THESIS for M.D. DEGREE.

THE EPENDYMA.

AN INQUIRY INTO ITS ANATOMY,

PHYSIOLOGY, and PATHOLOGY.

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INTRODUCTORY.

On perusing treatises on diseases of the Nervous System, or looking over post-mortem records, one cannot help noticing the occurrence and recurrence of such statements as the following:—"Ependyma smooth" "Lining membrane of ventricles rough and thickened" "Floor of 4th ventricle granular". Many writers too, of a poetic turn of mind, have drawn on their imagination and have compared the naked eye appearances of the ependyma, in its so-called granular condition, to various natural objects as sand, jewels, shagreen; or have spoken of it as "bedecked with dewdrops", or glistening like the leaf of an ice-plant. Beyond these descriptions, however, of naked eye appearances, very little seems to have been done for the pathology of the Ependyma. The microscopical structure of the changes in it has received but little attention; while, apparently, no attempt has been made to compare and classify these changes. Even in our largest works on Anatomy, the normal structure of the Ependyma receives but scant treatment, when compared with the amount of language bestowed on other structures.

Nothing is beneath the consideration of the true lover of Science; hence it seemed worth our while to investigate the Structure of so humble and despised a formation as the "thin, diaphanous veil", which lines the...
cavities of the brain and Spinal cord, forms a link with our Embryological past, and is known technically as the Ependyma Ventriculorum.

The present thesis is based on the examination of nearly 1700 Microscopical sections, representing the brain and spinal cord of man - adult and newly born - and the following animals: - Kitten, rabbit, pigeon, frog, codfish, and whiting. For the sections of adult human brain fifty-six cases were selected, giving a variety of diseased conditions, which are shewn in detail in the table in the appendix.

The thesis is divided into 5 Sections according to the following arrangement:

Section 1. ANATOMIC - PHYSIOLOGICAL.
This section deals with the anatomical Structure of the Ependyma, as exemplified in common vertebrate types, and its physiology so far as has at present been ascertained.

Section 2. PATHOLOGICAL.
This section deals with the Morbid Anatomy and Pathology of the membrane.

Section 3. This section contains a detailed account of the fifty-six cases; their history, and the results of the post-mortem and microscopical examinations.

Section 4, contains photographs, photomicrographs and micro-sketches.

Section 5, consists of appendices on microscopical technique, tables, bibliography, lists of sections, &c.
It seemed advisable to summarise the various microscopic and photographic processes used; these, therefore, together with a list of the books consulted, tables &c, are incorporated in this section.

The thesis is illustrated by about 50 water-colour sketches, several photo-micrographs, and a large number of photographs of the 4th and lateral ventricles - see section 4. In addition to these there are several spirit specimens and a number of mounted sections accompanying the thesis. A list of the sections will be found in a table in Section 5 of the thesis.

As regards the references in the thesis; these are in every case enclosed in brackets and given along with the statement or quotation to which they refer. The first number in the bracket indicates the number in the bibliographical table. See Section 5 - the other number refers to the page of the book quoted. Where the reference is to a paragraph rather than a page, the word “Paragraph” precedes the number. In the case of periodicals, the date is given; and where there are several volumes, the word “Vol” and its number precede the number of the page.

After these preliminaries we may proceed to the consideration of the Anatomy of the EPENDYMA.
SECTION 1.

ANATOMICO - PHYSIOLOGICAL.
SECTION 1. ANATOMICO-PHYSIOLOGICAL

In this section we shall consider the anatomical structure of the Ependyma, as exemplified in man and common vertebrate types, and its Physiology so far as it has at present been ascertained.

DEFINITION.

We must first define what is meant by the term "Ependyma". The word, which has been in use for a long time, is derived, according to Quain, from the Greek word ἔνδυμα, signifying "clothing", and in a sense very aptly describes the membrane. Probably the word has some connection with the Greek ἐπιτύρανς, an "outer tunic" or "covering," from ἐπιτύρω, "to put on over". In any case, the Ependyma may be described as the lining membrane of the iter and the ventricles of the brain, and the central canal of the spinal cord.

There is considerable difference of opinion as to what really constitutes the Ependyma. Does it consist of the layer of Epithelium only, of neuroglia only, or of both combined? That both a layer of Epithelium and a stratum of neuroglia exist in this region all the most recent observers are agreed. Rokitansky (14.349), in 1850, speaks of the internal membrane of the ventricles of the brain as being composed of a "very delicate continuation of the arachnoid and pia mater, and a layer of Epithelium". Kölliker (4.240), 10 years later, looks on it as a simple layer of Epithelium, with a striated layer of connective
tissue frequently developed under it; the latter is so often present that it may be considered constant at a certain age. Bucknill and Tuke (28, 481) about the same time are doubtful whether the "minute anatomists of the German School make any distinction between that which they call Ependyma of the lateral ventricles, & the arachnoid membrane in this locality". According to Obersteiner (3.143) the Epithelium together with the connective tissue or neuroglia layer, on which it rests, constitute the so-called Ependyma. Foster (8. paragraphs 614 & 647) also, considers the ventricles, and the central canal of the cord, to be lined by a layer of Epithelium, which, together with a special layer of neuroglia immediately under it, forms what is known as the Ependyma. Guain and Gray, on the other hand, limit the term Ependyma to the connective tissue basis on which the Epithelium rests. Quain (2. Vol. 3.98) says "the lateral walls of the 3rd ventricle have but a thin covering of neuroglia - Ependyma - under neath the lining Epithelium", and again (2. Vol 3.131) "the nucleus canâ€™tus, where it lies in the lateral ventricle is covered by a layer of Ependyma, and over this by the ciliated ventricular Epithelium". Gray (5. 677) speaks of a "thin, diaphanous lining membrane - the Ependyma - covered by nucleated Epithelium". Moxon states (37. Vol 1.1881. page 527) that the 4th. ventricle is lined by "Ependyma or proper lining of cerebral ventricles", and that this lining has "upon its surface a layer of thick close-set Epithelium".

Schopfshagen says (40. April 1889. 119) "the Ependyma is
composed of two layers one superficial and the other deep", in other words the one Epithelial, the other fibrillar. Virchow (40. April 1889, 119) opposes the idea that there is a true and proper membrane; he apparently has demonstrated the presence of an Epithelial layer lining the cavities of the brain and the central canal of the cord, with a slender connective tissue under it, identical with the general neuroglia, and looks on this "epithelial veil" as the Ependyma. Bristowe (21.886) describes it as a delicate membrane continuous with the general neuroglia, identical in structure with it, and furnished with an Epithelium.

