has no difficulty in recognising the results of irritation, and owing to the nature of the experiment and the distribution of the lesions the reaction cannot be otherwise than due to lymphogenous toxicity. The lesions must map out the course of the toxic lymph, and therefore pathology teaches us, in this instance, the path of lymph-flow in nerves.

But we are inclined to go one step further, and apply our results to the pathology of general paralysis of the insane, in which the irritative vascular phenomena and those of the supporting tissues of the brain are a constant, marked, and progressive feature. Just as in this series of experiments, so in general paralysis of the insane the adventitial lymph-space infiltration, composed of proliferated adventitial cells and plasma-cells, is one of the most striking histological findings. Clinical and pathological investigations point clearly to the fact that general paralysis of the insane is a toxi-infective encephalitis of a subacute or chronic nature, and the changes found are not comparable to those seen in blood infection or intoxication. We suggest, therefore, that whatever may be the exciting agent in the causation of this disease, its primary and even its later effects are exerted *via* the lymph-channels connected with those of the central nervous system, and that absorption of toxins along nerves is worthy of attention.

Ependymal Alterations in General Paralysis. By HARVEY BAIRD, M.D.Edin., Senior Assistant Medical Officer, Cardiff City Mental Hospital.

A GRANULAR condition of the ventricular ependyma, especially that of the fourth ventricle, has long been recognised as one of the most important of the *post-mortem* lesions of general paralysis. In the opinion of the writer it is present in at least 90 *per cent.* of the cases, and the more carefully the examination of the ependyma is made, the greater will be the percentage of cases showing granulation in asylum *post-mortem* books. In the *Journal of Mental Science*, July, 1905, the writer (1) recorded the frequency of this condition in an analysis of 131 consecutive *post-mortems* on male paralytics at Wakefield

https://doi.org/10.1192/bjp.56.232.89 Published online by Cambridge University Press

Asylum, and on 112 male and 19 female cases at Horton Asylum. The percentages were 87·8, 90, and 100 respectively. Blatchford (2) (*Journal of Mental Science*, 1903, p. 483) states 70 *per cent.* of paralytics were recorded as exhibiting granular ependyma, and of the non-paralytic deaths 16·6 *per cent.* of men and 5·3 *per cent.* of women. There were 83 paralytic deaths and 369 non-paralytic. The writer is convinced that granularity of the ependyma, especially that of the fourth ventricle, is the most valuable naked-eye diagnostic sign of general paralysis. This statement is supported by that of Bolton (3), who considers the most characteristic naked-eye sign of dementia paralytica to be granularity of the ventricular ependyma, referring specially to the lower half of the fourth ventricle.

Apart from general paralysis, granulations are stated to be met with occasionally in hydrocephalus, in dementia associated with senility or cardio-vascular degeneration, and in some coarse organic lesions. In the writer's opinion one is most likely to meet the condition in cases of progressive senile dementia. In the dementia cases the lateral ventricle more frequently and more prominently exhibits the condition. The writer has, however, observed in the case of a woman, æt. 73, well-marked granulations down to the calamus scriptorius.

Admitting, then, the frequency and importance of the lesion, its nature of formation may be discussed. It is somewhat strange that, considering the vast amount of work in connection with general paralysis, comparatively little attention has been paid to this condition. Thus no mention is made of it in Bevan Lewis's (4) text-book, which devotes much space to the pathology of general paralysis, and only a few lines in the portion of the recent atlas of Nissl and Alzheimer (5) dealing with the histo-pathology of the disease. Ernest Jones (6), in a recent address on the pathology of general paralysis, makes no mention of the ependyma. It is also curious that, notwithstanding the enormous amount of attention given to the examination of the cerebro-spinal fluid, little should be said of the cells lining the cavities in which much of that fluid lies.

Various opinions have been given as to the nature of granular ependyma. Beadles (7) (*Journal of Mental Science*, vol. xli, p. 32), assumes as irritant causes degeneration and proliferation of epithelium, probably causing downgrowths. Then

connective tissue from the neuroglia and the outermost coats of the vessels undergoes active increase, causing wart-like growths on the surface. Pelizzi (8) (*Rivista Sperimentale di Freniatria*, 1896, p. 496) says the granulations are essentially composed of proliferated neuroglia, and surface epithelium plays no part in their formation. Weigert says the granulations are due to the loss of the resistance of the normal epithelium checking the growth of the neuroglia. Bolton thinks that the cholin and nucleoproteid in cerebro-spinal fluid cause an irritative overgrowth, and also that syphilis may play a part. Dagonet (9) ("La Neuroglie dans la Générale," *Soc. Clin. Med. Ment.*, June, 1908) states that the granulations are thickened tufts of neuroglial fibres, which project into the spaces of the cavities, but states that some of the ependymal fibres may play a part in their formation.

