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SOME POINTS IN THE PATHOLOGY OF AND PROGNOSIS IN GLIOMA OF THE RETINA, WITH CASES.

BY

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This paper formed my Presidential Address in the Ophthalmological Section of the Cheltenham Meeting of the British Medical Association in July 1901. In it I have endeavoured briefly to give the chief points in the pathology of retinal glioma, and also to consider the prognosis in such cases. The occurrence in my practice at St. Bartholomew's Hospital of no less than six cases of glioma during the years 1899 and 1900 gave me the material for studying the disease, and suggested this use of it. The number of cases in such a short period of time is remarkable, as on looking over our Ophthalmic Ward books, which contain notes of every case admitted, I could find records of only six cases between 1871 and 1898.

I have illustrated my remarks with four photogravures chosen from the numerous microscopic slides made. The macroscopic specimens of the eyes are to be found in our museum, and also many microscopic specimens from them.

The microscopical specimens from which the photogravures are taken were prepared by Dr. Andrewes and Mr. Brewerton, to both of whom I am deeply indebted for the care bestowed on the specimens, and also for much assistance and information. The six cases have furnished seven eyes for examination, as in one case (Case I.) both eyes were affected. Case VI. is also probably a binocular case, but the left eye was excised before the patient came to the hospital, and no microscopical examination of it was made. These seven eyes form a series, including all the different stages and phases of the disease.

The notes of the cases appended are as brief as possible, and

mainly of pathological interest. The fuller clinical notes of Cases I., II., III., and IV. are to be found in St. Bartholomew's Hospital Reports, vol. xxxvi. pp. 253-259. It is usual, clinically, to divide cases of glioma into three stages. *First stage*, in which there are no clinical signs of irritative or inflammatory changes having occurred; *Second stage*, or glaucomatous, where there is increased intra-ocular tension, but the growth is still confined to the eye; and *Third stage*, where the growth has become extra-ocular. This threefold division is of exceedingly doubtful use or expediency.

For my own part I should divide glioma for clinical, and especially for pathological work, into only two stages: the intra-ocular and the extra-ocular. The glaucomatous stage of the intra-ocular is often well marked, but it is not a certain phase of the disease, and pathologically it is certainly only to be marked by the position of the growth. In some cases, owing to the degeneration of the tumour, the eye may never pass into the glaucomatous stage, but may even have a very low tension although no perforation of the tissues has taken place. Then, again, observers differ so greatly as to tension that small degrees may be not perceived, or even over-perceived. The eye may also have passed into the extra-ocular stage, and yet the tension be raised, as in the right eye of Case I.

The difference between the intra-ocular and the extra-ocular condition is very marked as far as the pathological changes are concerned; and clinically, it marks a great division as to the chance of recurrences, fatal issue, and general prognosis.

In these six cases I have made the division into intra-ocular and extra-ocular, merely noting the tension when necessary.

The six cases, or rather the seven eyes, examined arrange themselves into: Intra-ocular, I.B (left eye), II., III., VI.; Extra-ocular I.A (right eye), IV., V. The eyes of Case I. are early stages in the intra-ocular and extra-ocular classes respectively.

CASE I.—*Binocular Case—Left Eye, early Intra-Ocular Stage—Tension normal—Excision with* 15 *mm. of Optic Nerve; Right Eye, early Extra-Ocular Stage—Optic Nerve invaded—Tension,* +1*—Excision with* 12 *mm. of Optic Nerve—Recovery.*

Ophthalmic Ward, 1890, No. 2529.—L. G., æt. 15 months, admitted November 2, 1899.

Mother says that when the child was three months old she noticed that the right eye was larger than the left eye, and

when six months old that there was a skin over the right eye, which was partial at first, but rapidly spread over the pupil. Three weeks ago she saw a skin appearing over the left eye, which has probably spread since then. The child is not in pain.

Right Eye.—The eye is prominent and bulging, but the lids close over it; conjunctiva normal; sclerotic bluish-grey, with a bulging at the upper and outer edge of the cornea, where the subconjunctival vessels are much injected; cornea hazy; anterior chamber practically absent; iris darker grey than the left, and bulged forwards on the temporal side, where it almost touches the back of the cornea; pupil displaced to the nasal side, somewhat dilated, does not react to the reflexes; lens opaque. No details can be seen behind the lens owing to its opacity. Tension, + 1.

Left Eye.—Lids, conjunctivæ, cornea, and anterior chamber normal; pupil central, circular, and acts normally; lens normal. By focal illumination a yellowish nodular mass, more marked at the temporal than the nasal side, is to be seen in the fundus, and retinal vessels can distinctly be seen passing over it. In the centre is a small space, where the growth is seen very much farther back, and gives the appearance of looking into a funnel; tension normal; vision, perception of objects held in front of her.

November 28.—The right eye was excised under chloroform, and about 12 mm. of the optic nerve removed with it. As the growth on examination proved to be glioma, the left eye was excised on December 12, with 15 mm. of the optic nerve. The child is alive and in good health.

Pathological Report.—Right eye, sagittal section; iridic angle obliterated; sclerotic slightly bulged at outer side of optic nerve; the retina is pushed forward (complete detachment) and surrounds the tumour, though it cannot be traced posteriorly along the edges of the growth. The tumour shows calcareous degeneration, and on section cuts grittily.

