*Observations on the Normal and Pathological Histology of the Choroid Plexuses of the Lateral Ventricles of the Brain.**

By JOHN WAINMAN FINDLAY, M.D., Pathologist to the Crichton Royal Institution, Dumfries.

I HAVE lately been engaged on a research into the normal and morbid histology of the choroid plexuses of the lateral ventricles.

This inquiry, begun at the suggestion of my colleague, Dr. Gilmour, would have failed but for Dr. Rutherford supplying necessary instruments, placing unlimited time at my disposal, and generally facilitating the work, in the course of which I examined microscopically the choroid plexuses in sixty-five cases. Of these fifty-nine were from the insane, and the remaining six were from patients dying in a general hospital, while for the further study of the normal structure I made preparations from several absolutely fresh choroid plexuses of the sheep, ox, and calf. Forty-nine of the plexuses from the insane were given me by Dr. Ford Robertson, to whom I am also indebted for much valuable help; while Dr. Sutherland, of the Glasgow Western Infirmary, kindly supplied me with the six plexuses from the sane. I also desire to express my thanks to Dr. John Reid of Milngavie for many practical hints in photo-micrography.

Some of the results attained I now have the pleasure of bringing before you, and shall pass in review a few of the more salient features in the anatomy and pathology of the choroid plexus. A demonstration of this nature, however, must necessarily be incomplete, and I shall be unable to do more than glance at the theories and opinions of those who have already made a study of this subject.

Normal Histology of the Choroid Plexus.—It is generally accepted that the choroid plexus is formed of pia mater, while the velum interpositum is composed of two layers of pia mater, between which arachnoidal tissue and blood-vessels are contained.

As the choroid plexuses are only fringes of the velum interpositum, one would expect to find arachnoidal tissue here also; but such is not described, the generally accepted view being that they are composed of pia mater alone.

Lately, however, Middlemass and Robertson have formu-

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lated the view that in the soft coverings of the brain two distinct membranes do not exist. They hold that there is essentially only one structure throughout, and therefore only one membrane, which they propose to call "pia-arachnoid."

To my mind, after an examination of Dr. Robertson's sections, this contention of the oneness of structure of the pia mater and arachnoid has been proved, and it seems to me that the basis of the choroid plexus consists essentially of the same structure as the pia-arachnoid covering the surface of the brain, and likewise resembles a spongy lymph sac.

The basis, then, of the choroid plexus is delicate white fibrous tissue. The white fibres are gathered together into bundles or trabeculæ of varying thickness and length. These bundles interlace with and cross over one another after the manner of a network, forming numerous spaces of all shapes and sizes. These spaces, inaccurately placed above and alongside of one another, form freely communicating cavities containing fluid, and are lined throughout by a single layer of flattened endothelial cells with large oval nuclei.

In the pia-arachnoid on the surface of the brain these spaces are largest in the centre of the membrane, where they form the so-called "subarachnoid spaces," or about the base of the brain the "arachnoid cisterns."

Much the same condition may be seen in the more central parts of the "glomus" of the choroid plexus—the fusiform swelling of the plexus regularly found at the junction of the body of the lateral ventricle with the descending horn,—where these cavities often attain a considerable size. (See Photograph I.) This might be taken as evidence that the choroid plexus consists of two distinct structures, viz. an external layer of pia mater and a central mass of arachnoidal tissue. Such, however, I cannot believe. It seems to me that, as in the case of the pia-arachnoid on the surface of the brain, there is only one structure throughout. Most marked in the centre of the "glomus," the spaces get smaller and smaller as we pass towards the surface, till it becomes difficult to make them out. But even here in many cases it is possible to do so, and at most these relatively dense portions of the plexus are nothing more than loose areolar tissue formations lying alongside distinct and easily recognised sinuses.

The choroid plexus is a very vascular structure, and has been described by some authors as an erectile or cavernous tissue. Appearances very suggestive of such a condition are seen, more especially in the glomus, but these are, I feel sure,

due to nothing more than the remarkable tortuosity of the veins and arteries. (See Photograph II.)