Ford-Robertson (10) states that the ependymal granulations are neuroglial, though submitting elsewhere (11) that the granulations in the pia-arachnoid are epithelial.

Before committing one's self to an opinion as to the formation of granulations, a description may be given of the appearance of sections of cases in all stages, from that of normal to that of marked "frosted-glass" granulations. Twenty cases were taken. The stains principally used were Nissl's blue, hæmatoxylin, and Weigert's neuroglia stain.

Normally, the ventricular aspect of the medulla is covered by a layer of epithelium, cubical or cylindrical in shape, the nucleus staining deeply with Nissl's blue, the body of the cell fairly deeply. Underneath the epithelium is a layer containing few nuclei, and consisting mainly of fibres running parallel to the surface. The thickness of this layer varies; it is usually more evident towards the middle line. Thirdly, one comes upon many more nuclei, deeply stained, and the cell-body sometimes showing. This is continuous with the general structure of the medulla, but the cells proliferate to such an extent in some cases that it may be called a layer. In the lateral ventricle it is a distinct thin layer over the grey matter. The principal feature to bear in mind is that there is first epithelium, next a layer with very few cells, then a considerable number of cells.

When the ependyma appears granular to the naked eye many differencies appear on section, and in the slighter cases

especially similar naked-eye appearances may be the result of dissimilar microscopic alterations.

(1) Firstly, there may be simple proliferation of the surface-cells, with no downgrowths. There may be seven or eight layers of epithelial cells, those on the surface being dead. This condition alone is rare in the medulla in general paralysis; it is usually accompanied by downgrowths or by budding-out granulations, but in senile dementia there may be simple proliferation only, and in the lateral ventricle in general paralysis. The writer has also noted this epithelial proliferation in a case of melancholia dying of phthisis, but in which there had been syphilis.

(2) There may be invaginations or foldings, giving a wavy or convoluted aspect to the surface, accompanied by very slight or almost no epithelial proliferation. Deep invagination, with very slight epithelial proliferation, the writer has only seen in the lateral ventricle.

(3) Ingrowths, associated with localised proliferation of epithelial cells, are probably the commonest alterations seen in the slighter cases of granularity. A row of cells may grow directly downwards or in a slanting direction. Often at the end of the row is a distinct clump or cluster. On the other hand, a localised aggregation may be just beneath the surface. This later condition may also be observed in senile cases, and there may be no naked-eye evidence of granularity in such.

(4) Sometimes the surface-cells proliferate densely at places, and become more or less arranged in rows. The inner cells tend to have their long axes transverse before any fibres are laid down. At other places, instead of a dense row of cells only, it appears as if the original layer split into two rows, and enclosed between are cells with their long axes parallel to the surface, and with some fibre formation. Elsewhere this fibre formation is still more distinct, and the inner layer of cells, like those on the surface, may or may not persist. The result of this process is to produce a thick fibrous membrane, consisting of rows of cells and fibres parallel to the surface. The external layer of cubical cells may disappear.

(5) Distinct budding-out granulations may be the most evident alteration. The granulation is a projecting tuft which may be entirely covered with the usual surface epithelium, or only partially so, or not at all. Some show surface cells half

way up their sides. Probably trauma is responsible for the loss of the upper part. Occasionally the granulation has a pediculated aspect, and it may even at times resemble somewhat a figure of eight. The interior of the granulation consists of cells parallel to the surface and a few fibres. The cells are usually smaller than those just described in the fibrous membrane formation, and the fibres fewer. Sometimes the granulation appears to consist almost entirely of epithelial cells, arranged in whorls, and with scarcely any fibre formation. Just below the granulation is very frequently a cluster of epithelial cells of the same nature as the surface cells. Often the cluster is obviously the termination of a direct downgrowth from the epithelium on the surface, there being a continuous row of cells. Again, one often sees a big cluster at each side of the base of the granulation, and a row or two connecting the clusters. Frequently isolated clumps of epithelial cells which have grown inwards are arranged circularly, appearing like a transverse section of a gland, or like the central canal of the spinal cord. These clusters are also seen not connected with granulations. Often the in-grown cells form a distinct layer, which may extend the whole distance of the surface of the ventricle.

