numerous yellowish nodules projecting upon the surface.

The pancreas weighs 89 grams and appears to be normal. No abnormality of the pancreas was observed on microscopical examination.

The brain is adherent in many places to the dura which over the right hemisphere is removed with difficulty. The arachnoid is edematous and lifts from the pia rather easily. No other abnormality was found.

Anatomical Diagnosis.—Partial absence of the interauricular septum; hypertrophy and dilatation of the heart; thrombus in the right auricular appendage; old pleural adhesions; chronic pulmonary tuberculosis; tuberculosis of bronchial lymph nodes with calcification; chronic passive congestion of viscera.

The pineal body is found to be enlarged but in normal relation to the adjacent structures. There is no evidence of inflammatory change about the pineal or of pressure upon the neighboring brain tissue. It is pyriform in shape measuring 16 mm. long, 8 mm. broad and 5 mm. from above downward. It is found to be the site of

FIG. 1. Showing the enlarged pineal body with cysts (Case I).

multiple non-communicating cysts which vary in diameter from microscopic to about 5 mm., the largest cyst being situated in the basal part (Fig. 1).

Microscopical examination of the pineal body shows in certain localities the usual arrangement of islands of pineal cells partially surrounded by septa. In other localities a somewhat chaotic arrangement of the supporting tissue in relation to the pineal cells is observed. An occasional band of fibrous tissue resembling a sectioned septum makes its appearance. The septa in places are strikingly vascular.

Various neuroglial plaques containing cysts of different shapes and sizes occur at intervals. These cysts are usually round, oval or elliptical, though they may be at times irregular in contour. Neuroglia of variable thickness from almost nothing to a millimeter or

more in width form the walls of the cavities. The neuroglial fibers are usually arranged circularly. In contact with the cystic cavities the neuroglia is fragmented and there is a loss of structure. Sometimes the neuroglia is well preserved and gives a smooth lining, but none of these cysts are lined with cells. The contents are somewhat granular and take a slightly acid stain. These plaques of neuroglia end rather abruptly at their periphery though a few fibers go to the

FIG. 2. Showing cysts in the pineal body surrounded by a zone of neuroglia (Case I).

adjacent cells and the adjacent connective tissue septa. In a few instances a small wedge-shaped process of neuroglia extends from the plaques a short distance into the surrounding pineal tissue, but it becomes frayed out and soon lost (Fig. 2).

The predominating cells of this pineal body are round or oval and have as a rule but little cytoplasm. The nuclei are vesicular; the chromatin is collected in masses at the poles or periphery of the nucleus. It is not uncommon to find a nucleus with a nucleolus. Cells with divided nuclei are occasionally seen. These cells in most instances are in intimate contact with neuroglia fibers which appear to pass through them (Fig. 3). In addition to the above type of

cell there is a smaller neuroglial cell with inconspicuous cytoplasm which is continuous with neuroglial fibers. It is not possible to distinguish sharply between the two varieties of cells because there are many cells of an intermediate character. Concretions are fairly numerous; some of them have a scalloped border.

FIG. 3. Showing the character of the pineal cells and the relation of the neuroglia fibers to the pineal cells (Case I).

CASE II.—The brain after removal was brought to the laboratory and no history or protocol was obtainable.

The pineal body is somewhat egg-shaped measuring 15 mm. long and 9 mm. in its other dimensions. The organ is firm and the cut surface appears dense. No evidence of compression of adjacent structures can be discovered. No adhesions of any character are observed about the pineal (Fig. 4).

The usual arrangement of islands of the pineal cells partially surrounded by septa is present, although in most localities the septa are represented by bands of connective tissue which separate individual pineal cells and small groups of pineal cells. This intercellular tissue resembles the septa in staining qualities though numerous neuroglial fibers are scattered throughout. An occasional neuroglia plaque, containing a microscopic cyst, is seen. Laminated

bodies with scalloped margins are fairly plentiful and are frequently infiltrated to a greater or less degree with calcium salts. The predominating cells are fairly large, are round or oval and exhibit considerable uniformity in size; cytoplasm in most instances is unrecognizable on account of the intimate approximation of the inter-

FIG. 4. Showing the enlarged pineal body torn from the wall of the third ventricle and still attached to the falx cerebri (Case II).

cellular tissue about the nuclei. The nuclei are vesicular and the chromatin is collected in masses mostly at the poles or periphery. Occasionally a double nucleus is seen within a cell which has a very narrow rim of cytoplasm. Nucleoli are not infrequently found. There are a few smaller cells with round or oval nuclei which

stain deeply. These cells have the characters of neuroglial cells and are intimately connected with neuroglial fibers. White fibrous connective tissue cells are found within the septa and occasionally in the connective tissue dividing the cells into groups.