The surface of the plexus is beset with a large number of highly vascular villous projections. These are of all sizes, and the largest may branch and subdivide many times before the ultimate villi are formed. Each larger villus has an afferent artery and efferent vein, which open into a capillary network lying near the surface. In the smallest villi a capillary loop in the form of a bow may be seen close under the epithelium which everywhere covers the plexus. The greater part of the villus structure consists of epithelium and capillary, the smaller remainder being made up of homogeneous connective tissue, with a few oval, spindle, or ramifying cells.

The free surface of the villi is everywhere covered by an epithelium. This epithelium is described by all authors, with the exception of Luschka, as being composed of a single layer of cells. Luschka, however, has described this epithelium as approaching the stratified formation, recognising not only two or three layers of cells situated above one another, but also different developmental forms.

In many cases it can be demonstrated that only a single layer of cells is present, but then just as often three, four, or more layers of such cells may be seen, the two conditions lying alongside one another. Haeckel regards the latter condition as due to pathological proliferation, but such seems almost too common for a pathological change, being found in all my cases, in parts without exception, and likewise in the choroid plexuses of sheep, calves, and oxen examined.

The individual cells vary in size, ranging from ·01 to ·015 mm. They are irregularly rounded or polygonal in shape, and fit closely by means of delicate processes which interlock between neighbouring cells. In the deepest layer small and slender processes pass down from the angles of the cells into the subepithelial layer. It seems to me that this point is of great importance as tending to support the view that the choroid plexus epithelium is homologous with the ependymal epithelium, which has such processes even in adult life. The protoplasm of the epithelial cell is very granular, and contains a large spherical nucleus. In addition there is usually present in the protoplasm a clear yellowish, or even brownish-coloured highly refractive globule, sometimes approaching the dimension of the nucleus itself, but as a rule only attaining a half or a third of that size. By means of an oil immersion lens, however, it may be seen that the granular appearance of the

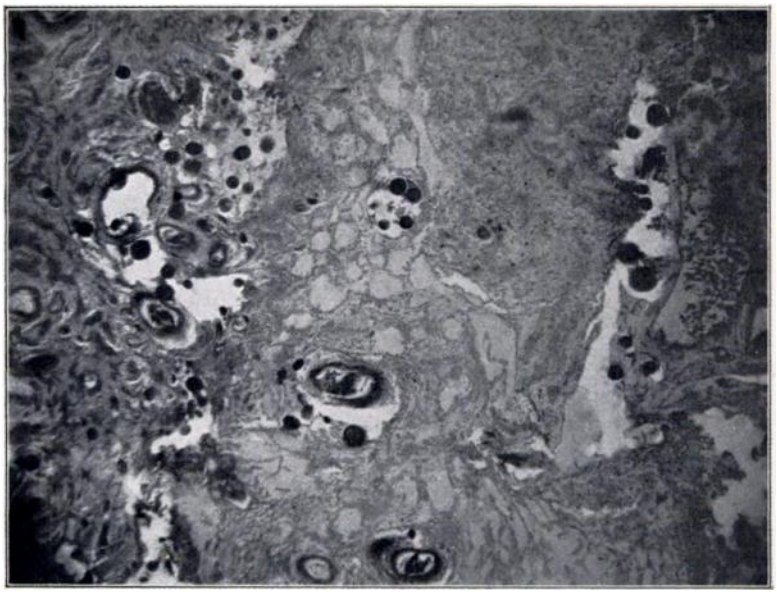

FIG. 1. Central part of glomus, showing large and distinct spaces. Puerperal Insanity. (× 26.)