Microscopically.—The growth is composed of round cells with a few rosettes in places; there are numerous "worm-like processes," that is, vessels surrounded by a mantle of cells about twenty or thirty deep (fig. 4); between these processes there are areas of degeneration consisting of badly staining cells and containing calcareous deposit, which make the sections difficult to cut well. The optic nerve for 2 mm. near the globe shows numerous round tumour cells, but farther back its structure is normal.

Left Eye.—Sagittal action; iridic angle free; a long pedicle

formed by the retina passed forwards from the optic nerve; the growth which is encapsuled is situated above the nasal side of and behind the ciliary processes.

Microscopically.—The cells vary somewhat in size and are slightly oval in shape; the nuclei are large, as a rule about 10 μ, and stain well with hæmotoxylon; there is scarcely any cell protoplasm. Here and there are a few branched cells, but they are very much in the minority and may be glial cells.

In the growing part of the tumour (figs. 1 and 2) the growth consists of small round and oval cells arranged in distinct alveoli with some rosettes (fig. 3); the tumour is surrounded by a fibrous capsule formed by the hyaloid membrane and the internal limiting membrane; there is a well-marked stroma or matrix which gives it the appearance of a connective tissue tumour; the blood-vessels of the tumour, which are not very numerous, have well-developed walls. In the peripheral portion of the growth there are no areas of degeneration or worm-like processes; but in the older portions there are a few degeneration areas shown by the tissues in places staining badly (fig. 4), and in them are to be seen the worm-like or finger processes. The lumen of each process is lined by endothelium, and next it is a distinct vessel wall, surrounded by a palisade of columnar cells, whilst still further beyond are round and oval cells arranged as a mantle twenty or thirty deep; these last cells are the same size as the other tumour cells.

The retina is seen quite distinct though in contact with the tumour. In one place the growth seems breaking through the retina. I cannot see any proliferation of the inner or outer nuclear layer, but in places the external layer is somewhat thickened, but not more than is found from inflammatory changes. The sections, especially those prepared in paraffin, show an appearance which resembles endothelioma more closely than any other form of growth.

Case II.—*Right Eye, Intra-Ocular Stage—Tension,* + 1—*Excision with* 12 *mm. of Optic Nerve—Recovery.*

Ophthalmic Ward, 1899, No. 391.—A. D., male, æt. 16 months, was admitted on February 7, 1899. Mother noted one month ago "cloud in the sight" of the right eye, and three weeks ago she saw a yellowish appearance in pupil.

Right Eye.—Slight conjunctival congestion; anterior chamber shallow; pupil reacts sluggishly to light; tension, + 1.

By oblique illumination three yellowish nodules are to be

seen in the fundus near the optic disc; the retinal vessels pass over them, and there are small vessels on their surface, evidently of new formation.

By Ophthalmoscope.—A large detachment of the retina is to be seen above.

Excision of the eye with 12 mm. of optic nerve.

November 1902.—Child alive and well.

On section the growth was found as nodules near the optic nerve, and extended forwards towards the lens, the retina being separated all round and presenting an umbrella detachment.

Microscopically.—The specimens were not very satisfactory, and showed only areas of degeneration, worm-like processes, and round cells. The optic nerve was normal.

CASE III.—*Left Eye, Intra-Ocular Stage—Tension,* + 1—*Excision with* 11 *mm. of Optic Nerve—Recovery.*

Ophthalmic Ward, 1900, No. 1014.—A. T., female, æt. 1 year 11 months, was admitted on May 14, 1900. Mother says that the child was noticed eleven months ago to squint with left eye, and that three months ago "the pupil looked like a cat's eye in the dark."

The right eye is natural in all respects.

Left Eye.—Marked convergent concomitant squint; no apparent vision or perception of light; tension, + 1; lids and conjunctivæ normal; cornea clear; anterior chamber obliterated except at nasal side, where it is very shallow. Iris pushed forward against the cornea, but no change in colour. Pupil widely dilated; does not react to light or accommodation. A yellowish-white reflex to be seen with naked eye through pupil (typical amaurotic cat's eye).

Ophthalmoscope.—Yellowish reflex as above described, with faint pink tint throughout; retinal vessel seen over a complete detachment or pushing forwards of the retina. The swelling seems closely applied to the posterior surface of the lens. At the temporal side a patch can be seen looking distinctly white and more opaque.

Under chloroform the left eye was excised, and the piece of optic nerve removed was 11 mm.

November 1902.—Child alive and well.

Pathological Report.—Eye divided horizontally, vitreous chamber nearly filled by soft growth extending forwards in a V-shaped manner from the optic nerve to the ciliary region; retina detached and involved in the growth.

Microscopically.—The tumour consists of round cells with large

nuclei and very little cell protoplasm; no definite matrix made out; many blood-vessels with well-formed walls; there are some worm-like processes and degeneration areas staining badly; hardly a trace of retina to be seen; apparently a case of diffuse glioma; optic nerve healthy.

CASE IV.—*Right Eye, Extra-Ocular Stage—Tension,* — 1; *Exenteration of Orbit—Death from Cerebral Complications.*

Ophthalmic Ward, 1899, No. 35.—C. P., male, æt. 13 months, was admitted on February 3, 1899.

Mother noticed that seven months ago the child became cross-eyed, and shortly afterwards that the right pupil was brown in colour; the white of the eye was often very red; fourteen days ago the right eye became very prominent; child fretful and much out of health for six months.

