CYST FORMATION IN THE PINEAL GLAND.

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(PLATES XII.—XIV.)

THE presence in the pineal gland of one or more simple cysts, filled with fluid and recognisable to the naked eye, is not of very rare occurrence, and microscopical examination shows that minute cysts, though not always present, are nevertheless not uncommon. Such cysts are unaccompanied by evidence of tumour formation, and are attended by but few further changes, simple in character, in the structure of the epiphysis cerebri. Although the existence of pineal cysts is well known, their mode of origin does not appear to have received much attention at the hands of investigators.

The present work, which has for its object the study of cystic formation in the pineal gland, is based upon the examination of fifteen pineal glands obtained from autopsies occurring in asylum practice, and of two pineal glands obtained from healthy subjects killed by accident. In addition, comparison has been made with the structure of the epiphysis of the calf, dog, cat, rabbit, and of *Ammocetes*.

Cysts accompanying tumours¹ of the pineal gland, as also Dermoids and Teratomata, are excluded from the present article.

GENERAL STRUCTURE OF THE PINEAL GLAND.

Before proceeding to discuss the nature of cystic change in the pineal gland it is necessary to enter in some detail into the normal histology of this structure, in order to know what modes of cyst formation are possible. Since pineal cysts may conceivably arise out of more or less incompletely obliterated vestiges, it is further necessary to make brief reference to the development of the epiphysis and of associated structures.

As is well known, the epiphysis, which is cone-shaped, is placed horizontally in the middle line above the groove between the anterior corpora quadrigemina (Plate XIII. Fig. 5, *f.*). On each side are seen the peduncles of the pineal gland which run from the epiphysis along the inner surface of the trigonum habenulæ, becoming continuous with the striæ pineales, and consist of small medullated nerve fibres ($4\ \mu$ in diameter, a few fibres reaching $9\ \mu$). Between

¹ Cf. Max Neumann, "Z. Kenntniss der Zirbeldrüsengeschwülste," *Monatschr. f. Psychiat. u. Neurol.*, 1901, Bd. ix. S. 337-367.

the peduncles, at their attachment, is seen a white band running transversely, which is known as the commissura habenulæ. This white band is divided into two parts by the prolongation of the third ventricle, known as the pineal recess *p.r.*, which reaches the base of the pineal gland and occasionally penetrates a short distance into its substance. So that under the term pineal gland we may include—(1) the epiphysis proper; (2) the peduncles; (3) the commissura habenulæ; and (4) the pineal recess.

Of all these structures we are concerned, for the purpose of this paper, chiefly with the first, and but little further reference will require to be made to the others.

The method adopted in the present investigation into the structure of the pineal gland in the human adult has consisted in the preparation of a complete series of sections of each epiphysis studied. By means of such sections—horizontal, sagittal, or frontal, mounted in series at known intervals—the pineal gland is thoroughly explored and can be reconstructed.¹ Owing to the presence of brain sand it is necessary to decalcify with nitric, picric, or other acids in dilute solution. Of staining methods the most useful is van Gieson's; but staining with methylene-blue, fibrin and neuroglia stains, by the iron hæmatoxylin method, and by that of Pal, also give valuable results. The pineal gland is usually readily detached from the connective tissue by which it is surrounded. The cases from which the pineal glands, selected for examination are taken, are referred to later (see Table, p. 218).

A section of the pineal gland (Plates XII. and XIII. Figs. 1, 2, 4, 5) shows it to be bounded externally by a fibrous capsule (not represented in the illustrations), enclosing a number of cellular elements, arranged in collections, separated and surrounded by tissue composed of neuroglia, and containing the blood vessels of the gland. In addition, masses of brain sand are found, and sometimes, but not always, one or more cavities. At the base of the pineal gland is seen the pineal recess *p.r.*, bounded by the peduncles on each side, and above and below by the commissura habenulæ *c.h.*, which blends beneath with the posterior commissure. Each of the constituents of the pineal gland will now be considered in detail.

The capsule consists of fairly abundant loose connective tissue, containing numerous blood vessels, derived from the pia mater, into which it merges. In the cases examined it was usually only slightly adherent to the pineal gland, and stripped readily; in the case with which detachment could be effected it presented considerable resemblance to the pia mater covering the outer surface of the cerebral hemispheres, which, in eleven out of seventeen cases examined, stripped without difficulty. It must be borne in mind that in all but three of these cases the pia arachnoid was more or less opaque and thickened, and brain atrophy was usually present. The capsule generally contained free or loosely attached cells in its meshes, but this was obviously part of the general cell infiltration of the pia arachnoid which was present. These cells were more or less rounded in outline and usually exhibited only a small amount of cytoplasm; they were not perivascular in disposition, but lay in the spaces of the connective tissue. The strands of connective tissue forming the capsule were mostly coarse, but fine wavy fibrils were also present. Elongated nuclei were seen in small numbers lying on the connective tissue bundles. The blood vessels contained in the capsule are both large and small, most of the former not belonging exclusively to the pineal gland. The capsule sometimes contained brain sand (Plate XII. Figs. 2, 3, 4).