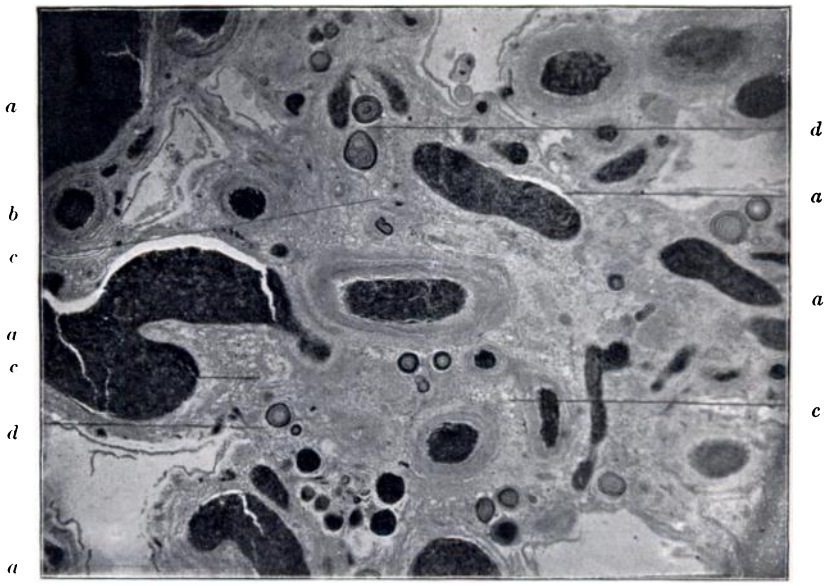

FIG. 2. Glomus showing usual distribution of veins. Alcoholic Insanity. (× 26.) *a*. Veins; *b*. Arteries; *c*. Open trabecular arrangement; *d*. Hyaline concentric bodies.

To illustrate Dr. FINDLAY'S Paper.

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protoplasm is in reality due to an immense number of small globules, which appear of the same nature as the single large one. Where there are several layers of cells *in situ* it may be made out that this vacuolation increases steadily as we pass to the free surface until cells are reached entirely transformed into globules, and showing no nuclear staining. Beyond this again the cells discharge their contents by breaking up, sometimes leaving an empty cell membrane to indicate where they have been. Before the cell actually breaks up the globules may run together to form a single large sphere. Drops and globules similar to those met with in the epithelial cells themselves may be demonstrated in the ventricular fluid. Probably, however, they do not remain as such for any length of time, but break down or become dissolved.

There is no doubt to my mind that the choroid plexus is an actively secreting structure, discharging its secretion into the ventricular cavity. This secretion is formed by a constant proliferation of the epithelial cells, which elaborate in their interiors peculiar mucin-like globules, and only seem capable of doing so once. The cell wall ultimately gives way, and these globules are discharged into the ventricular fluid. Such transformation and discharge is continually going on, and the outermost layers of epithelium are practically dead structures. They have fulfilled their purpose, and may be said to have died in doing it.

Pathological Histology of the Choroid Plexus.—Passing to consideration of pathological appearances met with in the choroid plexus, we take first the hyaline concentric bodies, which constitute a border-land between the normal and the abnormal. W. F. Robertson, who has investigated the origin and nature of these bodies in the dura mater and pia-arachnoid, is of opinion that they exist normally, but that they are found in a profusion in the insane that they are never met with in the mentally sound; and I may say that I am of like mind.

The usual form of these bodies is round, and as a rule each is surrounded by a well-marked hyaline capsule, or even a capsule of fibrous tissue. They are marked with concentric rings, these markings varying in intensity and number in individual bodies. The round is not the invariable shape: many different forms may be produced from several spheres coming together. Thus we may have dumb-bell, trefoil, or very irregularly shaped figures, the interior showing distinct concentric bodies with rings of their own, while beyond these

is a surrounding stratification common to the whole structure. Rod-shaped bodies are occasionally found, but they are decidedly rare. (See Photograph III.)

These concentric bodies are not merely deposited from the tissue fluids, as Virchow and others state. They are the result of proliferative and hyaline-degenerative changes in the endothelial cells lining the connective tissue trabeculæ of the plexus, as W. F. Robertson has shown in the dura mater and pia-arachnoid.

The endothelial cells swell up, lose their affinity for nuclear stains, and finally assume the form of a homogeneous hyaline sphere, staining faintly with eosine in hæmatoxylin and eosine preparations. Each may attain a very considerable size. One of them may form a small concentric body, but as a rule several spheres, probably of a semi-fluid consistence, coalesce to form the more usual concentric body. The concentric markings appear subsequently, and, as W. F. Robertson suggests, are most likely due to shrinkage. The fibrous capsule so frequently present is added later, after the manner in which nature encapsules all foreign bodies, and in all probability the fibrous tissue is developed from the still healthy endothelial cells.

While the above is the most common mode of development of concentric bodies, I do not think that it is the invariable one. When hyaline degeneration attacks the arterioles it may obstruct them and convert them into hyaline rods. Venules and capillaries, the walls of which are thickened by hyaline degeneration, also form concentric bodies, the ultimate occlusion of the vessels being brought about by a proliferation of the endothelial cells lining the vascular tube. (See Photograph IV.)