Right Eye.—The lids are much swollen and reddened. On opening the lids, the conjunctivæ are of a deep red colour and thrown into folds. The eye is considerably proptosed and displaced downwards. The cornea is opaque in appearance, of a greenish-yellow colour, flattened from above downwards and vascularised at the periphery. The iris is pushed close against the posterior aspect of the cornea, obliterating the anterior chamber. The pupil is blocked by a yellowish mass. Tension, — 1.

February 6.—Exenteration of the orbit. Child made rapid recovery, and was evidently much relieved of pain. He left hospital apparently well on February 22. Three weeks afterwards the child died with symptoms of acute meningitis, but a post-mortem examination was refused.

The eyeball showed a tumour bulging from the posterior upper and outer part of the globe, well defined behind and completely encapsuled. The optic nerve was surrounded by it except on its inner side; a small stalk of nerve protruded behind the mass of growth.

On section the growth felt hard, firm, smooth, and inelastic, and almost filled the whole of the eyeball, being in intimate connection with its coverings on the upper, outer, and lower portions. The globe was somewhat flattened, but the flattening of the cornea gave a false impression of the alteration in shape.

Measurements.—Maximum transverse diameter, 22 mm.; depth, 21 mm.; length from centre of cornea to ocular end of nerve, 36 mm.; length from corneal centre to limit of growth, 31 mm.

The tumour was bulging through the upper and outer part

of the globe, and had perforated the sclerotic posteriorly above the optic nerve.

The optic nerve was much thickened, and so infiltrated with cells that scarcely any nerve fibres could be found.

Microscopically.—The growth was so old and degenerated that no rosettes or blood-vessels surrounded by cells could be found. It looked exactly like a round-celled sarcoma, as also did the extra-ocular portion. The degeneration areas were in parts calcareous.

CASE V.—*Right Eye, Extra-Ocular Stage—Tension, + 1—Excision with 12 mm. of Optic Nerve—Subsequent Exenteration of Orbit—Recurrence in Right Orbit and Death.*

T. C., male, aged 4, admitted October 29, 1900.

The mother says that the right eye has been looking queer for some months.

Right Eye.—Slight congestion of conjunctival and sclerotic vessels, cornea small, transversely scratched, steaminess below, stained with fluorescine. Anterior chamber shallow; milk-white fluid gravitating to lower part of anterior chamber. Iris greenish blue; pupil dilated 7 mm., does not react; by oblique illumination pupil is not black but yellowish colour, supposed to be from opacity of lens. Tension normal. Vision p.l. Eye painful.

The diagnosis was traumatic cataract with hypopyon following wound of cornea. The eye was treated with belladonna and atropine, but no absorption of the hypopyon took place, and there was pain and + 1 tension.

November 9.—Paracentesis of anterior chamber; cultures were taken, and found sterile.

November 11.—Hypopyon re-formed, and then disappeared again. Tension was always + 1 with much pain.

November 14.—Shallow central corneal ulcer which healed in two days; tension normal.

November 20.—The patient had more pain. Tension, + 2. Paracentesis was again performed, and the case thought now to be pseudo-glioma.

December 7.—Owing to the persistent high tension the eye was excised with 4 mm. of the optic nerve, which was much thickened. On microscopical examination it was found to be glioma, and complete exenteration of the orbit with 9 mm. of the optic nerve, which was much enlarged.

January 12.—The patient went out quite well to the Sevenoaks Infirmary.

In February Dr. Ward wrote that the patient suddenly became unconscious and remained so for some days, but recovered consciousness, evidently suffering from the intracranial trouble (torpor, slow pulse). There is some recurrence in the orbit.

March 7.—The patient died. No post-mortem examination.

Pathological Report.—The eye divided vertically from before backwards, length 23.5 mm., width 22 mm. Iridic angle obliterated: the retina was completely detached, showing a cheesy looking growth of an exophytic character. The optic nerve and choroid were enormously thickened.

Microscopical Examination.—The chief mass of the growth consists of small round cells with many thin-walled blood-vessels; these cells appear to be the nuclei of large degenerated cells; they show no surrounding protoplasm, and stain badly. In the areas of degeneration there are colloidal masses. The choroid is densely infiltrated with large cells, showing well-marked nuclei.

The iris is also infiltrated near its base, and anteriorly its cells have burst through the endothelial lining of the iris into the anterior chamber, and from thence into the posterior chamber. The anterior chamber contains small balls of cells, these being the same size as the tumour cells elsewhere, and were the cause of the apparent "hypopyon." The optic nerve is about twice the natural size; its centre is composed of necrotic glioma cells; the peripheral portion shows cells staining readily. The proximal end of the nerve removed after exenteration is also infiltrated with cells; the rest of the orbital tissues is healthy.

CASE VI.—*? Binocular Case—Left Eye—Tension, −2—Excision—Glioma Nodule in Orbit—Exenteration; Right Eye—Intra-Ocular Stage—Tension, +1—Excision—Neurectomy—Death.*

Ophthalmic Ward, 1900, No. 2780.—H. M., male, æt. 3 years, was admitted on October 24, 1900. The mother noted at birth a small brown speck on the left eye, which gradually grew. In March 1900, the eye being much inflamed, was removed at home by Dr. Corner, who described it as a congenitally malformed eye with tension −2 (it was not examined microscopically). It probably was a case of crypto-glioma.

