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COMMUNICATIONS

PATHOGENESIS OF MICROPHTHALMIA

BY

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Case No. 1 (By kind permission of Mr. Juler)

History.—L.J., a female child, aged four days, out-patient Royal London Ophthalmic Hospital. Mother, aged 23 years, unmarried and this is her first baby. No history of any miscarriage, delivery was quite natural, no instruments used. Mother quite healthy. There is no history of any inflammation of the eyes since birth.

Grandmother had ten children of whom five are alive, one child was born with congenital contraction of fingers and toes on both sides. He had no nose but two tiny holes instead. The eyes, as far as could be ascertained, were quite normal.

The alleged father in the present case is described as a big, tall and handsome boy, motor driver by trade.

Examination.—The baby looks quite normal and there is no other abnormality present. The orbits are well formed, but the eyelids are on the small side. Lid retractors are necessary for a thorough examination on account of entropion and spasm of the lids.

There appears to be no development of the eyeball on either side. The sockets are lined by conjunctiva all through, the conjunctival sacs are well formed but nothing in the shape of nodules, etc., is detected by the fingers,

On the left side in the centre of the conjunctival sac is a small depression at the bottom round which there is some slightly pigmented scar tissue. This seems to be the only representative of the eyeball present, and, on histological examination it would probably prove to be the posterior retinal epithelial layer, thus illustrating the lowest form of microphthalmia. I do not mean to discuss anophthalmia in this paper.

Case No. 2 (By kind permission of Mr. Doyne)

B.W., a female child, aged 14 days, was brought to the Hospital for Sick Children, Great Ormond Street, on January 9, 1925, with a deformity of the right eye.

History.—There is no history of any deformity in the parents, mother has three children, all girls, the eldest being five years. The other two are perfectly healthy. The present child was born at full time, confinement being quite normal. There is no history of any inflammation of the eyes at birth.

Examination.—The child is very poorly developed and inclines her head to the right side. There are four pedunculated dermoids present; three are well shown in the photographs, the fourth being situated in the right nostril. In addition there is an accessory auricle on the right side (not shown in the photograph). The right lower lid is bulged out by a plum-coloured swelling, soft in consistence, and the size of a large marble. This swelling was noticed at birth. The upper lid appears to be quite normal, and the conjunctival sac is well formed, but there is nothing to be felt in the shape of an eye. The left eye is apparently quite normal.

The fluid drawn from this cyst was unfortunately contaminated with blood. The pathological report is as follows:

Numerous red blood corpuscles. Some polymorphs and mononuclear cells. Cultures sterile.

The swelling on the lower lid was dissected out by the following operation:

First of all the outer canthus was slit open to allow eversion of the lower lid. A horizontal incision was made on the conjunctival aspect along the margin of the lid. The conjunctiva thus severed was dissected backwards and the swellings in the lid removed. Lying to the right, and posterior to the cyst, was found a dermoid which was accidentally punctured, a quantity of greenish fluid escaping from it. The retinal cyst itself was found to be attached to a small hard mass of tissue, a microphthalmic eye.

The eye along with the retinal cyst was divided vertically. On section the microphthalmic eye consists of a mass of fibro-muscular tissue in the centre of which is a cavity containing uveal pigment. In shape it resembles a round disc except at its postero-inferior

border where the optic nerve enters it. Here there is a slight protrusion. In the section the optic nerve has been divided longitudinally and is traceable right on to the cavity of the eyeball. In the cavity which is situated slightly to the posterior

CASE No. 2.

Note bulging of the right lower lid due to retro-palpebral retinal cyst and two dermoids along the line of naso-orbital suture.

aspect of the centre of the eyeball is the uveal pigment surrounded by darkish retinal elements. Lying to the infero-medial surface and reaching the anterior end of the eyeball is the retinal cyst. It is the shape of a half moon. Its communication with the cavity of the microphthalmic eye is situated at its postero-superior end, *i.e.*, just anterior to the entrance of the optic nerve into the cavity of

the eyeball. The cyst wall is about 1.5 millimetres in thickness, and is lined by a brownish membrane which is probably a retinal layer. Its outer covering looks like fibrous tissue. Celloidin sections of the microphthalmic eye and the retinal cyst were cut serially and stained, some with haematoxylin and eosin, others with Weigert's stain.

Microscopic description.—The rudimentary eyeball consists of a round mass whose outer portion is composed of fibrous tissue

CASE NO. 2.