The substance of the pineal gland within the capsule is chiefly made up of

¹ If, before sectioning, incisions are made into the pineal gland in two planes at right angles to each other, and to the plane of section, then the exact relation of the individual sections to each other is defined. The hardening fluid usually adopted was 4 per cent. potassium bichromate solution, but alcohol, formol, corrosive sublimate, and Weigert's copper-iron-alum solution were also used.

cells placed side by side, arranged in more or less imperfectly separated collections (Plates XII. and XIII. Figs. 1 to 5). These cells are fairly uniform in size, such as are least irregular in shape being about $6\ \mu$ to $9\ \mu$ in diameter. They exhibit a well-formed nucleus surrounded by a very small amount of protoplasm, and are irregular in outline, not unfrequently presenting a shreddy surface (Plates XIII. and XIV. Figs. 6 and 8).¹ The nucleus exhibits a nuclear membrane and a very small amount of granular chromoplasm, with or without a single nucleolus. These cells are situated near each other, but are not continuous like surface epithelial cells, being separated by delicate neuroglia fibrils, the amount of which varies in different cases (Plate XIII. Fig. 7). Partly in consequence of the presence of these fibrils, which, even in the absence of a neuroglia stain, are more or less imperfectly seen, it is difficult to determine the form of the cells. They occasionally appear to give off short protoplasmic prolongations, but, in the absence of differential protoplasmic staining of the proper cellular elements, it is not easy to be sure of this. Sometimes the cells are massed together imperfectly, in rows or groups, as is shown in Plate XIII. Fig. 6 and Plate XIV. Fig. 8,² but such grouping is never strongly marked. In none of the cases examined did these cellular elements form well-defined solid tubules or masses, nor did they line hollow spaces.

Lying beneath the capsule is a feltwork of neuroglia fibres, resembling the subpial feltwork of the cerebral cortex, and like it separating readily from the pia mater. The thickness of this layer varies much in different pineal glands, varying from $30\ \mu$ to as much as $0.5\ \text{mm.}$ or more in thickness. In most of the cases examined, however, the neuroglia of the cerebral cortex was also increased in amount. From the subcapsular layer fibrils pass in among the individual cells of the pineal gland, and also in larger amount between the cell collections, which they separate more or less incompletely, thus forming imperfect septa or trabeculae. There is also a neuroglial feltwork, sometimes small in amount, generally abundant and occasionally of remarkable thickness, around any cavities which the pineal gland may contain (Plates XII., XIII., and XIV. Figs. 3, 4, 5, and 9). Furthermore, one or more masses of neuroglial feltwork, not surrounding cavities, connected with or separate from one another, are sometimes seen in sections of the pineal gland (Plate XII. Fig. 2), and are occasionally of very considerable relative dimensions. Beneath the epithelium lining the pineal recess, also, a similar more or less abundant feltwork of neuroglial fibres is seen. The individual neuroglia fibrils are very delicate, being $0.5\ \mu$ or less up to $2\ \mu$ in diameter. They are uniform in aspect, and are straight or curved but not wavy like collagen strands. They interlace, but do not anastomose. Occasionally, but in the cases examined, rarely, spider cells were met with. Numerous round or slightly elliptical nuclei are met with in the neuroglia feltwork; these are best observed when the fibrils are uncoloured, for example, in methylene-blue stained sections.

The blood vessels of the pineal gland are fairly abundant. They lie in the neuroglial tissue in the spaces between the cell collections and send a few offshoots into the interior of the cell masses. They are mostly thin capillaries, consisting of intima only, not containing muscular fibres or adventitia. A variable number of neuroglia cells also run along the blood vessels, lying parallel to their long axis. They are more numerous about the larger vessels than on the capillaries.

In sections of most pineal glands the presence of brain sand forms a striking feature (Plate XII. Figs. 2, 3, 4). Occasionally it is present in very small amount, so that sections of the gland can be made without previous decalcification;

¹ Cionini, *Riv. psch. di freniat.*, Reggio-Emilia, 1886, describes these cells as neuroglia cells.

² In these two sketches the separation of the pineal cells is unusually marked. The decalcification which is usually necessary, in order to prepare sections, causes a certain amount of shrinking of the cell elements.

frequently it forms collections recognisable to the naked eye as golden-yellow, transparent, hard, gritty masses, which, when treated with acetic acid, give off bubbles of gas. The largest masses of brain sand, whose diameter may be as much as half that of the pineal gland, itself enlarged, form irregular mulberry-like collections, which, on section, show a concentric lamination (Plate XII. Fig. 4). The smaller masses, which are simpler in construction, show more clearly a concentric arrangement of layers, and exhibit the grouping of the smaller units by the coalescence of which the larger mulberry masses are made up. These units are of varying size, the largest being $40\ \mu$ or more in diameter, and showing several concentric rings, while the smallest are about $4\ \mu$ to $12\ \mu$ in diameter, and are usually free from evidence of lamination. The mulberry masses are seen in Fig. 4; the smallest masses in Plate XIV. Fig. 8. It is not clear how these individual units originate. They cannot be shown by staining methods to arise in cells or out of cells, nor can they be shown to possess a cellular envelope. The grouping they exhibit suggests that several units arise originally separately, being some distance apart, but later coalesce. Subsequently, as they increase in size, the concentric laminae, which at first form around individual units, as soon as coalescence occurs, envelop the entire group with but little reference to the separate components. Neuroglia fibres do not penetrate within the masses of brain sand. Brain sand is found both in the cell collections lying in contact with the cells and their neuroglial framework, and also in the intervening neuroglial feltwork. It is further found occasionally in the capsule, and sometimes forms prominent collections lying upon the peduncles of the pineal gland beneath the ventricular epithelium. Gaskell¹ has suggested that brain sand is the representative of the retinal pigment of the median eye.²

Pineal cysts when present consist of a clear fluid lying in the substance of the pineal gland, which is altered in the immediate neighbourhood of the fluid content by the presence of an abundant feltwork of neuroglia fibres, which thus form a cyst wall, and a corresponding diminution in the number of pineal cells (Plates XII.-XIV. Figs. 3, 4, 5, 9). Further details of their structure are given in the next section.