(6) Lastly, an advanced case, with great thickening, may be described. Here we find no cubical cells on the surface, but at once come upon an enormous number of flattened cells and fibres, all parallel to the surface, and arranged very uniformly. The thickness of the layer as a whole varies, being usually very marked centrally, and completely obliterating the V of the lower part of the medulla. The layer may consist of as many as forty rows of these cells. Next we come upon clusters and rows of cells like the original epithelium, and similar to the clusters the result of downgrowth, described previously. The clusters here are so numerous that they practically form a layer, though an irregular one both as regards depth from surface and arrangement. A cluster may be in the midst of the flat cells, but most of them are below. Next is the layer with few cells, which varies much in thickness. At places it may be as thick as the outside layer of flat cells, at others it is very thin. It is to be noted in all these sections that in whatever way the epithelium has altered, whether by forming budding-out granulations or a more

uniform thickened membrane, this layer with few cells is always underneath. The layer is itself certainly increased in thickness frequently.

From these remarks it is evident that one must conclude that in granular ependyma by far the main element is epithelial change. There is proliferation, downgrowth, cluster formation, the laying down by the outer cells of fibres and the cells becoming arranged in layers parallel to the surface. The presence of budding-out granulations or of a membrane thickened generally, depends probably on whether the epithelial change is localised or general. If localised the proliferating cells below shoot the granulation out. The view that the condition is due to ordinary neuroglial overgrowth seems to me untenable. Why should the neuroglia specially bud out beneath the ependyma, and not, say, on the surface of the cortex? In sections stained by Weigert's method one does not see the surface belt of neuroglia turning up into the granulation. Often one can demonstrate the two to be apart, *e.g.*, a row of epithelial cells may separate them. The fibres, however, if present in a granulation, can take on Weigert's stain. Hence the view may be held that these granulations consist of a kind of neuroglia, not formed by outgrowth from the ordinary neuroglia beneath, but, both neuroglia and ependyma being epiblastic, by the ependymal cells practically becoming neuroglia cells as they lay down fibres.

Another point to consider is the primary or secondary nature of the epithelial change. Probably the majority of observers have concluded that the epithelial proliferation is the result of irritative products in the cerebro-spinal fluid. The writer is inclined to believe the condition a primary one. If the lesion were confined to the surface, irritation from the fluid might cause overgrowth, but even that is doubtful. Warts on the hands, for instance, are not caused by external agencies. Further, the granular ependyma is evident, no matter how early the case. It appears more likely that the condition is one of those general proliferative changes which characterise general paralysis, *e.g.*, subdural false membrane formation. Again, these proliferated epithelial cells, many of them arranged like cells of glands, must have a secretion. This secretion probably alters the cerebro-spinal fluid. The secretion may be toxic. The neuroglial overgrowth may be

FIG. 1.

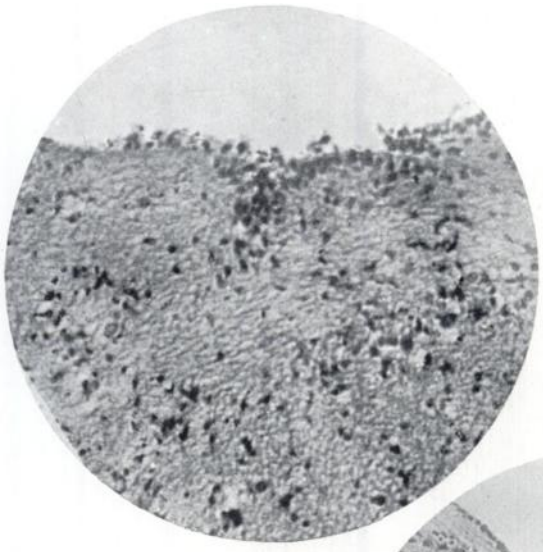


FIG. 2.

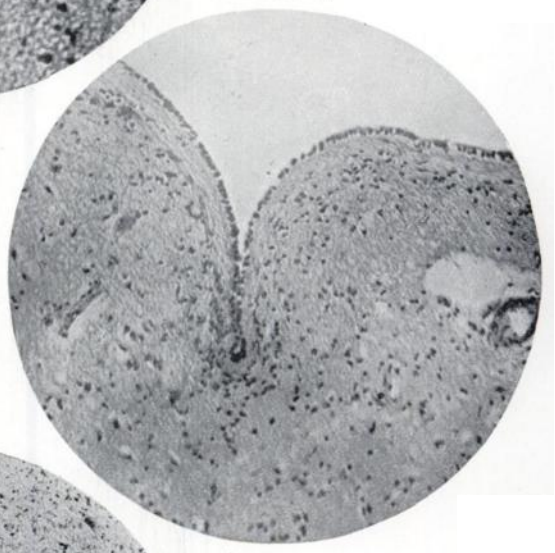
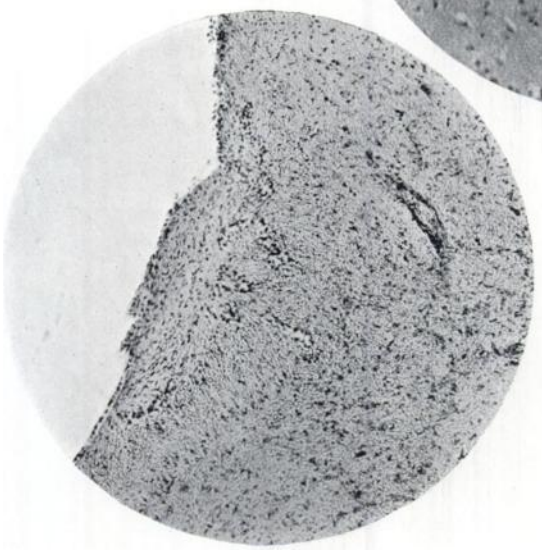


FIG. 3.