There is undoubtedly, as will be seen later on, a close relationship between the Epithelium and the stratum of neuroglia immediately subjacent to it; a kinship, in fact, sufficient to warrant the conclusion that they both enter into, and are integral parts of, one layer, the ependyma. We shall, therefore, in this thesis, follow the lines of Foster and Obersteiner, and look on the Ependyma as being composed of two layers, an outer one of Epithelial cells, and an inner one, immediately subjacent, of fine interlaced fibrils; and shall not, with Quain, Gray and others, limit the term to the inner fibrillary layer only.

It is perhaps advisable, at the present stage, to define the meaning of a term which will be frequently used, viz- Sub-ependyma. This word, or its adjective subependymal, refer to the layer of tissue - neuroglia &c., immediately below the ependyma; in other words to the
outer portion of the general brain substance which abuts on the Ependymal membrane.

Having now decided on the meaning that we intend to attach to the term "Ependyma", we can proceed to the consideration of its structure &c. This it will be best to arrange under the following heads:

A. Its Situation.
B. Its Structure.
C. Its origin.
D. Its physiological significance.

These will now be dealt with in rotation.

A. SITUATION.

In the mammalian brain the Ependyma forms a lining membrane to the cerebro-spinal cavities. Commencing in the cerebrum we may trace it as follows:—it lines the lateral ventricles with their cornua, passes through the foramina of Monro into the third ventricle, then through the aqueduct of Sylvius on to the floor of the 4th ventricle—with expansions on to the peduncles of the cerebellum—, over the calamus scriptorius into the canal of the medulla and spinal cord, and ends in the conus medullaris at the tip of the spinal cord. So far as is known it forms a continuous membrane throughout these cerebro-spinal cavities.

The fifth or ventricle of the Septum lucidum being external to the brain proper, and merely an enclosure between the developing cerebral hemispheres, where they come in contact, has no ependymal lining.
According to Quain (2. Vol. 129) it is lined by a layer of connective tissue on the top of a thin layer of grey matter. Kolliker (4. 240), on the other hand, has stated that the Ependyma does line the 5th ventricle.

In the embryonic brain the hollow within the olfactory bulbs is also said to be lined with Ependyma (4. 240).

Foster (8. Paragraph 647) says the ependyma may be looked on as a continuation of the central gelatinous substance of the spinal cord, which expands out to form a lining membrane to the cerebral ventricles.

B. STRUCTURE.

We shall consider the structure of the Ependyma, firstly, generally throughout the cerebro-spinal System, and secondly, with reference to any special details in the spinal cord and the various ventricles of the brain.

To the naked eye, when viewed in the cerebral ventricles, it forms a thin, somewhat transparent, gelatinous-looking membrane or film, greyish in colour; through it the superficial vessels can frequently be distinctly seen. It is smooth on the surface, and adapts itself to the prominences and depressions of the ventricle walls. In cross sections of the spinal cord it appears as a greyish gelatinous speck in the posterior commissure.

Microscopically it may be said to consist of an Epithelium resting on a delicate reticular or fibrillary layer. Its thickness, when measured with a micrometer, may vary from 60 to 120 micro-millimeters.
EPITHELIUM. In the human brain there is generally a single layer of columnar or cubical cells, arranged regularly side by side, giving in some places a palisade-like appearance, in others that of a row of beads, according as the cells are elongated or squarish. The regular arrangement is well shewn in micro-sketches 16 and 30. It would appear that the single layer of cells is the normal type in adult forms, whether human or animal - see photomicrographs of the iter of the frog, 1 & 2. It is certainly unusual to find more than one layer in the human brain. In young forms however, the cells are usually 2, 3 or several layers deep; this will be referred to later on. Sketch-3-, of the iter of a very young kitten, shews the multiplicity of layers in places.

As regards the shape and structure of the cells, these vary much in different parts of the nervous system; they are also better developed in the lower animals than in man. According to Obersteiner (3,148), in the human nervous system the cells are not everywhere equally well preserved; they are least altered in appearance in the central canal of the cord, the floor of the 4th. ventricle and the aqueduct of Sylvius; in other places they are less perfect. The shape of the cell varies from an elongated columnar cell to a short, squat, cubical one. Quain says (1,40) that the cells may be short or cubical in the cerebral ventricles. Gouëd & Ranvier (17,36) state that non-laminated pavement epithelium of cubical type is met with in the ventricles of the brain. It would seem that the
long cells occur in the canal of the spinal cord and in the calamus scriptorius - particularly in the deeper parts of the medium furrow - while as the Ependyma becomes flattened out to cover the floor of the 4th ventricle or the rounded surface of the optic thalami, the cells become more cubical and squat; this point will be referred to under the consideration of the 4th ventricle. In the spinal cord & the calamus the cells approach most nearly to the usual type of ciliated columnar epithelium.

The cell units are granular, as a rule, and nucleated. The nuclei are rounded or oval, often granular, and situated nearer the lower or fixed end of the cell - this is most evident in the columnar forms. Nucleoli are said to be present. The cells, particularly the long forms, taper towards the fixed end, and very frequently end in a fine long filament. Obersteiner (3.148) says that the "bases of the cells are continued into processes, usually one, rarely two, for each cell." Quain, (2. Vol 2.13) says "it is certain that even in the adult the cells which line the central canal and ventricles of the brain extend a long & indefinite distance into the grey matter"; and (2. Vol 3.96) "some of the Ependymal fibres are attached to neuroglia cells which occur at various levels in the course of the fibres".

The cells are said to be ciliated. According to Obersteiner, (3.148), this is so difficult to prove, that it is doubted by some observers.

Kolliker (4.240) says the Ependyma is ciliated
in some places, and perhaps is so all over. Gray says (5,677) the cilia are scattered here and there in patches. It is quite probable that the cells are ciliated in the human brain in early life, but become cast off and lost in adult forms. In animals the cilia are certainly present in young forms - they are well seen in sections from the 4th ventricle of a very young kitten - in adult forms their existence is doubtful. According to Obersteiner (3,148) they are seen, in the lower animals, on the free surface of the cell, and project into the ventricle or the central canal, as the case may be.