In conclusion, the hyaline material is an exceedingly unstable substance, causing considerable variations and anomalies in staining. In senile cases, however, these bodies are usually found to be impregnated with lime salts, as proved by effervescence on addition of hydrochloric acid. Moreover it seems not at all unlikely, from the reaction with osmic acid, that they, previous to calcification, undergo retrogressive fatty change, as so frequently happens in the case of calcifications elsewhere.

Still on the border-land of the pathological are the cysts of the choroid plexus. These cysts are so commonly found that Faivre, writing in 1855, described them under the name of "choroid vesicles," as normal and peculiar to the human

subject. I found them in fifty-seven per cent. of cases examined.

These cysts may be little larger than a pin's head, or they may reach the size of a pea. In some cases they are few in number, in others they are very numerous, the whole glomus being converted into a cluster of cysts like a bunch of grapes. The walls of the cysts are very delicate, and numerous fine vessels may be seen coursing over their surfaces, which display a fine white dotting, due to concentric bodies embedded in them, or to small aggregations of cells filled with fatty granules. The surface of the cyst, moreover, is very often destitute of an epithelial covering. Near the base of such a cyst the epithelium may be quite distinct, but as the summit is approached the cells become scattered with a bare patch here and there, till finally a portion is reached where no epithelial cells can be seen. The interior of the cyst is made up of a very open network of connective-tissue trabeculæ, which are lined by degenerated and degenerating endothelial cells, scarcely one of which presents normal features. The spaces are filled with a thin fluid, in which float cells in different degrees of degeneration. Concentric bodies are of very frequent occurrence throughout the cyst. All around this looser and more open network, and gradually blending with it, is a dense tissue in which there has been very extensive proliferation of the endothelial cells lining the trabeculæ, and associated with this usually some thickening of the trabeculæ themselves. (See Photograph V.)

I have arrived at the following conclusions as to the origin of these cysts. Hyaline concentric bodies and hyaline spheres are very commonly found in them. The degenerative process in the endothelial cells of the trabeculæ in cystic formation is very similar to that which precedes the development of concentric bodies. Indeed, so close is the resemblance that it is very questionable if we are entitled to discriminate between them. Still, to my mind there is no doubt that cells break down into fluid in the cysts in a manner that never occurs apart from them. But this degeneration of cells alone does not seem sufficient to account for the development of these cysts, though there is no doubt that the fluid found in them is in part due to this bursting of the endothelial cells affected with colloid or hyaline degeneration. In all the cysts which I had an opportunity of examining the fluid was quite limpid. Colloid cysts with gummy viscid contents have, however, been described by Wallmann and Hoffmann.

It seems more than probable that there are two processes engaged: firstly, a proliferation and degeneration of the endothelial cells, frequently associated with hyaline changes in the trabeculæ; and secondly, a resulting condition of œdema.

Through the spaces of the choroid plexus there must be a constant circulation of lymph. This proliferation and degeneration of cells in many cases completely fill up these spaces, and must constitute a serious obstacle to the flow of lymph. Hyaline spheres may also eventually block them up. Concentric bodies must have the same effect, and these are never present in any numbers without a concomitant development of cysts. There exist, then, very numerous points of obstruction, behind which the lymph stream is constantly pressing. There is, in short, an obstructive œdema. The spaces of the pia arachnoid become more and more distended with the lymphatic fluid, and larger spaces still are produced by the breaking down or absorption of intervening trabeculæ, while the cyst itself results from a number of such spaces lying adjacent to one another. The degenerating endothelial cells add to the fluid, and where the tendency is for the cells to rupture, then are the contents of the cyst colloid. In other cases, again, where the greater number of the degenerated cells goes to the formation of concentric bodies, the cystic fluid tends to be thin and limpid. Finally, such a collection of fluid may be shut off from surrounding parts by the occurrence behind the fluid accumulation of the same changes which led to the obstruction in front; and the frequency with which dense tissue is found all around the cyst seems to point to such a conclusion.