Ziegler (4) makes the statement that the most common abnormalities of the pineal body are hyperplasia, cyst formation and psammoma but does not discuss these lesions in detail. Hyperplasia according to Marburg should not be confused with true hypertrophy of the pineal body in which there is a distinct increase in the size of the pineal cells. Marburg (5) has carefully described an instance of hypertrophy and hyperplasia chiefly of the neuroglial cells with gliosis of the pineal body; the brain was greatly enlarged and there was hypertrophy of glial cells and hyperplasia of neuroglia throughout the brain. Virchow (6) described briefly an instance of hypertrophy of the pineal in which the cells were abnormally large. Blanquinque (7) has described a case in which the pineal was about 2 cm. long and was made up of small cells which with connective tissue composed the principal part of the enlargement. Concretions and globules of amyloid were present. Blanquinque does not claim that the individual cells were larger than normal pineal cells but designates the condition hypertrophy. It is not improbable that several lesions described as glioma are identical with those in Cases I and II. Virchow was of the opinion that many of the so-called glioma of the pineal body represented a hyperplasia of the pineal cells; the cells in these tumors being similar to pineal cells. Lawrence (8) described a case in which the pineal measured 14 mm. in transverse and antero-posterior diameters and flattened from above downward measured 7 mm. There was an outer zone composed of cells of considerable size having large oval deeply stained nuclei. The cells of this layer were evidently pineal cells. The central zone was composed of finely granular material staining slightly. An open network of delicate fibers was seen in many parts of the central zone. No cells or nuclei were present in this zone. Between the two zones in the anterior part of the pineal body was a third zone consisting of a close network of very delicate interlacing fibers and scattered cells of small size. This layer was closely connected with the central zone on the one hand and on the other hand was not sharply marked off from the pineal tissue at the periphery, but was prolonged into the pineal tissue cutting it up into well-defined areas. Lawrence thinks that the enlargement of the pineal is due to a gliomatous growth which has undergone softening.

Reports of cases of abnormalities occurring at the site of the

pineal body have certain similarities. These growths are sharply circumscribed, they do not infiltrate the surrounding tissue, do not metastasize, and are as easily detachable as the normal pineal body. These enlargements advance in the line of least resistance into the third ventricle, often producing by pressure over the Sylvian aqueduct internal hydrocephalus. Microscopically the enlarged bodies are not strikingly different from the normal pineal and are usually composed of cells like normal pineal cells and stroma. At the same time there is more or less gliosis and new formation of fibrous tissue.

The normal pineal body varies greatly in size. I have measured the pineal bodies of a series of forty-five brains. The shortest measured 6 mm. in length and the usual length was 8 or 9 mm., although one measured 12 mm. and the longest 15 mm. The usual width was from 5 to 8 mm., although one measured as little as 3.5 mm. and another as much as 11 mm. The depth ranged from 2 to 6 mm., though in most instances it was 3 or 4 mm. Where one dimension was noticeably increased it was in most instances at the expense of another. Nevertheless one or two pineal bodies in this series were fairly large but retained the normal shape and appearance. The pineal body of Case I under discussion measures 16 mm. long, 8 mm. wide and 5 mm. vertically—being thereby equal to more than three times the size in cubic millimeters of the average normal pineal body. Case II measures 15 mm. long and 9 mm. in its other dimensions, thereby being equivalent in cubic millimeters to more than 6 times the average normal pineal body.

In Case I the enlargement of the pineal body is brought about by increase in all the pineal elements that make up the pineal body, namely neuroglia, connective tissue and pineal cells. The presence of cysts increases the size of the body. The pineal cells are in intimate relation to neuroglia fibers and various transitions occur between this type of cell and the smaller neuroglia cells. In Case II the cysts are microscopic in size and infrequent. The pineal is larger than in Case I and there is greater hyperplasia of the elements which compose it. Pineal cells are especially abundant and have the characters of those found in Case I.