RETICULAR LAYER. This is the stratum immediately subjacent to the Epithelium. It consists of an interlace- ment of delicate fibrils forming a reticular meshwork; some of the fibrils, being out across, appear as fine points and give the meshes a granular appearance. Scattered through the reticulum, nuclei are seen; they are normally few in number compared with the general neuroglia of the brain; they stain deeply, and are usually elongated or oval in shape.

Kolliker (4,224) thought that the cells embedded in the Ependyma, from their "Stellated form and branched processes", were very similar to nerve-cells; he, however, ranks them with the plasm cells of the connective tissue.

In normal conditions there seem to be no blood vessels in this layer; apparently this point has up to the present been overlooked. The examination of a large number of sections has shown, with rare exceptions, no trace of blood vessels; in marked pathological conditions they
sometimes occur. We shall refer to this again later on.

Virchow (40. April 1889.119) apparently looks on this layer as a "Slender connective tissue" identical with the neuroglia. It, however, seems to be largely made up of processes from the epithelial cells; probably there is a neuroglia element present as well. Quain (1.40) states that the fixed non-ciliated ends of the epithelial cells pass into branching fibres which lose themselves in a network underlying the epithelium & which appears to be formed chiefly, if not entirely, by the interlacement of the ramified cell processes. Schopfagen (40. April 1889.119) says that the epithelial cells "give off delicate and very slender prolongations, which dip down into the layer beneath"; the latter being constituted of fibrillar tissue, among which numerous round and oval cells are found. According to Quain (1.40), Lockhart-Clarke and Gerlach have described an anatomical connection of the epithelial cells with subjacent cells and fibres, in reference to the columnar ciliated epithelium of the cord and of the iter. In sections of the fourth ventricle, stained with alum-carmine, fine fibrils are frequently seen extending from the fixed ends of the epithelial cells & traversing the subepithelial layer for some considerable distance. We have made several attempts to apply osmium-silver-bichromate method to these epithelial processes; but, though good results were obtained with the neuroglia elements, nothing definite was made out as regards the epithelium. The Weigert-Pal haematoxylin method shewed the tails of the epithelial cells
very distinctly in the brain of the frog – see photomicrographs 1, 2, & 3. Obersteiner states (3,148) that the
Epithelial cells have one or two basal processes each, and that these may be followed far down into the nervous
substance in the human brain; that in the frog they
continue the principal axis of the cell; and that in the
"Spinal cord of anguinus, Klaussner followed these
processes, some as far as the posterior nerve-roots, others
into the anterior commissure". In sections, which we have
examined, from the 4th ventricle of a newly-born child and
of a very young kitten, the tails of the Epithelial cells
can be seen, in places, stretching across towards the
subependymal region. In the 4th ventricle of the frog the
cells have processes which are very long, and which seem
to end in an open mesh-work. In the iter of the frog,
stained by Weigert - Pal method, some of the processes
were measured, and could be distinctly traced for 250 to
300 micro-millimeters; see photomicrographs 1 and 2.

Whether this layer is made up of the ramifications
and interlacings of the tailed processes of the epithelial
cells or not, it is very difficult to determine; for the
present we shall leave it, and refer to it again after we
have considered the origin of the Ependyma.

We have now to consider the special features, or
deviations from the general type, which the Ependyma
presents in the various situations in which it is found,
beginning with the Lateral Ventricles.

According to Foster (8, paragraphs 614 & 694) the
Ependyma is thin and scanty in this situation; the Epithelium over the ventricle wall generally consisting of ordinary short columnar, apparently ciliated, cells, with more or less transparent cell-substance. We find that the Epithelial cells are more cubical in the lateral ventricles than in many other parts of the cerebro-spinal cavities, and that the reticular layer under the Epithelium is narrower & much less defined than in other situations - see microsketches 16 and 30.

Sections of the lateral ventricle of the pigeon shewed a single layer of nucleated cells, of cubical type, resting on a somewhat indefinite reticular layer with few nuclei & occasional small blood vessels; in places the cells were two or three deep. In the rabbit, the conditions are very similar; the Epithelial cells are somewhat flattened in type, and sometimes shew more than one layer; the extent of the Ependyma being somewhat indefinite, and shewing no distinct demarcation from the general neuroglia. Below the Epithelium, cells, very similar in type to Epithelial cells, lie scattered about.

Andriezen (38. Winter 1894. 656) in speaking of the Structure of the Ependyma, states that in the brain of the rabbit, in the lateral ventricles, it is composed of three layers, Viz: 1. An Epithelial cell-layer, one cell deep, of columnar or cubical cells with a beaded or striated border; 2. a "fine subepithelial intrinsic plexus" formed by the interlacing of one stout basal process & several radiating fine fibrils which are given off from each cell; and, 3, a
"stratum of Stellate fibre-cells", which are coarser & more irregular in their processes than the ordinary stellate cell; beyond these we get into the extra-or sub-ependymal region. We have not succeeded in making out these strata so definitely, though we have frequently seen conditions closely akin to them in the human brain.

In the brain of the frog the lateral ventricles shew a single layer of cells with long nuclei resting on a mass of nerve cells; there is no definite intervening layer. The cells have short processes; & occasionally appear two or three deep. In places the neuroglia shews straight fibrils running from the Epithelial layer.

We frequently see in the ependyma of the lateral ventricles a condition which we have termed the "ependymal convolution"; it is often very distinct in this situation in the human brain. It will be fully described when we consider the 4th ventricle. Gland-like tubes are often seen; these are involutions of the Ependyma lined by Epithelial cells of a distinctly glandular character. They are often associated with the "convolution" just mentioned. Whether they have actually any glandular function, or whether they are rudiments or accidental conditions, it is impossible at present to say.

The invaginations of the choroid plexuses are covered with an epithelial layer which they have pushed in before them. According to Kölliker (4.289) this epithelium is of simple pavement type, and in the mammalia, as also in the frog, is ciliated. Foster (8. paragraph 694) says that the
cells over the plexus are cubical, and often irregular in form. In all the sections, shewing the choroid plexus, that we have examined, the epithelial cells were cubic in shape, with distinct well-marked nuclei, and were decidedly granular.