In size, pineal cysts vary from a quarter of a millimetre or less to one or more centimetres in diameter. As a rule more than one cyst is present. Thus, out of eight cystic pineal glands, in only three was a single cyst present. The largest number counted in a single gland was eight.

Mention must be made of the form of the pineal recess. This is a short funnel-shaped diverticulum of the third ventricle, the point of which usually passes but a short distance into the base of the pineal gland (Plate XII. Figs. 1, 2, 3, 4, *p.r.*). It is quite simple in character, and in all the glands examined has been free from diverticula. In one case its apex was prolonged as a fine epithelium-lined tube, for a distance of nearly $1\cdot5$ mms. into the interior of the pineal gland, but this case appears to be exceptional.

Examination of the medullated nerve fibres of the peduncles and commissura habenularis was made with a view of defining their relation to the pineal gland proper. By Pal's method of staining it is seen that the nerve fibres do not penetrate between the cell collections, but run transversely in the commissura habenulæ. They measure $4\ \mu$ or less in diameter, a few, however, reaching $7\ \mu$ to $9\ \mu$.

The origin of the pineal gland has received a considerable amount of attention of late years. It rises in connection with the epiphysal tube, a dorsally directed prolongation of the lamina terminalis, passing in Selachians

¹ "On the Origin of Vertebrates, deduced from the Study of Ammocoetes," *Journ. Anat. and Physiol.*, London, 1898, vol. xxxii. p. 538.

² Bizzozero, "Beitr. z. Kenntniss des Baues der Zirbeldrüse," *Centralbl. f. klin. Med.*, Bonn, 1871, describes yellow or red pigment in the branched cells of the pineal gland.

and many reptiles to a sense organ lying beneath the skin covering the head dorsally, which the researches of Graaf¹ and Spencer² first showed to contain a cornea, lens, retina, and pigment layer. In the higher vertebrata the sense organ has disappeared, and the epiphysis lies deeply seated within the skull, not extending more than a very short distance beyond the limits of the third ventricle. The relation of this organ to a median eye has since been studied by Gaskell.³ In the works on comparative anatomy much attention is usually given to the complicated character of the epiphyseal cavity, but, in the human subject, the only portion of the epiphysis which remains hollow is the funnel-shaped diverticulum known as the pineal recess, which ends blindly. In the next section further reference will be made to the developmental history of the epiphysis in its bearing upon the formation of pineal cysts.

CYSTIC CHANGE IN THE PINEAL GLAND.

In the preceding section the normal structure of the pineal gland has been described in some detail as a necessary preliminary to the consideration of cystic change. Before proceeding, however, to discuss the immediate mode of production of pineal cysts, brief reference must be made to several conditions which may conceivably act as predisposing factors, such as age, sex, state of brain, and pia arachnoid, form of mental disorder, and accompanying chronic visceral affections. Several of these are referred to in the table, but, owing to the small number of cases examined, no statistical results can be given, and even the few conclusions which the table foreshadows must be regarded as purely provisional, pending the investigation of a larger number of cases. As regards sex, three out of the eight cases in which cysts occurred were females. The pineal gland was found to be cystic in adult subjects whose ages ranged between 32 and 73; the post-mortem examinations, however, were made only upon adults or adolescents. Of interest is the condition of the pia arachnoid, which generally presented some degree of opacity, usually slight, when no cysts existed; while, when cysts were present, the degree of opacity was usually marked. This suggests that there may be a greater tendency to cystic change when this state of the leptomeninges exists. In the two subjects, killed by accident, in which the brain and its membranes were healthy, no cysts were found.⁴ The brain weight was found to exhibit great variation, both when cysts were absent

¹ "Z. Anatomie u. Entwicklung der Epiphyse bei Amphibien und Reptilien," *Zool. Anz.*, Leipzig, 1886.

² Preliminary communication, *Proc. Roy. Soc. London*, 1886, vol. xl.; also "On the Presence and Structure of the Pineal Eye in Lavertilia," *Quart. Journ. Micr. Sc.*, London, October 1886. Cf. also Leydig, "Das Parietelorgan der Amphibien u. Reptilien," Frankfurt-on-Main, 1900.

³ "On the Origin of the Vertebrate Nervous System," *Brit. Med. Journ.*, London, 1890, vol. ii. pp. 1341-45. A description of the invertebrate median and lateral eyes is given by Lankester and Bourne, *Quart. Journ. Micr. Sc.*, London, 1883, vol. xxiii. pp. 117-212. Some interesting details respecting the development of the visual apparatus are given in Gaskell's later papers.

⁴ In none of the pineal glands of the lower animals which were examined were cysts found.

and when they were present; but no clear connection between low brain weight and cyst formation is indicated. The pineal glands were removed from the insane in all but two cases. The nature of the mental state does not appear to exert any clear predisposition to cystic change, and the same may be said of chronic visceral disease, from which the subjects suffered.

Table Giving Particulars of the Cases from which Pineal Glands were Obtained.