Left Eye.—Socket healthy.

Right Eye.—Conjunctiva and sclerotic, slight general conges-

tion; cornea, anterior chamber, and iris normal. Pupil dilated 6.5 mm., does not react; lens natural, reflex greenish-yellow, and a tumour can be seen apparently close up to the back of the lens, and chiefly on the nasal side. Vision, apparently no perception of light. Tension, +1.

October 30.—Excision of right eye, which was uniformly enlarged; division of the external canthus was necessary to remove it. Optic nerve cut off short, and therefore the nerve was sought for, and removed at apex of orbit.

November 7.—Last two or three days the left eyelids were swollen; under chloroform a swelling was felt in orbit, and a partial exenteration was done.

February 6, 1901.—Readmitted with growth as large as a Tangerine orange in left orbit. Complete exenteration, 12 mm. of nerve removed. Nerve appeared healthy, and growth showed round-celled sarcoma.

Pathological Report.—Right eye measurement: length, 27 mm.; breadth, 28 mm.

Right Eye.—On division horizontally the sclerotic is everywhere much thinned, most markedly at the equator. The iridic angle obliterated, and the retina completely detached. The growth is exophytic.

Microscopically.—The growth is very vascular; the vessels are large, and lined by endothelium, exterior to which is a thin, homogeneous wall, and supporting this wall in many places is a palisade of columnar cells, surrounded by oval cells, twenty to thirty deep. Here and there in the worm-like processes were a few solitary rosettes like the illustration in Flexner's case (2); these processes are surrounded by necrotic cells, the nuclei of which can scarcely be discerned. The peculiarity of this case is the large size of the vessels, as in the other cases the vessels are quite small capillaries.

The optic nerve shows no sign of glioma infiltration, but the lumen of the central artery of the retina is partly obliterated by endarteritis. The growth removed from the left orbit consists of masses of oval cells, and has the character, microscopically, of round-celled sarcoma.

Remarks.

There are certain definite points I wish to emphasise and examine from the description of these cases; the pathological, or rather the microscopic, appearances may be taken individually and collectively. Individually, it is necessary to consider the cells, matrix, blood-vessels, alveolar structure, rosettes,

areas of degeneration, worm-like processes. Collectively, I wish to endeavour to draw inferences from the association in different stages of these elements.

Cells, Intra-Ocular Cases.—These vary somewhat in size, and are slightly oval or round in shape; the nuclei are large, as a rule about 10 μ, and stain well with hæmatoxylon; there is scarcely any cell protoplasm. Multi-nucleated cells were seldom seen, but cells exhibiting colloid and hyaloid degeneration were frequently met with.

There are very few of the branched cells to be met with mentioned by Greef ([3]) after treatment with the Golgi-Cajal method; these were only found in Case I.B.

Arrangement of Cells.—In Case I.B, in the growing part of the tumour the cells disposed themselves as an alveolar structure, and in places as small balls or rosettes; in the older portion the cells are arranged in the worm-like processes.

Extra-Ocular Cases.—The extra-ocular growths in Cases IV., V., VI. exactly resembled round-celled sarcoma, consisting of masses of round and oval cells, with little matrix, and no special arrangement of the cells.

Rosettes.—These structures, shown in figs. 2 and 3, are small balls of tumour cells, and are seen in section as a central minute lumen about 7 μ, filled by a homogeneous colloid material, and surrounded by a single layer of well-stained cells.

The lumen does not contain blood, and is only about the size of a red blood-cell.

Numerous rosettes were found in the eye (Case I.B), especially in the growing part, and a few in Case I.A.

The rosettes were first observed by Flexner ([2]) and afterwards by Eisenlohr ([4]), A. Becker ([5]), Van Duyse ([6]), Wintersteiner ([7]).

Wintersteiner describes the rosettes as closed rings surrounded by cells, the lumen being lined by a distinct basement membrane; he says that in places rod-shaped protoplasmic processes extend into the lumen through the basal membrane. In my specimens we could not find this differentiation.

Intra-Cellular Matrix.—In Case I.B there is a well-marked supporting stroma, homogeneous, and with spindle-cells. This is best seen in the Van Gissen specimens. In the other cases no spindle-cells were to be found in the matrix.

In the extra-ocular growths there is no marked matrix to be seen.

Trabecular Structure.—In Case I.B, as shown in figs. 1 and 2, there is a distinct trabecular or alveolar arrangement of the cells. In places there are well-marked rosettes, but as a rule

it is a loose meshwork, some of the trabeculæ apparently being lined by endothelium.

In section these trabeculæ are never seen cut longitudinally, and therefore are not tubes.

Blood-Vessels.—In the early case (I.B) there are some new blood-vessels, but not in great numbers; they have perfectly formed walls. In the other cases the blood-vessels of the growth have well-formed walls; in some there is hyaloid degeneration of the vessel walls.

In the extra-ocular growths the blood-vessels are as in sarcomata, simply endothelial spaces without any formed walls.

Worm-like or Finger-Processes (fig. 4).—Intra-Ocular.—In all the eyes except Cases IV. and V. there is the accumulation of cells known from their arrangement as worm-like or finger-processes.

Each process is in reality a blood-vessel with distinct walls, surrounded by a palisade of columnar cells, and then by the tumour-cells arranged as a mantle twenty or thirty deep.

In the extra-ocular growths none of these structures were found.