So far as we know the Epithelium covers every part of the lateral ventricles and is continuous with that in the 3rd. ventricle through the foramina of Monro. The septum lucidum is also any trace of it, nor should we expect it, in the 5th. ventricle.

Third ventricle. According to Quain (2 Vol. 98), it is lined by ciliated Epithelium "which is thin and flattened over the roof", but is "longer and more columnar at the bottom and sides". "The lateral walls of the ventricle have but a thin covering of neuroglia - Ependyme - underneath the lining Epithelium, so that the white covering of the thalami comes to view through it" (2 Vol. 98). Here also, the Epithelium covers all the inequalities of the choroid plexus. In our experience the Ependyme is more defined in this situation than in the lateral ventricles; the Epithelial cells are, however, much the same in character.

In the brain of the frog this ventricle is represented by a slit, which is lined by a layer of elongated cells which send out long tailed processes into the subjacent tissue - see micro-sketch 5.

In the rabbit, the ventricle is lined by Epithelium, usually in one layer, sometimes in two or more; the Epithelial nuclei are large, oval or rounded in shape, and
granular. In places a fairly distinct subepithelial reticulum, with comparatively few nuclei and apparently no vessels, can be seen.

In the 3rd. ventricle of the pigeon there is a single layer of cubical cells, resting on a distinct subepithelial reticulum with few nuclei and occasional blood vessels. The processes of the epithelial cells are distinctly visible in places.

In the 3rd. ventricle, as in the lateral ventricles, the flattened expanse of surface seems to indicate the more cubical & flattened appearance of the epithelial cells.

Iter or aqueduct of Sylvius. According to Quain (2.Vol 3.96) this is lined by ciliated columnar epithelium; the attached ends of the epithelial cells extending as "radiating ependymal fibres through the thickness of the mid-brain to reach the surface, at least this can be seen to be so in the embryo and in small Vertebrates; and is probably also true for all".

In the frog, the iter is lined by a single layer of cells which send out long processes through the subjacent neuroglia; some of these processes were traced for a distance of 300 micromillimetres. See photomicrographs 1 and 2, which shew the epithelial cells & their tails very distinctly.

In the iter of the rabbit there are one or more layers of epithelial cells, the cells being crowded together; the nuclei are oval and granular, and of large
size. In places there is a thin reticulum below the Epithelium, with cells very similar to epithelial cells. Some of the epithelial cells show distinct tails.

In the floor of the iter there are considerable members of cells in the general neuroglia, they appear to be of epithelial origin.

In the pigeon the iter is lined by a single layer of Epithelium which is flattened and not at all columnar, and rests on a reticular bed with few nuclei and apparently no vessels. A large papilla with a mass of cells, apparently epithelial, and surrounded by a reticular network occupies the floor of the iter. Below this papilla there is a line of blood vessels.

In the fish, the iter or mesocoel shows, in its roof, cells several deep, crowded together and giving off distinct processes into a pale fibrillary stratum with few nuclei and no vessels; and at the sides, cells one or more layers deep, without any definite reticular stratum.

There cannot be said to be a well defined ependyma in the fish.

In a very young kitten - about 2 days old - the iter showed several layers of cells, except at one part, where there were well-marked "convolutions" which were covered usually by a single layer of long columnar cells. The epithelial nuclei were large, and rounded or elongated. A subepithelial reticular stratum was present; it was best marked under the "convolutions". The iter of the Kitten is well shown in micro-sketches 3 and 4; in these
drawings the ependymal convolutions are very distinct.

Optic ventricles. We may briefly refer here to these. In the frog they are lined by cells three or four layers deep; many of the cells shew short tails. In the eel, no distinct ependyma was seen; there were layers of round nuclei in places. In the whiting, a single layer of somewhat cubical cells was seen in places, in others a dense fibrous wavy layer.

Fourth ventricle. Landois and Stirling (7, 1015) state that it is lined by a layer of columnar epithelium. Foster (8, paragraph 610) says the true grey matter of the 4th. ventricle is covered by a superficial layer of tissue of a peculiar nature, similar to that which is found at the hind end of the conus medullaris in the spinal cord; and again (8, 694), the roof is "reduced to a single layer of non-nervous columnar epithelium which appears as a mere lining to the pia-mater overlying it". Moxon (37, vol. 1, 1881, 527) describes the cells in the 4th ventricle as being thick close-set cells of irregular cubical shape and very conspicuous. As we shall see presently the cells vary in type in different parts of the ventricle.

In the 4th ventricle of the eel, there are one or more layers of epithelial cells somewhat irregularly arranged, with a tendency in places to a bead-like or columnar arrangement. The cells give off coarse, thick, processes. At the bottom of the ventricle thick ribbon-like processes can be seen coming off into the central raphe. The actual extent of the ependyma is very doubtful; there
seem to be occasional blood vessels in it. There are numerous nuclei in what appears to be the subependymal region. In the whiting, the epithelial cells are elongated and have distinct and long processes which extend into a fibrous layer with fairly numerous nuclei. As in the codfish, the limit of the ependyma is not defined.

In the pigeon the 4th ventricle is lined by a single layer of cells. Along the sides of the ventricle the cells with their nuclei are flattened, while at the bottom of the central furrow the cells are more columnar with rounded granular nuclei. Over the central raphe there is a little papilla of large columnar cells in several layers, these cells have large oval granular nuclei, which lie near the fixed end of the cell. These columnar cells shew a marked contrast to the other epithelial cells. The subepithelial layer is reticular, with few nuclei; its limit is doubtful.

The 4th ventricle of the rabbit is lined by an undulating epithelial layer, usually of a single row of cells, sometimes two or three deep, resting on a clear reticular basis with a denser layer underneath. The epithelial cells are columnar in some places, in others they are more cubical or flattened. The ependyma is not defined, and no ependymal "convolutions" were seen.

In the kitten, the lower part of the ventricle shews a single layer of elongated cells apparently with short tails, the nuclei being towards the lower end of the cell; the subepithelial neuroglia is
narrow, coarse, & has few nuclei. In the upper part of the ventricle there is a single layer of columnar epithelium - occasionally two cells deep apparently - with rounded or elongated nuclei, and a clear band along the free end of the cells; the subepithelial neuroglia is reticular and shews a few large nuclei. Some of the epithelial cells appear tailed, and there are apparently well-marked cilia. The ependymal convolutions are very distinct on the lateral aspects of the ventricle. See micro-sketch 2.