No. of Case.	Size of Pineal Gland.	Pineal Cysts.	Sex and Age.	Pia Arachnoid.	Brain Weight.	Mental State.
					Grms.	
1	Not enlarged.	None.	M., 34	Slightly opaque.	1475	Dementia.
2	"	"	" 36	"	1405	Melancholia.
3	"	"	" 46	Opaque and thick.	1317	General paralysis.
4	"	"	" 18	Slightly opaque.	1090	Epileptic imbecility.
5	"	"	F., 64	"	1110	Melancholia.
6	Enlarged.	"	" 49	"	1110	Dementia.
7	Not enlarged.	"	M., 19	Normal.	1000	Idiocy.
8	"	"	" 32	"	1470	Normal.
9	"	"	" 26	"	1480	"
10	Enlarged.	One.	" 62	Opaque and thick.	1440	Mania.
11	Not enlarged.	"	" 32	Slightly opaque.	1510	Epilepsy.
12	Enlarged.	Many.	" 53	Opaque and thick.	1490	Melancholia.
13	"	"	" 73	"	1465	Dementia.
14	"	One.	F., 39	Slightly opaque.	1360	"
15	"	Many.	M., 35	Opaque and thick.	1300	General paralysis.
16	"	"	F., 49	"	1215	"
17	Not enlarged.	"	" 39	"	1175	Mania.

Frequency.—Of the seventeen human pineal glands examined, cystic change was absent in nine and present in eight. One of the former was enlarged, and in all but two of the latter enlargement was present. The existence of brain sand and increase of neuroglia was responsible for some of the enlargement, but this factor appears to be much less effective in causing relatively considerable increase in size than is cystic change. In five out of the nine cases in which no cysts were present, the pineal gland contained one or more large collections of neuroglial feltwork. The frequency of cystic change was high in the cases examined in which some degree of brain atrophy was present (fourteen out of seventeen). As cysts are often wanting in the pineal gland, they cannot be regarded as a normal constituent of this organ.

It has already been stated that pineal cysts are generally multiple, and that while some of the cavities are irregular in outline, and may perhaps have been formed by the coalescence of two or more cysts, the rule is for the cysts to be quite separate, and to show no indication of communication. The morbid process which leads to cyst formation affects the pineal gland in several independent foci, either simultaneously or in succession.

Position.—Cysts do not show any striking predilection for any particular site in the pineal gland. In forming a judgment as to the place of origin of cysts, attention must be directed specially to the smallest cysts, for the larger ones cause displacement of portions of the pineal gland, so that the original relations of the cysts soon become altered. The smallest cysts, which were about $250\ \mu$ in diameter, were found in the cases examined to be situated at any point in the substance of the gland. They do not reach the surface, though the large cysts may do so (Plate XII. Fig. 3, cf. also Plate XIII. Fig. 5, *a*). Though usually rounded in outline, they are not perfectly spherical. The larger cysts occasionally communicate with one another, and thus become loculated in character (Plate XIII. Fig. 5, *b* and *c*.) The smallest cysts do not show any special tendency to be situated in the long axis of the pineal gland.

Relation to the pineal recess.—In attempting to discover the origin of pineal cysts, the inquiry naturally presents itself: Can these be attributed to any structure which the gland normally has, or has had, at some period of its development? One explanation of the occurrence of pineal cysts, which a comparison of the human pineal gland with the convoluted¹ epiphysis (and paraphysis), seen in many of the lower vertebrata, suggests, is that these cysts are formed by the persistence of portions of such diverticula, retaining their original structure, which have become shut off from the main cavity. Sections of the pineal gland, however, show, as has already been pointed out, that the cysts are not lined by a well-defined layer of epithelial cells, as is the ventricular cavity of the cerebrum; but, on the contrary, the wall of the cyst is made up of a neuroglial feltwork containing but few nuclei. As already mentioned, no trace of well-formed recess diverticula has been found in the cases examined. The possibility of the origin of pineal cysts in such a way cannot therefore be entertained, in view of the histological appearances which are observable. Moreover, when several cysts are present, their arrangement does not suggest or support their origin in this manner.

A further criticism of this suggested explanation of the genesis of pineal cysts is afforded by the distribution of the neuroglia. It has already been pointed out that there is a thick neuroglial feltwork beneath the epithelium of the pineal recess, and this feltwork would naturally be prolonged over any diverticula given off by the pineal recess; and in case the diverticula became separated from the main recess, the persistence of the neuroglial feltwork would indicate its original continuity with the main recess. In other words, the feltwork enveloping the pineal cysts would be continuous with that forming the floor of the pineal recess. Two facts, however, negate

¹ The convolution of the epiphyseal wall is accompanied by a thickening of its epithelial lining.

this view: In the first place, when the pineal gland is reconstructed from serial sections, there is not constantly found a central mass of neuroglia fibres with or without lateral diverticula, such as this hypothesis requires; and, in the second place, the feltwork bounding the cysts, even when of considerable relative thickness, was, with one exception, never directly continuous with that bounding the pineal recess, no thickened connecting bands intervening (cf. Plate XII. Fig. 4). In one case (No. 6 in the table, and Plate XII. Fig. 2) a large central mass of neuroglia of irregular shape was present, but in this case no cysts existed. The exception just referred to is No. 16 in the table (Plate XII. Fig. 3); in this case the neuroglial feltwork covering the largest cyst, in consequence of its size and position, becomes continuous with the subepithelial feltwork of the pineal recess, but the remaining cysts are quite distinct. So that the disposition of the neuroglial feltwork, as also that of the structure of the cysts, affords little support to the view that they arise from the separation of portions of the diverticula originally present in the epiphysis. It may be here remarked that no conclusion can safely be drawn as to the connections of the neuroglia feltworks, or as to the presence of communications between apparently separate cavities which are present, from the examination of a single section of a pineal gland. Only when a complete series of sections, taken at close intervals, is studied can the structure of the pineal gland be satisfactorily ascertained.