Duffin (9), Raymond (10), Zemmer (11) and Carl Hart (12) have described as glioma, glial-sarcoma or angio-sarcoma tumors from 3 to 5 cm. in diameter in large part composed of cells having the characteristics of pineal cells. C. M. H. Howell (13) has described three similar tumors. The relation of these lesions to hyperplasia is not determined. Furthermore, cysts in the pineal body up to several centimeters have been described.

The symptoms which have occurred with enlargement of the pineal are fairly constant. General symptoms as headache, vomiting and optic neuritis are almost constant. Languor, mental apathy and sleepiness occurred in the cases reported by Ogle (14), Coats (15), Frankl-Hochwart (16), Gutzeit (17) and Duffin. Extreme thirst and hunger were observed in two cases reported by Howell and in the case of Daly (18). Howell points out that symptoms of pineal tumors in consequence of the position of the pineal body are equivalent to lesions involving the mid-brain and corpora quadrigemina and are characterized by ocular palsies, vertigo, staggering gait, tremors and deafness to which may be added pain and rigidity in the neck and sometimes definite *opisthotonus*. The patients of Duffin, Ogle and Daly had rapid loss of vision. Howell suggests that internal hydrocephalus with pressure on the chiasm causes blindness.

Pineal tumors have occurred, with few exceptions, during childhood or in early adult life. In the cases reported by Ogle, Frankl-Hochwart, Huebner (19), Gutzeit, Marburg (20), Oestreich and Slawyk (21), the age was not above ten years and, save in one instance, the patient was a boy. In four instances the tumor was a teratoma. In addition to signs of intracranial tumor these individuals showed psychical and physical development beyond their years and there was excessive growth of the body. The bones and external genital organs with pubic hair were abnormally developed and the voice became deep. Marburg's patient was a girl of nine and a half years old; her genital organs were normal but there was adiposity particularly noticeable in her breasts and over the abdomen. Marburg maintains that the pineal has a definite function at least in early life and explains its relations to the lesion as follows: Premature genital development he regards as hypo-pinealism, universal adiposity indicates hyper-pinealism and cachexia is the manifestation of a-pinealism. Howell hesitates to assign the symptoms which have been mentioned to lesions of the pineal body.

It is noteworthy that the urine from Case I reduced Fehling's solution but further evidence of the presence of sugar was not obtained. Garrod (22) reported a case of diabetes mellitus occurring in a boy aged 16 years. A pea-sized cyst was found in the pineal. The fourth ventricle and other parts of the brain were normal. The pancreas was unduly small and was found upon microscopic examination to be markedly fibrosed. In Case I the pancreas exhibited no abnormality.

Numerous investigators have endeavored to determine by experi-

mentation on animals the function of the pineal body. Extracts prepared by various methods have been administered. Dixon and Halliburton (23) injected an extract of sheep's pineal intravenously into anesthetized cats. They observed a fall in blood pressure which they showed was not due to cholin, as some investigators have claimed. Howell who has called attention to the symptoms which accompany tumors occurring in early life suggests that the pineals used in such experiments may have become functionless.

Various methods of extirpation have been practiced. Foa (24), after a brief study on pinealectomized cockerels, decided that some sexual precocity occurred. Recently Dandy (25) has removed the pineal from puppies from ten days to three weeks old. Following the removal of the pineal he observed no sexual precocity nor indolence, no adiposity nor emaciation and no somatic nor mental precocity or retardation. He states that his experiments have yielded nothing to substantiate the view that the pineal gland has an active endocrine function of importance either in the very young or adult. He finds that the pineal is apparently not essential to life and seems to have no influence upon the well-being.

Conclusions.—In none of the organs of internal secretion are there cells with characters similar to those of cells of the pineal body. The pineal cells in young individuals are similar in number and structure to those in pineal bodies of older individuals after involution is established.

Pineal cells are intimately related to fibers which resemble those of neuroglia and there are transitional forms between neuroglia cells and pineal cells. Pineal cells appear to be modified neuroglial cells.

In association with the process of involution there may be tumor-like enlargement of the pineal body characterized by proliferation of the pineal cells. In association with hyperplasia of these cells there is no functional disturbance in other organs of the body.

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