In the 4th ventricle of the frog there is a single layer of cells with large oval nuclei; the nuclei are granular and fill the greater part of the end cell. Some of the cells are tailed, the tails being very long and appearing to end in an open meshwork. A narrow reticulum appears to underlie the cells; the extent of this is not very definite however.

Human brain. In sections from the brain of a newly-born child, the 4th ventricle shews a regularly-set columnar epithelium, with large, rounded or oval, granular nuclei, which lie at different levels; some of the cells shew tailed processes. Between the epithelium and what is apparently the region of the subependyma a thin reticulum can be seen to be forming. Where it is most developed, this reticulum shews few nuclei; in other places, however there is a layer of nuclei, very like those of the epithelium, with processes stretching across to the epithelial cells, from which they would appear to have originated. The blood vessels keep to the line of
the subependyma. There are involutions of the epithelium in the central furrow, and on the lateral aspects of the ventricle ependymal convolutions may be seen; the latter shew a large number of these subepithelial nuclei.

In the adult brain the ependyma of the 4th ventricle is usually very well defined. It is deepest in the narrower parts of the ventricle, and where the ventricular surface broadens out it becomes narrower.

The epithelial cells are elongated and distinctly columnar in the neighbourhood of the calamus, and generally along the sides of the central furrow; their nuclei being usually oval. In the expanded portions of the ventricle, on the other hand, the cells of the epithelium are cubical and flattened, their nuclei at the same time becoming rounded or even somewhat flat; this is well seen in sections of the ventricle which include the lateral recesses. We have never seen cilia on these epithelial cells. The subepithelial stratum is composed of a reticular and granular material, the result of the interlacement of fine fibrils, the granules evidently being the cut ends of these fibrils. The nuclei in this region are few; they stain deeply, and shew very little or no surrounding cell substance; they seem to be intimately associated with the fibrils. So far as our experience goes there would seem to be no blood vessels in this reticular layer; occasionally they do occur, but it seems to be the exception. At the point where the
ependyma seems to be continuous with the general neuroglia of the medulla and pons, there is usually a distinct line of blood vessels - the condition is well seen in sections where the vessel walls are much thickened - and this regularity of occurrence would seem to favour the view that the presence of vessels in the ependyma itself in either accidental or pathological.

Sections of blocks of tissue fixed in formal shew minute capillaries exceedingly well; but though they - the vessels - were plentiful enough in the brain substance below the ependyma, the latter shewed them but rarely, and even they there were pathological conditions present. The neuroglia abutting on the ependyma, in what we have termed the "subependyma" for convenience, is somewhat denser than the reticular layer and shews more nuclei; blood vessels also, as stated above, are very distinct. In the 4th. ventricle the ependyma is not even in contour, but undulates more or less. In addition to these general undulations, which are not very striking, there is a condition, which we have termed the "ependymal convolution," which is very distinct and persistent. It consists of a number of well marked foldings usually two, three, or more, together. At first the condition was thought to be a pathological one, especially as some strands of fibrous tissue were seen near the folds in a section from the lateral ventricle; the frequency of their occurrence, however, their general structure, and the fact that they are
usually seen in one part only of the 4th. ventricle, as well as under conditions which cannot be looked on as pathological, warrants the conclusion that they are part of the normal structure of the ependyma.

With the exception of the fact that Woodhead (16.393) states, in describing the Medulla in a case of epilepsy, that the ependyma is "thrown into a series of folds, which are well supplied with blood", and again that the "epithelium is intact, and there is simply a slight exaggeration of the normal folding", we have been unable to find any reference to foldings on the surface of the ventricle. Whether Woodhead refers to the condition we are considering, or to some slight exaggeration of the ordinary undulating of the ependyma, it is impossible to say, as he does not explain himself further, nor does he shew any drawings. We are inclined to think he means the latter, as we have once or twice seen some slight folding of the ventricular surface, in association with blood vessels, which has no connection whatever with these "convolutions". These foldings on the lateral aspects of the upper half of the 4th. ventricle, where the ventricle surface begins to narrow towards the iter.

They occur in the curves or recesses where the ependyma bends round to form the roof of the ventricle. They are sometimes seen in the wall of the iter, and are frequent in the lateral ventricles. They are well shewn in sketches (3 and 4) of the iter of the kitten; we have seen them in the 4th. ventricle of a newly born child.
Their structure is that of the ependyma generally, with the exception that they frequently have one distinct blood vessel; they are bounded by a distinct layer of epithelium, which usually stains deeply and is well defined in the sulci between the folds. The convolutions may be rounded or squarish, and in pathological conditions are often seen grown over and united together by coarse masses of fibrous tissue. Very frequently mosaics of surface epithelium may be seen when they have been cut rather obliquely. We have termed them "ependymal convolutions" from the similarity which they bear in their most perfect condition to the convolutions of the cortex; this, of course, refers only to general appearances and not to any structural elements. They are illustrated in a number of micro-sketches from the iter, and the 4th. and lateral ventricles—see sketches 2, 3, 4, 8, 9, 10, and photomicrographs 4 & 5.

Spinal cord. In the cord the central canal—the permanent remains of the epiblastic canal, from which the former is developed—is lined by epithelium resting on a basis of neuroglia. Kölliker (4.219) termed this basis the "central ependymatic filament." It is, perhaps, better described as the substitute—substantia gelatinosa centralis. The canal is more distinct in the lower vertebrata than in mammals; according to Quain (2. Vol. 1. 60) it gradually atrophies in the latter, until it is eventually converted into the rudimentary tube which is persistent during life. Obersteiner (3.186)
says that the canal is only rarely completely pervious in the human adult; though it is almost invariably so in the child and animals. Quain (2, Vol. 3, 19) says it is not unfrequently obliterated by detached cells. Gray (5, 644) and Kölliker (4, 223) both speak of the canal being frequently occluded. In our experience, the upper part in the human medulla oblongata is almost always either blocked up, or represented by a mass of epithelial cells and reticular tissue. According to Obersteiner (3, 186) the blocking is "due to overgrowth of the epithelium" which lines the canal "as well as, usually, of the epithelial cells scattered about in the substantia gelatinosa centralis, and the subepithelial connective tissue." See microsketch 38.