Relation to the pineal cells and neuroglia.—Since no evidence is forthcoming as to the origin of pineal cysts in well-formed, epithelial-lined vestiges of the epiphyseal diverticula, it remains to be considered whether there is any evidence pointing to their origin in the cell collections of the pineal gland. This raises the question, What is the nature of the cell masses? Upon this point authors differ. Thus, in one of the text-books of human anatomy, the pineal gland is described as "composed of a number of hollow follicles, generally spherical, but in some cases tubular, separated from one another by ingrowths of connective tissue. The follicles are almost filled with epithelial cells, and often contain much gritty matter."¹ Again Edinger states that the pineal gland "consists essentially of solid epithelial tubules which have originated through proliferation of the primary evagination"² (that is, the epiphyseal diverticulum). But the statement that the cell collections form hollow follicles or solid tubules, which would at once suggest a simple explanation of cystic change, is not borne out by an examination of sections of the pineal gland (Plates XIII. and XIV. Figs. 6, 8, and 9). On the contrary, the proper cells of the pineal gland are broken up into very irregular groups, only occasionally forming imperfect rows or columns, thus constituting a type of structure which is unusual

¹ Quain's "*Anatomy*," 1895, vol. iii. pt. i. p. 114.

² "*The Anatomy of the Central Nervous System of Man*," tr. Hall, 1899, p. 276.

in the human organism. Furthermore, as Weigert¹ first pointed out, there are neuroglia fibres between the individual cells. The fact that the pineal gland is encapsuled by a neuroglial feltwork, which penetrates among its cellular elements and is, like the central nervous system, free from an internal framework of connective tissue, may indeed suggest that the cell masses are possibly made up of nerve cells, resembling the granules so abundant in various parts of the nervous system.² There is, however, no evidence³ in favour of this supposition, and the absence of nerve fibres among the cells of the pineal gland is opposed to it, while the evidence of comparative anatomy, that these cells are epithelial in origin, rests on too weighty a foundation to be overthrown. The fact that the cell masses are not arranged in follicles or tubules, to which they form a lining one or more cells thick, but are arranged in masses penetrated by neuroglia fibres, is not inconsistent with their derivation from the epithelium of the cerebro-spinal canal. A similar phenomenon occurs in the spinal cord of the adult in the neighbourhood of the central canal, around which, in sections, outlying cells, apparently derived from its epithelial lining, for every transition is met with between these cells and those lining the canal, are not infrequently seen, sometimes in abundance, embedded in a neuroglial feltwork. It may be observed, in further elucidation of this unusual behaviour of epithelial cells, that the lining of the cerebro-spinal canal represents, as Gaskell⁴ has pointed out, an invertebrate alimentary epithelium, and is, unlike the epithelial lining of the present alimentary canal, of a simple character, free from glands of any kind with the single exception of the primitive liver, which has completely disappeared in the higher vertebrata. The subsequent penetration of these cells around the spinal canal, and in the epiphysis by neuroglial fibres, is quite in harmony with the regressive tendency of the epithelium.

When cysts first appear in the pineal gland, they are seen to lie among the cell masses. The formation of cysts in the epithelial collections making up the pineal gland is apparently a very slow process, never resulting in fluid collections of more than a very small size, though, relatively to that of the pineal gland, they may be considerable. The result of histological examination is to show that in the formation of pineal cysts (Plates XII. and XIII. Figs. 3, 4, 5) three processes are concerned: disappearance of the proper cells of the gland, increase of neuroglia fibres, and collection of fluid.

¹ "Beitr. z. Kenntniss der normalen u. menschlichen Neuroglia," 1895, Frankfurt-on-Main, table xiii. fig. 3.

² Cionini's view, that the proper cells of the pineal gland are neuroglia cells has been already referred to.

³ I have made numerous attempts to stain pineal glands by Golgi's method and its modifications, but always with negative results as far as the demonstration of neurons is concerned.

⁴ "On the Origin of Vertebrates deduced from the Study of Ammocetes," *Journ. Anat. and Physiol.*, London, 1898, vol. xxxii. pp. 513-581.

Concerning the manner in which the pineal cells disappear, no positive statement can be made. Whether simple atrophy takes place, or colliquation of the cells, or any form of disintegration, or whether the disappearance is merely apparent, being due to an increase in neuroglia, cannot be decided from an examination of the pineal glands studied. In the neuroglial wall of the cyst, where any process of cell destruction would naturally be still in operation so long as cyst formation had not come to an end, the nuclei of the few cells still remaining are not conspicuously different from those of the neighbouring cell masses. It is difficult to decide whether any change is occurring in the cell protoplasm of the pineal cells, owing to the impossibility of accurately defining the cytoplasm by staining methods.