Note the microphthalmic eye with an orbital cyst on its inferior surface. The optic nerve is seen entering the posterior border of the eye. Its cavity is full of uveal pigment and retinal elements, which are seen protruding into the cavity of the cyst through a gap at the posterior end of the choroidal fissure.

lamellae arranged irregularly. In the fibrous tissue mass are situated some muscular bundles and areolar tissue. The thickness of this fibrous tissue is very variable. At its postero-inferior border is the entrance of the rudimentary optic nerve. It traverses the whole thickness of the fibrous tissue layer. Between the optic nerve and the fibrous tissue is a space continued right forward to where the nerve enters the interior of the eyeball. Here the fibrous tissue surrounding the nerve touches its sides. This is the vaginal space of the optic nerve. The nerve bulges out in the cavity of the eyeball, thus resembling the optic papilla, across which fibrous tissue lamellae stretch from one side to the other, so cutting off any communication between the nerve and optic cavity. The proper sheath of the optic nerve is composed of a thin layer of fibrous tissue. The nerve itself shows the typical appearance,

i.e., neuroglial bundles separated by fibrous tissue septa. Inferiorly and external to the fibrous tissue surrounding the nerve, a few millimetres from the entrance of the nerve, between it and the superior aspect of the posterior end of the retinal cyst, are two fairly large blood-vessels cut across. Further forwards and nearer

CASE No. 2.

Only a part of the slide is drawn. It shows the communication between the cavity of the eyeball and the cyst; optic nerve; the cyst wall and blood vessels lying between the postero-superior aspect of the cyst; and the inferior surface of optic nerve.

the nerve are two smaller vessels. I take these to be the central artery and vein of the retina arising from their parent trunk. These blood-vessels are buried in fat and loose areolar tissue. Though in none of the slides can I make out the artery or the vein actually entering the substance of the nerve, I have no doubt in my mind that if antero-posterior sections were cut this would be apparent.

The cavity of the eyeball is full of uveal pigment and fibrous tissue. The latter in this situation is much more cellular than that representing the sclera, and is mainly situated outside the finger-

like processes of uveal pigmented structure. Imbedded in the fibrous tissue forming the outer covering of the microphthalmic eye are bundles of muscle tissue and a piece of cartilage. Situated on the infero-medial side of this rudimentary eyeball is the retinal cyst. As stated in the macroscopic description, its communication with the interior of the eyeball is situated at the superior aspect of its posterior border. Prolonged through this opening into the cavity of the cyst are the contents of the globe, *i.e.*, uveal pigmented structure, some retinal epithelial cells, and fibrous tissue. The retinal cyst itself is composed of an outer fibrous tissue layer and an inner layer that resembles the two granular layers of the fully developed retina. Between the outer fibrous and the inner retinal epithelial layer is a variable amount of neuroglial tissue.

Under the high power of the microscope the inner layer is seen to be divided into two, with loose areolar tissue between them. These two layers rest on a basement membrane, and are composed of retinal epithelial cells somewhat resembling the two granular layers of fully developed retina. Scattered between these two layers are globular masses bulging towards the cavity. These consist of embryonic retinal cells held together by fibrous tissue. In some slides cystic spaces are found in the retinal layers of the cyst. These represent cystic degeneration in this poorly developed retina.

Summary.—We find in this case a rudimentary eyeball associated with a retinal cyst. The vitreous cavity is reduced to a mere slit situated between the tufts of pigmented uveal tissue. There is a gap left at the posterior part of the choroidal cleft, through which the cavity of the microphthalmic eye communicates with that of the retinal cyst. The contents of the eyeball, *i.e.*, uveal pigmented structure and retinal elements, are seen protruding through this gap into the retinal cyst. The uveal structures are not prolonged along the cyst wall, but the retinal elements line the cavity.

At this stage it is advisable to recapitulate some of the important points in the development of the eye.

Two hollow diverticula bud out from the lateral aspects of the forebrain. These, after the closure of the anterior neuropore, are called the optic vesicles. The peripheral part of each expands to form the optic bulb, while the proximal part gives rise to the optic stalk; growth in both these parts continues and this results in the invagination of the optic bulb to form the optic cup in which is received the lens vesicle arising as a thickening of the ectoderm overlying the optic bulb. The invagination of the optic bulb does not cease at its lateral end but is continued right on to its inferior surface and reaches the optic stalk. Through this, the so-called choroidal fissure, mesoblastic tissue makes its way into the optic

bulb and stalk; in the latter position an artery is developed (*arteria centralis retinae*).