The canal is lined by a single layer of columnar epithelial cells in the adult; in young forms the cells may be two or three deep. The cells are said to be ciliated. Foster (8, Paragraph 565) doubts whether the "processes which may be seen projecting from the surfaces of the cells are really cilia". Gray (5, 644) says the cells are ciliated in the foetus; but that the cilia have disappeared in the adult. St Landois & Stirling (7, 895) hold the same view. Kölliker (4, 224) has seen the cilia in chromic acid preparations. Quain (2, Vol. 3, 19) says the epithelium is ciliated; that each cell is provided with a bunch of cilia at its lumen end.

The epithelial cells rest on, or are surrounded by an area, composed of a substance which in a fresh
condition, has a gelatinous appearance, and in the hardened state, a reticular structure. There is no true basement membrane. This area of neuroglia, or whatever it may be, is composed of fine interlacing fibrils with nuclei scattered here and there. Amongst the fibrils are rounded or oval nuclei very similar to the nuclei of the columnar epithelium; probably they are included or migrating epithelial cells. Foster (8,565) says the "attached bases of the epithelial cells are branched, or taper to a filament, and become continuous with the branched cells or fibres of the neuroglia below." Quain (2. Vol:3.19) says the fixed end of the cells is prolonged into the reticular substance, and there becomes lost to view. In the sections we have examined, this area, the substantia gelatinosa, is free, or nearly so, from nervous elements, and as a rule, has no blood vessels. Obersteiner (3.186) states that it contains "scattered connective tissue cells, and more or fewer angular cells which may well be derived from the epithelium".

In the codfish there is a rounded or elongated canal, bounded by an epithelium consisting of two or three layers of cells; the nuclei are rounded and granular, and placed near the fixed end of the cell. The cells, in places, shew long broad tails, which appear in some sections to be nucleated. Thick ribbon shaped fibres appear to leave some of the cells; they are most marked, and form a bunch, at one side of the canal. The presence of cilia on the cells is doubtful. The surrounding
neuroglia is fibrous with few nuclei.

In the pigeon, there is a rounded canal, surrounded by two or three layers of elongated cells with round or oval granular-looking nuclei, and embedded in a granular or reticular substance containing numerous granular nuclei.

There are apparently no blood vessels in this reticular area. The epithelial cells do not shew any processes. The scattered nuclei are very similar in structure to those of the epithelial cells.

See micro-sketch 6.

In the rabbit, the canal is in the form of an oval opening or a slit, and is bounded by a single layer of columnar epithelium, with rounded granular nuclei which occupy the greater part of the cell. The surrounding neuroglia is reticular, and fairly well nucleated. There is no definite limit to the ependyma.

See micro-sketch 7.

In sections from the cord of a newly born child we see an irregularly shaped canal, with rows of long palisade columnar cells two or three deep, with the nuclei frequently towards the lower end of the cell. In the tissue round the canal are a large number of nuclei very similar to those of the epithelium.

See micro-sketch 1.

Andriezen in an article on the pathology of Insanity (88. Winter, 1894. 656) in speaking of the Ependyma of the spinal cord of the kitten, says that it is composed of "a. epithelial cells about three deep generally, surrounding
the central canal. Some of these cells are "short and squat; others more attenuated, the attenuated spiny projections. These attenuated cells have the nuclei situated in the deeper—more globular—part. These cells also give off a thicker basal process, and finer & shorter basi-lateral processes". He also mentions transitional forms which are apparently "passing through the grades of the attenuated epithelial cell, and approaching the cells of the next layer", which he terms the "subepithelial stellate cells". These, he says, "stellate cells" he says "form circular strata surrounding the epithelial layer". These results were obtained by Golgi's silver method applied to the spinal cord of very young kittens. We have not yet obtained these results; sections, however, of the iter and 4th ventricle of a very young kitten, and of the spinal cord of a newly born child, stained with haematoxylin or alum-carmine, seem to point in the direction of these results.

So much for the structure of the ependyma; we have seen that it consists of essentially the same elements wherever it is found, the minor differences being due to peculiarities in the various parts of the brain where it occurs. We must now briefly consider its

C. ORIGIN.

The ependyma is derived from the epiblastic layer of the embryo. Quain says (2. Vol 57) "The whole structure of the central nervous system is laid down in epiblast, and consists in the main of more or less modified epiblastic elements, except where mesoblastic tissues subsequently
penetrate into it, conveying blood vessels into its substance." According to Andriezen (38. Dec 1894. 659) the "elements of the ependyma are wholly and entirely epiblastic."

The medullary groove along the dorsum of the embryo becomes thickened along its edges to form the medullary folds; these folds bend over towards each other, fuse together, and enclose what ultimately becomes the neural canal. This canal is lined by epiblast. The anterior end of the groove or canal becomes enlarged and exhibits a succession of medium dilations separated by slight constrictions; these dilatations become roofed in and form the cerebral vesicles; from these vesicles the brain is developed, their cavities remaining as the ventricles of the brain.

The lateral ventricles result from a pair of vesicles which spring from the sides of the anterior primary vesicle, the cavity of the latter remaining as the 3rd. ventricle. The middle vesicle has its cavity reduced in the development of the brain, to a narrow passage, the interior aqueduct, while the hinder vesicle produces the 4th. ventricle. The cavity of the neural canal itself eventually becomes the canal of the cord.

The lining membrane, therefore, of the cerebral vesicles and the neural canal, in other words, of the cerebral ventricles and the canal of the spinal cord, may be said to be epiblastic, that is, is composed of a tissue epithelial in nature, and consisting of irregularly columnar cells set closely side by side. Quain says.
(2. Vol. 1. 57) the walls of the canal are at first
"wholly composed of long columnar epithelium cells, whose
free borders, which are at first smooth, but later become
parallel, line the cavity, and whose attached extremities
rest upon a homogenous limiting membrane which early makes
its appearance, bounding the embryonic cord and separating
it from the surrounding structures. These columnar cells,
therefore, at first extend through the whole thickness of
the embryonic cord, and they have the closely set palisade-
like character, with the nuclei at different depths, such
as it is usual to find in long columnar epithelium".