One of the original functions of the ventricular epithelium (in the invertebrate) was doubtless the secretion of fluid, and such a function might naturally be expected to recur as a pathological process in the regressive epithelium of the cell collections of the pineal gland of the human adult, but here the conditions under which secretion usually occurs are altogether changed in respect of the cells which originally lined epiphyseal diverticula, for they are no longer in close contact in a single layer, but are separated to a varying extent, neuroglia fibres intervening. It is, therefore, very difficult to predict or define the effect of exciting ancestral tendencies in these cells, and, although the formation of a fluid collection among the cell masses is hardly unexpected, yet it is not easy to fill up the intermediate stages of the process, either by physiological speculation, or from a histological study of the cysts.

A development of neuroglia fibrils accompanies cyst formation, a neuroglial feltwork, poor in cellular elements, constituting the cyst wall (Plates XIII. and XIV. Figs. 7 and 9). The thickness of this layer increases as the cyst becomes larger (Plates XII. and XIII. Figs. 3, 4, 5). Nevertheless, neuroglia fibres may be developed to an extraordinary degree in pineal glands which are free from cysts (cf. Plate XII. Fig. 2). The neuroglial feltwork is normally abundant in the pineal gland, and an increase in its amount is merely an exaggeration of the natural condition. In the glands studied this has formed part of a general neuroglial increase, affecting specially the sub-pial and sub-ependymal feltworks, but the extreme thickness of the feltwork around the largest cysts shows that this process is here something more than the expression of a general tendency; a local influence is at work, the nature of which can at present only be conjectured.¹ The fibres form-

¹ In one of the pineal glands examined (Plate XII. Fig. 4, *b*, *c*) the wall of a large cyst was formed, partly by neuroglial feltwork, partly by the cell collections. This appearance was probably produced by slight laceration, occurring during preparation of the organ for section. A similar appearance has not been met with in any of the remaining cystic glands. Fig. 4 represents an epiphysis, which was abnormal in the circumstance that connective tissue, which was abundant all round the pineal gland, had grown into its substance, separating some of its cell-collections (3 *b*, *c*, *f*.).

ing the neuroglial feltwork are of large size ($0.8\ \mu$ to $2\ \mu$ in thickness). The nuclei seen in the neuroglial feltwork when very dense are large, oval, possess a nuclear membrane, and contain a small amount of chromoplasm (Plate XIII. Fig. 7). The long axis of the oval nucleus is often, if not usually, parallel to the neuroglial fibres, when these preponderate in a given direction. Large spider cells are sometimes met with.

The collection of fluid in pineal cysts appears to form part of an active, as distinct from a passive, process. All the cystic pineal glands examined were, it is true, derived from atrophied brains, the leptomeninges of which contained fluid. This would perhaps favour the development of pineal cysts, and it may be observed that the perivascular lymph spaces of the cystic glands were also not unfrequently dilated with fluid.¹ The feltwork surrounding a pineal cyst is apparently open, and seems unlikely to offer any great obstacle to the passage of fluid, but the more or less rounded character of the cyst and the displacement of the tissue of the gland to one side, accompanied by a certain amount of flattening, shows that there is an increase of pressure in the cyst over that in the lymph spaces, and indicates that a transudation of fluid occurs into the cyst, causing in part at any rate its increase in size. The largest cysts present after death a slight degree of tension, and offer resistance to the pressure of the finger. It is, however, not easy to explain how this transudation of fluid takes place through a cyst wall so poor in cellular elements.

Cystic change is apparently a purely pathological process, which may be summed up as a primary focal degeneration of the pineal epithelium which becomes replaced by a fluid transudation, while at the same time the neuroglial feltwork in the immediate neighbourhood undergoes a marked hypertrophy.

Relation to brain sand.—There appears to be no connection between cystic change in the pineal gland and the formation of brain sand. The latter may be abundant when cysts are present, but it may also be absent when cystic change is found.²

Relation to the median eyes.—By many authors the pineal gland is described as a vestigial eye. Testut,³ for example, states that the epiphysis of man and the higher vertebrata "est donc au point de vue morphologique le représentant considérablement atrophie de l'œil pinéal des lacertiens." v. Gehuchten⁴ describes the pineal body as a

¹ Many of the pineal cysts studied presented on section an oedematous aspect; that is to say, the tissue spaces both of the cell masses and of the intervening neuroglia were wide, as is seen in Figs. 6 and 8. This appearance was more frequent in pineal glands containing cysts (in four cases out of five in which this condition was carefully determined) than in pineal glands free from cysts (in two cases out of five).

² According to Gaskell (*loc. cit.*) the pigment of the median eyes remains as the brain sand of the human pineal gland. But brain sand, which when present in large masses is of a light yellow colour, is not confined to the pineal gland, but is present in the ependyma of the pineal peduncles, in the choroid plexuses, in the dura mater, and in the pia arachnoid.

³ "Traité d'Anat.," Paris, 1900, vol. ii. p. 274.

⁴ "Anat. du système nerveux," Louvain, third edition, 1900, vol. i. p. 72.

rudimentary organ, well developed in certain Selachians and reptiles, and there constituting a parietal organ having much resemblance to an eye. Obersteiner,¹ quoting from various authorities, states that the pineal gland represents an unpaired eye. Gaskell,² in the course of his researches upon the origin of the vertebrate nervous system, states that the median eyes of ancestral invertebrata have become the pineal gland. In all these statements considerable confusion is apparent between the epiphyseal diverticulum on the one hand and the nervous structures forming the median eyes on the other. In the formation of a median eye there is concerned a diverticulum of the epithelial wall of the third ventricle, together with an optic ganglion and a layer of retinal end cells, the over-lying epiblast being, at the same time, changed in character, and it may be forming a lens. According as the optic ganglion or part of the optic ganglion adheres to, or is separated from, the layer of retinal end cells, the retina becomes compound or remains simple, while the character of the optic nerve is also correspondingly different in the two cases.