Areas of Degeneration.—It is typical of glioma that with the growth of the cells there is early degeneration. Even in Case I.B there are a few areas of degeneration to be seen in the oldest part of the growth.

In all the other cases there are numerous marked degeneration areas shown by the cells staining badly and being broken down, also by hyaloid and calcareous degeneration.

Now taking the many pathological points of the several cases and arranging them we find—

In the earliest case, I.B, the sections demonstrate the appearances to be like a connective tissue tumour, having a well-marked supporting matrix of spindle-shaped cells. The tumour cells are round or oval, and at first, in the growing part, arrange themselves in a trabecular manner—in places forming the so-called rosettes; the blood-vessels have well-formed walls. In the growing part there are no degeneration areas or worm processes, but these are present in the older part of the tumour.

Of the other intra-ocular cases, Cases II., III., and VI. showed the worm-like processes; in Case VI. the vessels were very large, and a few solitary rosettes were found. In the extra-ocular cases, the eyeball of Case I.A shows a few rosettes, but chiefly worm-like processes with degenerated areas; in Cases IV. and V. the ocular growth consisted simply of round cells with much degeneration.

Extra-Ocular Growths.—In I.A the ocular end of the optic nerve for about 2 mm. was infiltrated with round and oval tumour cells, which exhibited no tendency to any definite arrangement. In Cases IV. and V. the optic nerves were densely infiltrated with new cells tracking along the lymphatic spaces of the nerve, and in places undergoing great degeneration. In Case VI. the orbital growth was exactly like a round-celled sarcoma, which is the condition I have always seen in extra-ocular growths.

From the consideration of these cases it would seem that glioma probably commences as an alveolar condition, with marked connective tissue stroma, that at first rosettes are found, but as the tumour grows and degeneration begins, there occur the finger, or worm-like processes, consisting of a mantle of cells surrounding the blood-vessels. This is followed at times, even before the growth has moved beyond the eye, by loss of definite structure, and the growth assumes the form of a round-celled sarcoma. In all growths outside the eye the structure is that of a round-celled sarcoma. When also the growth invades and infiltrates the choroid or iris, as in Case V., the structure consists simply of cells without any tendency to definite arrangement.

Before expressing my own views, it will be, I think, most important to enumerate briefly the chief opinions as to the pathology and origin of glioma.

Pathology.—The pathological position of glioma of the retina has for years been a source of great controversy; it has been classified as a sarcoma, and also as a carcinoma.

Virchow ([8]) first gave the disease the name of glioma, and described it as a circumscribed tumour-like hyperplasia of the neuroglia. He also looked upon it as associated with sarcoma, and in some cases gave it the name of glio-sarcoma.

Hirschberg ([9]), Leber ([10]), Iwanoff ([11]), and Knapp ([12]) supported Virchow's views.

Delafield ([13]) called it a small-celled retinal sarcoma, and by others, as Vetsch ([14]) and Straub ([15]), it has been classified as a round-celled sarcoma.

It has been described as glio-angio-sarcoma, or tubular glio-sarcoma, by Gama Pinto ([16]) and Van Duyse ([6]), and cylindro-sarcoma by Schöbl ([17]); Klebs ([18]) called it neuroglioma.

Greef ([3]) and Hertel ([19]) have both shown numerous branched connective tissue cells and ganglion cells by the Golgi-Cajal method, and follow Virchow in deriving it from the glial tissues. Greef calls it neuroglioma ganglionare.

Flexner ([2]) was the first to suggest the name of neuro-

epithelioma, which has since been adopted by Wintersteiner (20) in his most valuable work on the subject, and the latter observer delegates the disease to the carcinomata.

Treacher Collins (21) states that glioma is not a sarcoma, and is inclined to include it as a carcinoma.

Origin.—The origin of glioma has been variously stated by different observers. Virchow (8) gave it as from the neuroglia tissue, and Greef (3) in a very able paper has again advocated this view, which has also been followed by Hertel.

Greef has shown, by the Golgi-Cajal method, in fresh tissue the presence of cells like neuroglia cells with numerous processes. He also found some round or angular cells like ganglion cells that were not so frequently met with as those of the neuroglial type, and are very different in form, and also in appearance and size.

Schweigger (22), Hirschberg (9), Knapp (12), Dreschfeld (23), and others have described the growth as commencing in the inner nuclear layer; Wintersteiner (20) gives it as from the outer nuclear layer and nerve cells. Iwanoff (11) and Manfredi (24) connect it with the cells of the nerve fibre layer of the retina. Treacher Collins (21) says the cells bear a great resemblance to the fœtal cells of the retina.

To explain the sarcomatous nature of glioma, Becker (5) suggests that the mesoblastic cells of the blood may be the origin of the growth. Eisenlohr (4) suggests that in embryonic life the mesoblastic cells of the vitreous may pass along the hyaloid artery and its branches to the central retinal artery, and so to the retinal tissue.

Flexner (2) first, and afterwards A. Becker (5), Van Duyse (6), and Wintersteiner (20) believe that a main point in the tumour is the presence of the rosettes previously described. The idea is that they are formed from misplaced cells of embryonic type in the neuro-epithelial layer of the retina. Wintersteiner found them in eleven out of twenty-six eyes examined.