According to Andriezen (3 Winter 1894. 659) the tails
of the epithelial cells may reach, as seen in the chick
embryo, to the pial surface of the cord; these pia-epend-
ymal cells give rise to the stellate fibre-cell of the
supporting framework. He says "certain of the epithelial
cells move or migrate to the deeper part of the
epithelial layer, the nucleus & main cell protoplasm
retreating downwards. As this happens, the attenuated
process which still reaches the free surface thins and
eventually atrophies, while pari passu the basilar fibrils
grow out and elongate laterally. Finally the primitive
surface process and the thick long basilar process both
thin down and atrophy, while the other fibrils grow out,
and the cell now assumes the elongated stellate shape."
The interlacing of the branches of these primitive cells,
or spongioblasts, forms a network—the myelospongium of His—and this network would seem to give rise to the general
neuroglia of the brain as well as to the reticular portion of the Ependyma, and indicates a the epiblastic origin of both. Since the subepithelial layer of the ependyma seems to be closely related to the general neuroglia, it behoves us to consider briefly the structure of the latter. As we have already seen it most probably originates from the primitive imagined neural epithelium, from the spongioblasts of His. There has been much dispute regarding its structure. Kölliker (1,270) thought it was derived, along with connective tissue septa, from the mesoderm surrounding the embryonic nervous system, a network, in fact, formed by the anastomosis of branched processes of connective tissue corpuscles. It has been suggested (35. Vol. 1. 764) that the fibrous plexus is elastic tissue, while the cells are connective tissue cells modified. Some (1,149) look on it as of the same nature as the intercellular substance of an epithelium, & the cells in it are considered to be analogous with the branched migratory cells which are sometimes found in the intercellular substance of an epithelium. Obersteiner (3,149) considers it to be a "connective tissue in which the intercellular substance is reduced to a minimum;" it forms a "close network of fine fibres which can be followed to connective tissue cells;" "proper cell protoplasm is usually wanting"; "the cell body is only represented by flat appendages of the nucleus," "which soon resolve themselves into cell processes." The connective tissue (3,152) & "supporting the epithelium of the ventricles seems
to be peculiar in the following respect:—the mass of fibres present in the ependyma suggests the conclusion that these fibres are not only the direct processes of its connective tissue cells, but also the products of its intercellular substance." Foster (8.563) looks on the neuroglia as composed of excessively branching cells with very small cell bodies, the cells and fibres being embedded in a homogeneous ground substance. He considers it to be of epiblastic origin. He says (8.565) the "neuroglia elements are transformed epithelial cells; and the continuity of the cells, which retaining the characters of epithelial cells, form a lining to be the canal, with the cells which have become branched & lost their epithelial characters, indicates the epithelial origin of the latter." Quain (2.Vol.1.322) says the neuroglia is not of the nature of connective tissue; that it is composed of greatly ramified cells; and that, in addition to these "stellate neuroglia cells", a further support is afforded to some parts by the ramified prolongations of the ciliated epithelial cells which line the central canal of the cord.

According to recent researches it would appear that there are two distinct elements in the neuroglia; the first of epiblastic origin, forms the true supporting framework of the brain; the 2nd. of mesoblastic origin comes in with the blood vessels during development, forms the so-called lymph-connective system, and only acts secondarily as a supporting agent. Andriezen (36.July 1893.227)
describes the cells of the first type as "neuroglia fibre cells", which form a "plexus system of well organised fibres" acting as a "passive supporting feltwork in the brain". The cells of the second type he terms "protoplasmic glia cells"; they constitute a "group of active protoplasmic elements present in abundance only in the grey matter, and having vascular and lymphatic relations of a striking character, and one which points to their active rôle in the circulatory and lymphatic economy of the brain". The morbid hypertrophy of the 2nd. type forms the "spider cell".

Bevan Lewis (24.78) describes two forms of neuroglia cells visible in fresh sections of cortex cerebri stained with aniline-blue-black. He says "a still further modification is found on the free surface of the cortex, immediately beneath the pia, where the branching cell fulfils the function of a flattened epithelial investment; whilst the surfaces not exposed to pressure, as the central canal of the cord, shew us the element as a columnar epithelium". E. Lewis evidently looks on the neuroglia cells as modifications of original epithelial or epithelial cells.

We may, therefore, in the light of present knowledge, consider the neuroglia as being made up of elements derived from two sources, the one epiblastic—derived from the epithelium through the myelospongium—and the other mesoblastic, brought in by invading blood vessels.

This brings us to the consideration of a point which has been already referred to, viz.: the structure of the recticular or subepithelial layer of the meninges. It was necessary that the structure of
the general neuroglia should be inquired into, as well as the origin of the ependyma, before proceeding to this.

We are inclined to look on this layer as being composed entirely of a fine fibrillary tissue produced by the ramifications and interlacings of the basal processes of the epithelial cells, and in the normal condition to be devoid of any of the mesoblastic elements of the general neuroglia; in other words to be closely allied to, if not a remnant of, the primitive myelospongium of the embryo.

Our reasons for this conclusion are as follow:-

1. The demarcation of the ependyma. In the adult human brain, and in some of the higher vertebrates, the ependyma is usually fairly defined, and is frequently sharply marked off from the rest of the brain tissue; this is usually very well seen in the floor of the 4th ventricle, and forms a distinct layer. This definition is shewn by:

   A. A frequent difference in the depth of staining, which probably means a difference in the texture of the subepithelial reticulum as compared with the general neuroglia.

   B. The presence of a line of blood vessels of varying size along the margin of what appears to be the brain tissue proper.

   C. The existence of a large number of nuclei in the same region as the line of vessels, the subependyma of this thesis.

2. The presence of the Epithelial tails. These basal processes pass into the fibrillary layer and there
become lost to view. We have repeatedly seen them in the human brain breaking up in the reticulum. Quain (2. Vol. 3. 97) says the ependymal fibres "often branch dichotomously, besides possessing many small lateral off-ssets."

3. The scarcity of nuclei are comparatively very few; when contrasted with the general brain neuroglia, the difference is very marked. The nuclei are usually of the small and deeply stained type.

4. The absence of blood vessels. Vessels seem to be absent from the ependyma in normal condition; at least this is so in the human brain. In the brain and cord of the codfish they may be seen very close to the epithelium, but here the demarcation of the ependyma is so indefinite, and it is so difficult to fix its limit it must essentially be very narrow that it is impossible to say whether the vessels are ependymal or subependymal. In the pigeon and rabbit a vessel may sometimes be seen very close to the epithelium, but it is exceptional.