Of great importance in this connection is the behaviour of the epithelial diverticulum of the third ventricle. This appears originally to have had a nutritive function (Gaskell); hence its close connection with the peripheral ganglion of the retina. At a later period, when the original nutritive function has disappeared, the stalk of the diverticulum no longer exists, but the blind end persists for a much longer period, remaining as a parietal organ, or *Stirn-drüse*, in some of the amphibian and reptilian embryos at a time when the nervous elements of the retina are no longer recognisable.

The diverticulum of the third ventricle does not itself constitute a median eye, though it enters into the formation of this structure. Moreover, the fraction of the diverticulum which is connected with the retina of a median eye is the blind extremity, the stalk early undergoing atrophy. It is therefore incorrect to refer to the whole diverticulum, or even to any part of it still persisting, as "the remains of a median eye" or as "a vestigial eye." All that can be asserted is, that such diverticulum entered at one time into the formation of a median organ of vision. If, however, it is incorrect to refer to the diverticulum as a vestigial median eye, it appears still more so to apply such a term to the epiphysis, for, according to the observations of Leydig, the diverticulum for the parietal organ, though it may arise from the tip of the epiphysis, may also arise separately from the base of the organ at its commencement.³

It follows, therefore, that as the pineal gland cannot properly be

¹ "The Anatomy of the Central Nervous System," London, 1900, p. 466.

² *Journ. Anat. and Physiol.*, London, vol. xxxii. p. 538. See also *Brit. Med. Journ.*, London, 1890, vol. ii. pp. 1341-5; and "On the Origin of the Optic Apparatus of Vertebrata," *Journ. Anat. and Physiol.*, London, 1901, vol. xxxv. pp. 224-267.

³ *Loc. cit.*, p. 529.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4, a and b.

FIG. 4, c.

described as one of the constituents of a median eye, so therefore cysts, arising as a pathological degeneration of the proper cells of the pineal gland, cannot with strictness be described as having a relation to the primitive median eye.

SUMMARY.

The principal points in this memoir respecting cyst formation, in the seventeen epiphyses studied, may be briefly summarised as follows:—

1. Cysts were found in 47 per cent. (eight out of the seventeen) of the human pineal glands examined, and were usually multiple. No definite relationship can be asserted in the cases examined, between cystic change and age, sex, mental, or accompanying visceral disease. In all except three cases brain atrophy was present; in one of these three cases a single pineal cyst was found, and cysts were absent in the other two; in the remaining cases cystic change was present in seven pineal glands out of fourteen.

2. Pineal cysts were not confined to any particular locality in the pineal glands examined.

3. Pineal cysts do not arise as well-formed diverticula of the pineal recess, and are not lined by a single layer of epithelial cells in contact with each other, resembling those lining the ventricles of the brain.

4. In the formation of a pineal cyst, disappearance of the proper cells of the gland occurs at the site of the cyst accompanied by an active transudation of fluid. At the same time hyperplasia of the neuroglia fibres all round the cyst takes place. In this way a neuroglial feltwork often abundant, especially about the larger cysts, is formed surrounding the cavity and constituting its wall. The proper cells of the pineal gland are present in this feltwork in small numbers and do not form a well-defined layer.

5. No relation between the presence and amount of brain sand and cystic change was observed.

DESCRIPTION OF PLATES XII.-XIV.

PLATE XII.

FIG. 1.—Sagittal section of pineal gland (No. 2 in the Table) showing the imperfectly lobulate structure of this organ; the lobules being made up of collections of cells, separated by incomplete septa containing blood vessels and neuroglia fibres, which also penetrate to a varying degree between the individual cells. No cysts are seen. The small black spheres represent brain sand. To the left is seen the pineal recess *p.r.*, bounded above and below by the commissura habenule *c.h.* ($\times 14$.)

FIG. 2.—Sagittal section of pineal gland (No. 6 in the Table). The structure of the gland is similar to that shown in the previous figure, but a larger amount of brain

sand, disposed in small discrete spheres and in large conglomerate masses, is seen. Towards the free extremity a mass consisting of neuroglial feltwork is found. The pineal recess, *p.r.*, is seen to the right, bounded above and below by the commissura habenuaris *c.h.*, which rests below upon the posterior commissure *p.c.* ($\times 12$.)

FIG. 3.—Horizontal section of pineal gland (No. 16 in the Table). Towards the pineal recess, *p.r.*, is seen nervous tissue, as in the preceding figures. The organ is irregularly enlarged, owing to the presence of four cavities, one much larger than the others. All of these cavities, but particularly the largest, are bounded by an abundant lining of neuroglial feltwork. In the examination of a series of sections it is found that two of the smaller cavities shown in the figure are connected, but otherwise the cavities are distinct from each other. In other respects the structure of this pineal gland is similar to the preceding. Some masses of brain sand are seen lying centrally in the section; a few others lie just outside the pineal gland in the connective tissue surrounding it. ($\times 8$.)