Among the truly pathological alterations met with in the choroid plexus, the hyaline fibroid change in the vessels is perhaps the most important. This condition may be found in all the vessels, but it seems to affect mainly the arteries and capillaries. Of the arteries, the smaller ones and the arterioles show this degeneration to the greatest extent. The adventitia alone, or the intima and media together, may be affected, but by far the most common condition is to find the whole three coats involved.

Hyaline degeneration of the adventitia consists in a homogeneous thickening of the longitudinally running fibrous tissue. This swelling may be slight or considerable, stains a faint pink with eosine, and, as a rule, is devoid of granu-

larity. In the normal condition in the arterioles the adventitia is only made out with difficulty, whereas the diseased adventitia alone may be two or three times the thickness of the original wall. The adventitia never becomes much thickened without the muscular coat showing similar changes, as shown by the loss of nuclear staining in the media and the presence of dilatations.

The muscular coat of an artery, as a rule, is only involved secondarily to a hyaline degeneration of the intima, the explanation of this being that the media derives its nourishment from the interior of the vessel, and not from without as in the case of the adventitia. Consequent on the intimal thickening a starvation of the muscular fibres is brought about, and this leads to their degeneration. The nuclei of the muscular fibres lose their property of staining with hæmatoxylin, and ultimately a homogeneous, finely fibrillated, or granular mass results, staining faintly or darkly with eosine.

Normally in the arterioles, when cut longitudinally, the intima appears as a thin even band of tissue. The intima rarely becomes so much thickened and swollen as the adventitia. In some cases this hyaline thickening is very irregular on its external surface, dipping down into the degenerated muscular layer, and pushing the elastic lamina before it. In no case, so far as I have seen, does the elastic lamina itself undergo this hyaline change. It may become absorbed and disappear, but when present it continues to separate the intima from the media, dipping down into the latter, and forming in it numerous loops in order to fulfil its purpose.

The hyaline thickening of the intima is ultimately replaced by fibrous tissue, mixed up with which may be seen elastic fibres or bundles, and instead of the single normal fenestrated membrane there may be several elastic laminæ, two, three, and four being met with. (See Photograph VI.) In these endarteritic vessels the wavy course of the elastic lamina becomes still more wavy, and the lamina itself is increased in thickness. In other cases, again, it looks almost as though the entire intimal thickening was due to an hypertrophy of the elastic lamina, with only a few cellular elements separating the different layers.

Under normal conditions, in any of the arteries in the choroid plexus the elastic lamina appears as if composed of a single layer of elastic tissue, this layer varying in thickness with that of the artery. Still it may be possible that even here, as in the case of the larger arteries elsewhere, the elastic

lamina is made up of two or three layers, though such cannot be demonstrated.

That the extra elastic laminæ owe their origin to a bursting asunder of these layers by new-formed tissue, as held by Carl v. Rad and Rumpf, seems not at all unlikely. Thus two elastic laminæ are explained by the division of the primary layer, three by a further division of the secondary lamina, and so on. But it seems to me that the process, though in part, is not altogether mechanical, for there is no doubt that in many cases the elastic lamina is very distinctly hypertrophied. It becomes thickened and lengthened, so that its normal sinuosity is much increased. If the elastic lamina did not play an active rôle the thickened intima would tend to obliterate the normal windings, making the elastic layer in parts quite straight.

Heubner has observed several elastic laminæ in syphilitic endarteritis, and explains their occurrence as follows:—"When the endothelium is no longer caused to proliferate cells from syphilitic irritation its normal function begins. It forms a fenestrated membrane over the new-formed tissue, as it formed the same in young organisms over the muscular layer." This further explanation of Heubner appears to me to be in accordance with the facts, and has more lately been supported by Löwenfeld. It accounts most satisfactorily for those cases in which a secondary elastic lamina is found immediately under the endothelium, separated by a considerable distance from the original lamina by new fibrous tissue, and, so far as can be seen, in no way connected with the original lamina.

As already mentioned, cases are occasionally seen in which the entire intimal thickening seems to consist of elastic tissue. From a consideration of these we must, I think, conclude that the elastic lamina is a vital structure, and that under certain circumstances it is capable of proliferation and growth.