My specimens throw no exact light on the origin of glioma. I had hoped to have found something definite in the early case I.B, and am sure that it is only in such early stages that a clue can be found. The changes in most cases take place so rapidly that even the alveolar condition is soon lost, and degeneration begins. The specimens of I.B show that the origin of that case was not from the nuclear layers, as the slight thickening in places of the internal nuclear layer was not more than is found in inflammatory cases from irritation of the retinal

elements. The tumour cells in I.B are not the same size as those of the nuclear layer. I should myself agree with those who think the origin is from some developmental embryonic tissue (Cohnheim's theory). This would account for both eyes being affected so frequently (20 per cent.), and in such cases for the growth starting in each eye separately. The rosettes which Wintersteiner ([20]) lays such stress on are found chiefly in the early stage, and as far as I know only in the intra-ocular stage. I cannot find any evidence in my cases for the formation of the rosettes from the elements of the outer nuclear layer and rods and cones as described by Wintersteiner.

These have been found in congenitally malformed eyes, and in microphthalmic eyes by Dötsch ([25]), Ginsberg ([26]), &c. In my cases I cannot differentiate the protoplasm in the interior of the rosettes into columnar cells, or find any small processes in the interior of the very small lumen. It is strange, if these are tubular processes formed from the retinal layer, that they are always cut transversely and never in length. This fact suggests the cells being arranged in balls as described by Steinhaus ([27]).

In conclusion, as far as the origin is concerned, it seems to me that nothing definite has yet been proved as to the exact place from which glioma starts, except that it evidently commences in the tissues of the retina. The different theories are more or less speculative.

As to which class of tumours glioma belongs, the evidence to me seems to point to the sarcomata. I can find no reasons for supposing it to be a carcinoma. Observers have, I think, chiefly been led to the carcinoma type from the fact that the retinal elements are considered epiblastic. The development of the eye, like the nervous system, as worked out by Gaskell, certainly leaves the exact epiblastic or mesoblastic origin of the parts in a very undecided position. Gaskell ([28]) believes that the central nervous system, and therefore the retinal ganglia, is an amalgamation of the invertebrate nervous system and its alimentary canal. The sustentacular tissue of the vertebrate nervous system is therefore double, partly the portion in connection with the lining cells of the tube (the old alimentary canal) in the retina the Mullerian fibres, and partly the neuroglia of the original invertebrate nervous system.

The microscopical specimens illustrating this paper seem to indicate the form of sarcoma as an endothelioma, and this

would account for the extra-ocular growths having lost their definite structure as they grew older, as mentioned by Ziegler ([29]) in his description of endothelioma.

In the alveolar condition (figs. 1 and 2), the growth resembles endothelioma more than any other growth, and the stage (fig. 4) of the worm-like processes around the blood-vessels points also to this. In Ziegler ([29]), p. 450, a diagram fig. (287) of endothelioma of the dura mater would pass almost for this stage. This is borne out by the extra-ocular growths, which are exactly like round-celled sarcoma without any of the special characteristics of the intra-ocular growths. It is a tendency of endothelioma to become diffuse as it grows.

That there is abundant endothelial tissue for a tumour to commence in the retina the following quotations from Quain ([30]) show :—

"The veins resemble capillaries in structure, their walls consisting of a single layer of endothelial cells without any muscular tissue. Outside the endothelial layer is a space (perivascular lymphatic space, His.) both in the veins and capillaries, bounded externally by a second endothelial layer (forming the wall of the lymphatic space). Outside this again is found, as in the case of the veins, a layer composed of a peculiar retiform tissue. These perivascular lymphatic spaces are in communication with the lymphatic spaces of the optic nerve, and may be filled by injecting coloured fluid under the sheath which that nerve derives from the pia mater."

The distinctive structural growth is only found when the growth is in the interior of the eyeball. Where extra-ocular it is exactly like small-celled sarcoma, and this is also the fact when the tumour invades the choroid, ciliary body, and iris. In Case V. this is very well shown.

The clinical history is not in the province of this paper, but I know nothing in it to point more to glioma being a carcinoma than a sarcoma.

The usual spread along the interior of the optic nerve sheath, the lymph spaces of which are in direct continuity with the lymph spaces of the retina, is what would be expected in an endothelioma originating from the lymph spaces.

I hope that future observers will pay especial attention to the very early stages, and probably this microscopically can only be done in the binocular stage, as in Case I., when the diagnosis has been made from the other eye. The early alveolar or trabecular stage, with the accompanying rosettes, is

clearly the stage from which the exact origin is to be found. The worm-like or finger processes (fig. 4) are only present in the intra-ocular stage, but I think, as they are always present when degeneration has begun, that they are probably due to the degeneration. The mantle of cells may be produced owing to the fact that the cells up to about twenty or thirty deep are able to obtain nourishment from the central blood-vessel, but beyond this zone the vascular supply is so poor that they degenerate.

The glial theory, though somewhat strengthened by Greef's work, is by no means proved conclusively. One would expect the cells to be found otherwise than by the silver method, and also that they would be present in much larger numbers.

The round-celled sarcoma theory is due to the diagnosis being made from the later stages after the alveolar condition has disappeared. I can find no reason for its being called an angio-sarcoma, as the blood-vessels are only affected secondarily; nor tubular sarcoma, as at first the structure is not tubular. For the carcinoma theory that the neural elements of the retina produce the tumour and that the retinal elements are present in the rosettes, I have already stated that my cases show no signs of such elements, nor of any reason for glioma being called neuro-epithelioma.