FIG. 4, *a*, *b*, *c*.—Three successive horizontal sections of an enlarged pineal gland (No. 12 in the Table). The shape of this pineal gland is unusual and its outline is irregular, especially towards the free extremity where some of the cell collections appear to be detached. The gland is embedded in unusually dense fibrous tissue, which in two places penetrates into the gland (4 *b*, *c.t.*). The portion of pineal tissue forming the free extremity of the gland in *b* appears to be completely separated from the main mass, but this is not really so, for an examination of serial sections shows, as will readily be understood from a glance at *c*, that the apparently detached portion is, in another level, continuous with the rest of the gland tissue. The sections *a*, *b*, *c*, which are about 1 mm. apart, show two cavities, one small and the other large, both of which remain separate. Both are surrounded by a wall of neuroglial feltwork, which is especially abundant about the larger cavity, where however it is incomplete in *b* and *c*, chiefly posteriorly; this deficiency is not seen in any of the other large cavities met with in the various pineal glands examined, and is apparently the result of slight accidental laceration during preparation of the sections. In 4, *b*, a large collection of neuroglial feltwork, not surrounding a cavity, is seen above. The septa between the cell masses are well defined. A number of masses of brain sand are seen, the larger exhibiting a concentric arrangement and presenting a mulberry surface. Beneath the ependyma of the pineal recess a thick neuroglia feltwork is seen in *a* and *c*, but is not so clear in *b*. *Ch.p.*, portion of choroid plexus of third ventricle cut across. ($\times 9$.)

PLATE XIII.

FIG. 5, *a*, *b*, *c*, *d*, *e*.—Five successive frontal sections of a pineal gland, which on inspection appeared of a natural size and aspect (No. 17 in the Table). The sections are made at intervals of $\frac{1}{4}$ mm. A large cavity, lined by a thick layer of neuroglial feltwork, is seen in *a*, *b*, *c*, giving off two small diverticula in *c*, and entirely disappearing a short distance beyond *d*. In addition, numerous smaller cavities, which remain discrete and are lined by a thinner layer of neuroglial feltwork, are seen in the lower part of the pineal gland. The proper substance of the organ is unaltered in appearance. Brain sand is also present in small amount ($\times 4\frac{1}{2}$). *f* is a diagram of the pineal gland, showing the position of the frontal sections *a*, *b*, *c*, *d*, and *e*.

FIG. 6.—Section of a portion of the pineal gland shown in Fig. 1. Part of a cell mass is represented. Numerous nuclei, some out of focus, are seen surrounded by protoplasm, the outline of which is not clearly defined. The cellular elements are irregularly massed together, occasionally arranged in imperfect rows. The edges of these masses and of the individual cells, when separate, are shaggy, and appear, by the method of staining used, to become continuous with the irregular shred-like material between the cell masses consisting of neuroglial feltwork (cf. Fig. 7). The protoplasm of the individual cells

FIG. 5.

FIG. 6.

FIG. 5.

FIG. 7.

FIG. 8.

FIG. 9.

appears to be sometimes abundant, sometimes scanty, but it is difficult to make precise statements on this point, owing to the impossibility of sharply defining the cell outline. van Gieson's stain. ($\times 650$.)

FIG. 7.—Section of the pineal gland shown in Fig. 5, under a higher magnification. The portion shown is at the outer edge of the thick covering of neuroglial feltwork surrounding the largest cavity. To the left the nuclei of the proper cells of the pineal gland are seen in small numbers, lying side by side or separated by short distances with neuroglial fibrils passing freely between them. To the right the feltwork is much more abundant and the nuclei are fewer. The large black spheres represent brain sand; the small black masses, placed side by side, are red blood-cells contained in capillaries. The former are of small size; two are separate and three are adherent. The feltwork becomes denser as the central cavity to the right is approached, while if the section is moved to the left the proper cellular elements of the pineal gland are seen to become very numerous. The neuroglial feltwork is made up of fibrils varying much in thickness, some being exceedingly fine, some relatively coarse. Some of the fibrils are nearly straight, most of them are curved, and a few form loops, but the very fine waviness and creasing seen in connective tissue fibrils is absent. The fibrils do not branch. The nuclei, which are rounded and elongated, or irregular in form, show a nuclear membrane, and contain a framework of chromoplasm, consisting for the most part of granules of irregular shape and varying size. Occasionally, but on the whole rarely, a nucleolus is seen. The cell protoplasm is unstained. Weigert's neuroglia stain. ($\times 170$.)

PLATE XIV.

FIG. 8.—Section of pineal gland showing the appearance of the cell masses, when stained by methylene-blue. The cells are, as in Fig. 6, grouped irregularly together, some being single. The tendency to grouping is rather more marked than in the latter figure, as is also the arrangement in lines or rows. Between the cell groups, and attached to them, is much irregularly disposed lightly tinted material, presenting a woolly aspect, and representing the neuroglial feltwork, which by this method does not exhibit differential staining. At the lower part of the figures, two blood capillaries are seen. At the lower right-hand corner a portion of one large and numerous very small spheres of brain sand are seen. Methylene-blue. ($\times 550$.)

FIG. 9.—Section of the pineal gland shown in Figs. 5 and 7. A cavity is seen surrounded by cell collections. At the edge of the cavity a feltwork of neuroglia fibres, among which very few cells are to be seen, is found forming a cyst wall. Within the cavity some granular débris is to be seen. The pineal cells are arranged in imperfectly formed groups of irregular form. van Gieson's stain. ($\times 75$.)