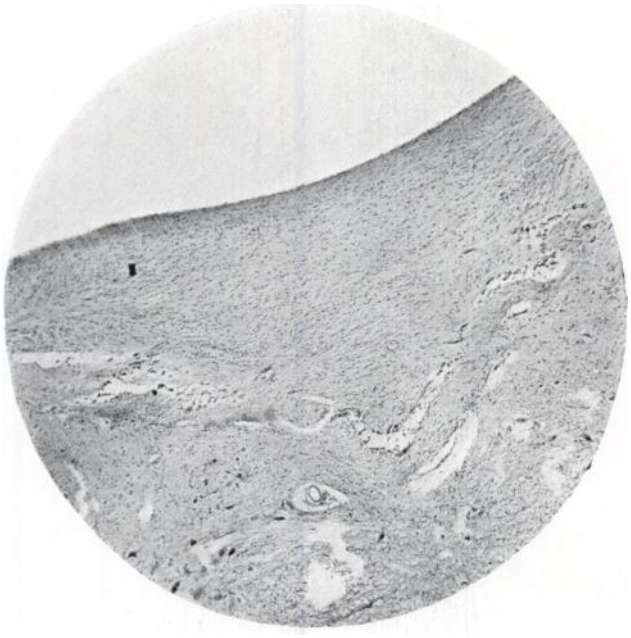
To illustrate Dr. Harvey Baird's paper.

Adlard & Son, Impr.

https://doi.org/10.1192/bjp.56.232.89 Published online by Cambridge University Press

FIG. 4.

FIG. 5.



To illustrate Dr. Harvey Baird's paper.

Adlard & Son, Impr.

https://doi.org/10.1192/bjp.56.232.89 Published online by Cambridge University Press

FIG. 6.

FIG. 7.

To illustrate Dr. Harvey Baird's paper.

Adlard & Son, Impr.

the result of this toxic secretion. There appears to the writer thus to be an analogy between cancer and general paralysis. The epithelial proliferation, ingrowth, and formation of clusters are suggestive, coupled with the progressively fatal course of both affections.

References.

(1) "Statistical Observations on General Paralysis," *Journal of Mental Science*, vol. li, p. 581.
(2) "Granular Ependyma in General Paralysis," *ibid.*, vol. xlix, p. 483.
(3) *Ibid.*, vol. liv, p. 40.
(4) *Text-Book of Mental Diseases*, pp. 548–575.
(5) *Histologische Studien zur Differenzial-diagnose der progressiven Paralyse von Alois Alzheimer*, 1904, p. 139.
(6) *Lancet*, No. 4 of vol. ii, 1909, p. 209.
(7) *Journal of Mental Science*, vol. xli, p. 42.
(8) *Rivista Sperimentale di Freniatria*, 1896, p. 496.
(9) "La Neuroglie dans la Générale," *Soc. Clin. Med. Ment.*, June, 1908.
(10) *Pathology of Mental Diseases*, p. 182.
(11) *Ibid.*, p. 125.

DESCRIPTION OF PLATES.

[For these micro-photographs I am indebted to my colleague, Mr. E. Barton White, who devoted much care to their preparation.]

FIG. 1.—An early stage. Note localised proliferation and downgrowth of epithelium.

FIG. 2.—An unusual deep downgrowth in lateral ventricle. Same section exhibits epithelial proliferation elsewhere.

FIG. 3.—Epithelium has grown in, forming a layer, below which the layer with few cells is well seen. Above, the appearance is as if a granulation had sunk in.

FIG. 4.—A granulation under high power. Note the epithelial cells beneath arranged in circular fashion, also clumps of cells showing line of ingrowth.

FIG. 5.—An advanced case, showing enormous epithelial overgrowth, with fibre formation, beneath which is layer of actively proliferating epithelial cells.

FIG. 6.—Another advanced case exhibiting three distinct layers: (1) Epithelial overgrowth with cells arranged parallel to surface; (2) cells actively proliferating; (3) pale layer well seen.

FIG. 7.—The same under high power. Note the acinous arrangement of epithelial cells.