Little fusiform dilatations and sacculations, of the smaller arterioles especially, are frequently met with, and these, without doubt, are closely related to and dependent on hyaline degeneration in the vessel coats. A form of this is what Löwenfeld calls "die Rosenkranzform des Muscularisrohres," from its resemblance to a rosary. There is throughout the arteriole a mild degree of hyaline degeneration and thickening of the intima, and this, though slight, has been sufficient to interfere with the nutrition of the muscular layer. The elastic lamina is present through

practically the whole length of the section. Wherever the media has degenerated, as shown by the loss of nuclear staining in the muscular fibres, the vessel wall has yielded to the pressure of the blood, leading to the formation of a little fusiform dilatation. Moreover where sacculation has occurred it may be noted that the thickening of the adventitia—likewise hyaline in this case—is less marked, while at the one point where the vessel presents a narrowed lumen this thickening is more extreme.

Such an arteriole may become occluded, more usually by thrombosis occurring on the altered vessel wall than by the hyaline thickening alone. The thrombus ultimately becomes hyaline, and it is impossible to distinguish it from the original wall of the arteriole.

Very rarely the "Rosenkranzform" dilatation becomes more and more extensive, till ultimately a miliary aneurism is formed. The development of such an aneurism must have been gradual, allowing sufficient time for a reparative process to take place in its walls. This would be brought about first of all by the proliferated endothelial cells invading the hyaline mass, till a condition of endarteritis would be produced. But the growth of the aneurism would not be arrested here. So long as the tissue was incompletely formed dilatation would go on, and would only cease with the complete conversion of the granulation into fibrous tissue. These miliary aneurisms are true aneurisms, and not merely, as Eppinger holds, examples of ectasis or dilatation in which all the coats of the vessel are present. No muscular tissue can be detected in the wall of a miliary aneurism, and the arteriole entering it shows hyaline degeneration of both its intima and media.

So far as my experience goes, vascularisation of either the hyaline or fibrous thickenings does not occur to any extent. Newly formed capillaries are not infrequently found in the thickened adventitia, but never have I seen new-formed vessels in the thickened intima of the arteries and arterioles found in the choroid plexus.

In the time at my disposal I have been unable to overtake more than the pathology of hyaline concentric bodies, cysts, and blood-vessels. The two former are due, in the main, to proliferation and degeneration of the endothelial cells lining the trabeculæ, which may, however, proliferate and degenerate otherwise. In conclusion I may state that all the connective-tissue and endothelial changes commonly found in

the pia-arachnoid of the insane are similarly met with in the choroid plexuses of the lateral ventricles.

Discussion.

Dr. FORD ROBERTSON said he agreed so fully with Dr. Findlay that he had no criticism to offer, but he had to express the very great pleasure they had in seeing those beautiful photographs, and to follow his description of the pathological changes. He had quite demonstrated that the choroid plexus was a secreting gland. That was of the highest importance in neurology.

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*The Correlation of Sciences in Psychiatric and Neurological Research.**—By IRA VAN GIESEN, M.D., Superintendent of the Pathological Institute of the Commission in Lunacy of the State of New York.†

BEFORE this body it is unnecessary to revert to the inadequacy of conducting scientific investigations in psychiatry along the restricted plan of confining the research to material found within the asylum by some one exclusive department of investigation, such as the routine governed and mechanical methods of microscopical research. This restricted plan has largely governed psychiatric research up to the present time. Now, however, that many of the sciences tributary to psychiatry have attained a growth and capacity to be of service in psychiatric research, the restricted plan of research may be relegated to the past.

The phenomena of insanity are manifold, and the comprehension of them can only be grasped when viewed from many different standpoints—from the standpoints of many sciences. A co-operation of many sciences will bring forth a rich return

* For presentation to the Annual Meeting of Medico-Psychological Association, Edinburgh, 1898.

† In an official report of thePathological Institute of the New York State Hospitals to the State Commission in Lunacy for transmission to the legislature, the writer has endeavoured to urge the necessity of a more comprehensive view of study of the science of psychiatry. This report is composed of the following sections:

1. The beneficial results of scientific investigation of insanity.
2. The inadequacy of the present methods of investigating nervous and mental diseases.
3. The correlated branches of research in the scientific investigation of insanity.
4. The unclassified residuum.
5. General remarks on the organisation and conduction of the Pathological Institute.

From its nature this report had to be written in an untechnical form. This paper embodies in substance Sections 3 and 4 of this report.