Lastly, Treacher Collins' theory, that the cells are like fœtal retinal cells, and therefore epiblastic. Gaskell's work shows that the retinal cells are not all necessarily epiblastic, and also the cells Collins describes are evidently from cases where the cells are no longer structurally arranged, and though some cells with the processes he describes are often present, they are in the minority.

The new growth called glioma is probably therefore an endothelioma, and belongs to the sarcomata. It commences in connection with the endothelial tissue of the retina, and is first found as an alveolar or trabecular structure consisting of cells arranged round a small lumen, and there is a tendency for the cells to form spheroidal masses round a lumen—the so-called rosettes. After this stage has lasted a short time degeneration commences, and the cells arrange themselves round blood-vessels, forming the so-called worm-like processes. These conditions are only met with in the intra-ocular stages. Directly the tumour cells invade such vascular areas as the choroid, ciliary body, or iris, all definite arrangement is lost and the cells are found distributed without any predilection, and, as in the extra-

ocular growths, they present the characteristics of round-celled sarcomata.

Prognosis.—With regard to the six cases here recorded, three are still alive and well two years and more after operation.

Of the three cases alive, two (II., III.) were in the intra-ocular stage of the disease. In one (I.) the left eye was in the intra-ocular stage, while the right eye was entering on the extra-ocular, the optic nerve being infiltrated with tumour cells at the ocular end; however, the nerve was divided well beyond the diseased portion. Of the three cases dead, two were in the extra-ocular stage; in one (VI.) the right eye was in the intra-ocular stage, but the left orbit had growths in it, and the left eye before excision was probably in the extra-ocular stage and a cryptoglioma.

These cases are, of course, too few in number to establish any rule as to prognosis.

The six cases would give 50 per cent. of recoveries. Lukovicz ([33]) mentions 5 recoveries in 27 cases (18.5 per cent.). Lawford and Collins ([32]) find 8 recoveries out of 60—that is, 13.3 per cent. In my collected cases ([34]), numbering 333, I find the percentage about 24.3.

These percentages depend, however, on the stage the patients were in, and further ones are needed with division into intra- and extra-ocular cases.

In the six cases of this paper the intra-ocular would be 100 per cent. of recoveries, and the extra-ocular only 25 per cent. The three successful cases (50 per cent.) tend to show that in the intra-ocular stages excision may be expected to be followed by a successful result. Case I. also shows that this may be obtained even when the nerve is slightly infiltrated.

Wintersteiner says that in seven cases operated on in the first stage there was return. ([7])

In the extra-ocular stage it is probably very seldom that any operative procedure can save the patient's life, and recurrences will generally occur.

I still adhere to my statement ([34]) that recurrence occurs very rapidly in glioma, and that there is little to fear of recurrence *in situ* if the orbit is healthy three months after the operation of excision. A case is safe if alive and well one year after the removal of the eye. Wintersteiner also says that if one year, or at most two years, pass without recurrence the case is cured.

It must be remembered that there has been no recorded case in which glioma untreated has undergone a spontaneous cure, and therefore, if a case be left to itself, the issue must be fatal.

To insure the greatest chance for the patient I am certain that the most important point in the operation of excision is that the optic nerve should be divided as far back as possible. If care be taken at least 10 mm. and even 15 mm. of the nerve may be excised with the globe. This is best effected during the operation of excision by cutting one of the lateral recti (the external rectus in the right eye, and the internal rectus in the left eye) on the orbital side of the tenotomy hook. After the other muscles are divided as usual on the ocular side of the hook, the operator catches hold of the portion of the lateral rectus muscle left on the eyeball with the fixation forceps. He now pulls the eyeball forwards, putting the nerve well on the stretch, and by this means, having a better idea of the position of the nerve, he can divide it much further back.

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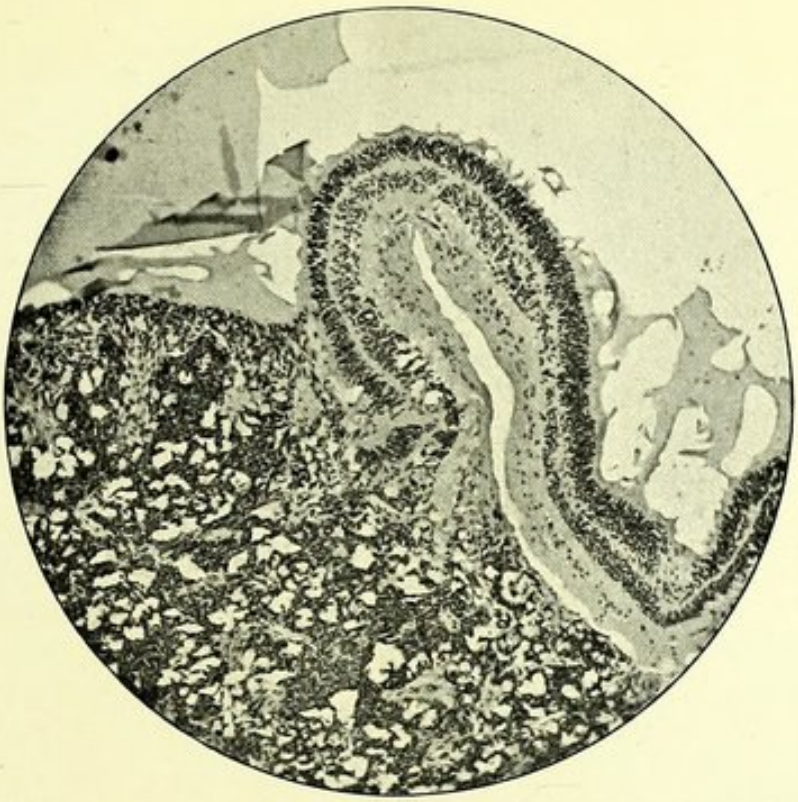