5. The results of impregnation with nitrate of silver, Golgi's methods, already discussed. We have not yet been able to get satisfactory results. See 38. Winter 1894. 656.

6. Pathological conditions. Increase of the subependymal nuclei and their apparent migration, the subepithelial reticulum remaining quite passive. These will be described in detail in the next section. We come now to:

D. PHYSIOLOGICAL SIGNIFICANCE.
The physiology of the ependyma may be said to be at present purely speculative. Nothing definite seems to be known.

The hypotheses of Gaskell and Bland Sutton (38. Winter 1894. 656) (36. 1894. Vol 1. 57) make the ventricles of the brain the remnant of a prevertebrate cephalic stomach and alimentary canal. Andriezen (same references) opposes these hypotheses, and suggests the possibility of the ventricles having some relation to a water-vascular system, and being of use in the early life of the brain as a means of carrying nourishment and removing effete matter, before the blood vessels are developed. He says (38. 656) "The obscure and little known ependyma was a fruitful ghost to conjure with, till the investigation of its structure and our real knowledge of it by the use of Golgi’s method, and its phylogenetic significance as a water vascular tube permeating the central nervous axis in ancestral and acraniate vertebrata, have combined to assure us of its significance, as one far different from the invertebrate gut hypothesis."

Andriezen carried out experiments on amphioxus, ammocoetes and other animal forms, and shewed, by means of carmine particles suspended in the water in which they were, that there was a communication, through the pituitary body, between the buccal cavity and the cerebral ventricular cavity. After an exposure to the carmine of an hour and a half fine particles were found lining the ventricle; after a longer exposure, they could be traced into the
central canal of the cord. He says (36. Vol. 1. 1894. 55) "It was then obvious that there was a raison d'être for the buccal ventricular duct where the stream of water entered, for the ciliated epithelium of the central nervous cavities, which propelled this stream, and for the neurenteric aperture which formed the outlet for the exit of the water current after its passage through the central nervous system." And again "the duct portion of the pituitary was then the inlet of a water vascular stream which brought in oxygen to the central nervous system; while similarly the neurenteric canal, which opened into the exterior posteriorly, served as the outlet to carry away the waste products by means of the outgoing water-vascular current in ancestral vertebrata." He further looks on the pituitary body as partially a secreting structure, which pours some secretion into the water as it journeys through into the ventricular cavities of the brain. He does not state whether the epithelial cells, which line the ventricular cavities, have any secretary function, or whether he considers them merely passive supporters of the cilia which cause the onward flow of the fluid through the cavities.

We think his theory, so far as we understand it, fails to account physiologically for the presence of the ependyma lining the cerebro-spinal cavities, though its application to the function of the pituitary body seems very plausible.

Quain (1.40) remarks on the resemblance of the epithelial cells to nerve-epithelia in the lower
invertebrates. Possibly the long tails to the epithelial cells, in the iter of the frog for example, disappearing into the brain substance might suggest this; we have never been able to trace these fibres to nerve cells. Obersteiner says (3,148) "An unconditional inclusion of the epithelial cells amongst the nervous elements is at any rate premature."

If the Ependyma is anything more than a developmental remnant, its most probable function would seem to be that of secretion. In young mammalian forms, as the kitten, and in the lower vertebrates, the cells in the ependyma are frequently two, three, or more, layers deep; this would seem to point to some special function, and to be the possibility of the outer cells being cast off and new ones developed from below. Obersteiner (3,148) states that this renewal of cells does occur. We know also that the ependyma in man does undergo changes in character after childhood. The conclusion seems to be that the ependyma, in conjunction with the cells of the choroid plexuses, has to do with the secretion or excretion of the cerebrospinal fluid. Bruce (30.169 & 171. Anatomy of Brain) states that the choroid plexuses are duplications of the pia into the ventricles, and are covered externally by a layer of granular cubical cells, and that the fluid in the interior of the brain is secreted by the epithelium of these plexuses, which project into the lateral, third and fourth ventricles, and possibly also from the general epithelial linings of these cavities. Foster (8.694) says that the cell substance of the cells of the choroid plexuses is
loaded with granules, some of which are pigmentary; and that the cells "have very much the appearance of active secreting cells."

On examining sections showing the choroid plexus, we see an undoubted resemblance in the cells covering it, to secreting cells in other parts of the organism, as well as a definite blood supply; but a difficulty confronts us when we come to the cells of the Ependyma. If the latter are ciliated it is probable that they have to do with the outward movement of fluid; this may be the case in young forms, in adults the presence of cilia is questionable, however.

The "convolutions" already discussed in the floor of the 4th ventricle and elsewhere, would seem to point to an increase in the superficial area of the ependyma for some reason; this increase would undoubtedly be of more use for secretory purposes, than for either protection or ciliary motion. The great resemblance of some of the nuclei bounding these folds and of occasional involutions of the epithelium to gland tubes, and of the epithelial cells in them to gland cells, seems to point in the direction of a secretory function having, at all events at some period in the history of the organism, been associated with them. We must not forget the fact that these convolutions are very frequently supplied with a blood vessel. Andriezen (38 Winter 2894, 661) raises a very interesting point. He states that vasomotor nerve fibrils seem to cease in the vessels in the pia, and that similar plexuses have been found surrounding and getting distributed to vessels in the choroid plexus, and also some
fibrils to the epithelium of the choroid plexus. He asks whether these choroid cells are "of the nature of secreting cells"; and if so, whether the fibres are "the endings of secretory nerves distributed to these cells in company with the vascular nerve?"

For the present we can only say that the evidence is in favour of the ependy whole having, at all events in early mammalian life and in lower vertebrates, something to do with the secretory and excretory economy of the brain, and not of its being simply a developmental remnant. In the adult mammal its function may be ended, it may be merely an inert and passive stratum, in which case it will help to form a protective covering to the structures beneath it.

**CONCLUSION.**

In concluding this section of the thesis we may say that we have endeavoured to give, as concisely as possible, the various views that have been put forth, from time to time, by different observers, regarding the Anatomy and Physiology of the Ependy whole, as well as the results of our own observations on the same structure.

We have laid special stress on the non-vascularity of the ependy whole; on the presence of the ependymal folds or convolutions ; and on the epiblastic origin of the ependymal layer.

Much however, still remains to be done, before it can be said that the mysteries of the ependy whole are solved, and its structure and functions are fully understood.

End of Section 1.