FIG. 1. — Case I.B, from growing edge of tumour, showing a bend of the retina and the trabecular or alveolar structure of glioma. The connective tissue stroma is shown supporting the alveoli and a few blood-vessels with well-formed walls. The lighter spaces are not due to degeneration. x 60

FIG. 2. — Case I.B, greater magnification of portion of Fig. 1, showing alveolar structure and rosettes. No degeneration. x 150

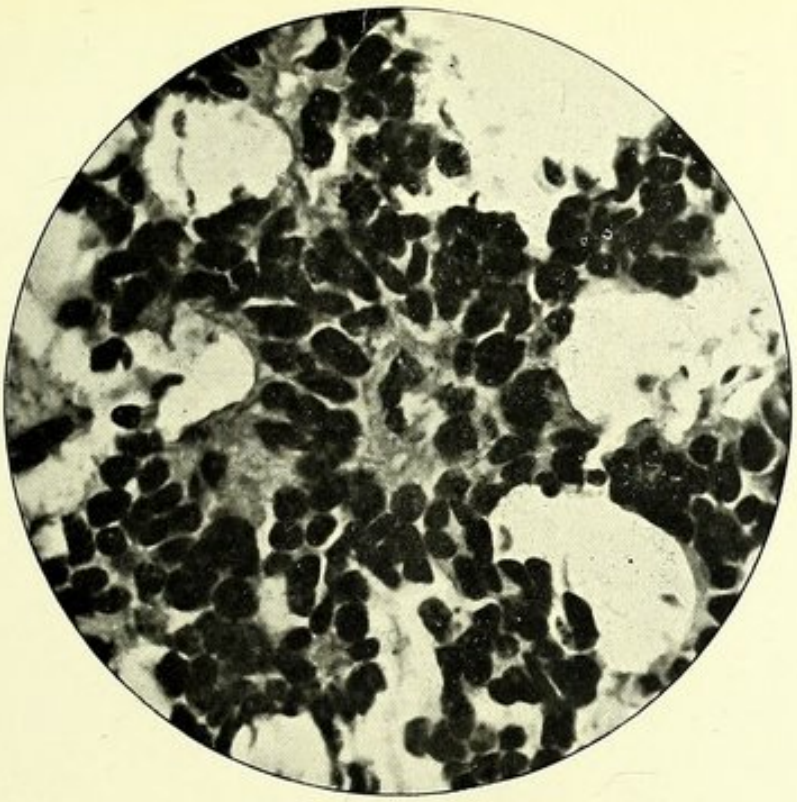

FIG. 3.—Case I.B, a rosette showing its central lumen and layer of cells round it.
x 500

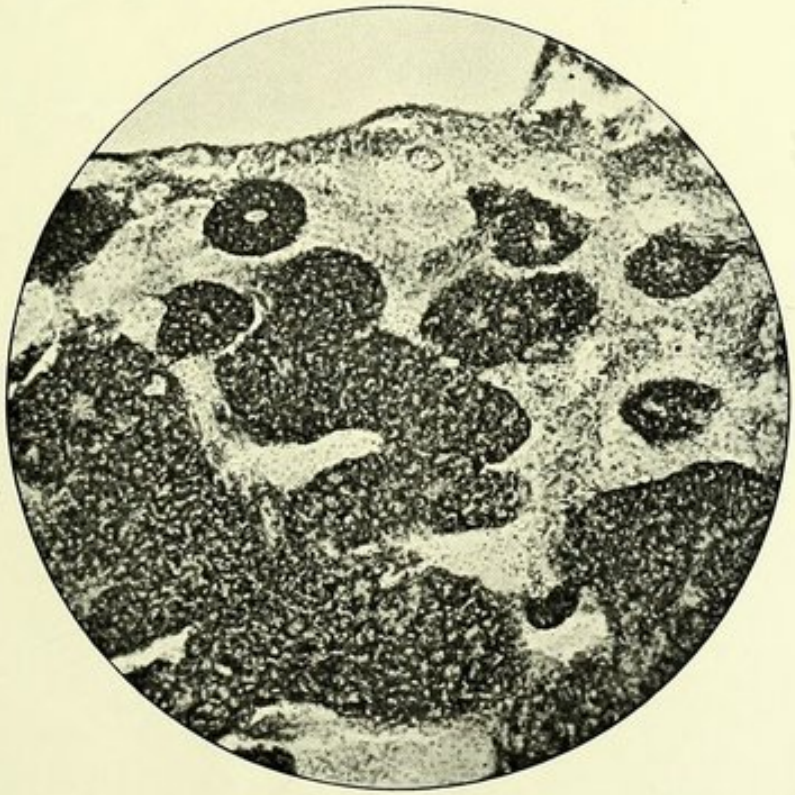

FIG. 4. — Case I.A, showing the worm-like or finger processes, consisting of a blood-vessel with a mantle of cells round it. The light spaces are areas of degeneration.
x50

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