Of course the whole of the optic elements at this stage are surrounded by mesoderm. We need not consider here what happens to this, but the fate of that portion of it which is inside the optic bulb and that which fills up the choroidal fissure, *i.e.*, between the two lips of the groove situated on the inferior surface of the optic bulb, does concern us. The former gives rise to the vitreous body. The mesoderm that enters along with the lens vesicle has nothing to do with the formation of the vitreous body, as proved by Hermann Becker⁽¹⁾. In his case the eye was removed from the body of a child five months old. It had increased in size since the baby was one month. On histological examination there was absence of the lens, pupillary opening, iris, ciliary body, and anterior chamber. A choroido-retinal coloboma with thinning of the sclerotic was present. The condition of the retina and pigment showed that the primary vesicle had developed into the secondary, but its inversion had not proceeded in the normal manner. Becker believes that no lens was formed in this case. He cannot decide with absolute certainty as to whether the introversion of the primary optic vesicle ever took place. Vitreous existed though no lens was ever formed. This mesoblastic origin of vitreous explains the occurrence of fat, cartilaginous tissue, and bone in the atypically developed vitreous. As the vitreous body increases in size ample room is afforded for the developing retina to spread out. The plug of mesoderm between the two lips of the choroidal fissure decreases in size *pari passu* with growth of the retinal layers. Ultimately the two retinal layers fuse with their fellows of the opposite side, thus cutting off any connection between the mesoderm that forms the vitreous body and that which surrounds the optic elements and forms the sclerotic, etc. The site where the fusion of the two retinal layers takes place is a weak spot, and if by any means the tension in the vitreous cavity of the developing eye increases, this gives way, with the result that the contents of the globe escape into the surrounding mesoderm and form a retinal cyst. It is quite conceivable that the degree of vascularity of the plug of mesoderm between the two lips of the choroidal fissure influences its fate. If it is very vascular the retinal layers fail to suffocate it by their growth, and instead of fusing with their fellows they curl over. This has been proved histologically by van Duyse⁽²⁾, who demonstrated four retinal layers at the neck of a retinal cyst. van Duyse, Junior⁽³⁾, describing a case of true coloboma of the rudimentary optic nerve, aplasia of their retro-ocular segments gliosis of colobomatous cyst, and entropion of the border of iris in a rabbit one year old says: "In one eye on account of the

minimal development of the vitreous the small space devoted to the development of the retina has pushed that structure outside; it came in contact with the invaginated mesoderm and is evaginated and herniated. Its external expansion at the entrance of the rudimentary optic nerve on the infero-nasal side, has caused the formation of a colobomatous retro-ocular cyst."

The optic stalk of course gives rise to the optic nerve. This is brought about by obliteration of its cavity and the growth in it of nerve fibres most of which are centripetal and are the axons of the nerve cells of the ganglionic layer of the retina.

This case illustrates microphthalmia at a more advanced stage than Case No. 1.

These two cases illustrate arrest of development of the eyeball at a very early stage and I mean to discuss them before I describe the other two, in which arrest of development, or aberrant development as the case may be, has taken place much later.

Case No. 1.—This case illustrates the lowest type of microphthalmia and I am unable to find in the literature of this subject, any other recorded case that resembles the present one. In the absence of histological examination it is very difficult to say at which stage the development has been arrested but the appearance of the depression with the pigmentation all round, strongly suggests that the invagination of the primary optic vesicle has occurred and that the pigmented structure is really its posterior layer laden with pigment granules. What happened to the retina proper, that is the structure arising from the anterior layer of the primary optic vesicle, is very difficult to say.

Case No. 2.—This case illustrates *par excellence* microphthalmia associated with an orbital cyst, an affection not very infrequent.

In this case the development has proceeded quite normally up to the stage of the formation of the vitreous body. This structure arises from the mesoderm that is invaginated through the choroidal fissure which is situated on the inferior surface of the optic vesicle. The amount of vitreous depends on the consistence and vascularity of the intruded mesoderm (Carl Hess)⁽⁴⁾. If this is thick very little vitreous is formed with the result that the developing retina cannot get space to spread, and consequently gets folded, and thus the tension inside the globe is increased with the result that a few folds of retina are extruded through the choroidal fissure, this being the weakest spot, and ultimately give rise to these orbital retinal cysts. This is what has happened in this case. The usual position for these retinal cysts is the middle of the lower lid or the lower part of the orbit, but according to van Duyse⁽⁵⁾ they are occasionally retro-ocular. He describes a case of microphthalmia with an orbital cyst which had two compartments, retro- and sub-ocular and an extra-orbital retro-palpebral.

Rindfleisch⁽⁶⁾ who examined a microphthalmic eye associated with a retinal cyst from a foetus six to seven months old, which was hydrocephalic, and consequently the orbital roof was pressed down so that it was convex below, came to the conclusion that alterations in the orbital roof compressed the globe so bringing about a re-opening and widening of the choroidal cleft and an extrusion of the retinal tissue into the surrounding mesoblast.

This peculiarity was also noticed by van Duyse⁽⁷⁾ in a new-born child 12 months old who had dolichocephalic hydrocephalus with an antero-posterior diameter of 17.5 centimetres and 14 centimetres transversely. The left frontal boss projected strongly in front of the glabella, the two frontal bones were separated, and there was double hare-lip and cleft palate. The child had talipes equino-varus on both sides, six fingers and a rudimentary penis. He goes on to say that in the actual subject the ventricular pressure had depressed the orbital roofs which were flat; this peculiarity was also noticed in the first child of the same parents. It is such as to exert an influence on the shape of the bulb so as to diminish its sagittal diameter.

The three cases quoted above would show that in some cases an alteration in the shape of the orbital roof presses the globe downwards, thus causing an increased intraocular pressure that opens up the defectively closed choroidal fissure and pushes the fold of the retina, which gives rise to these cysts, out; but this alteration in the orbital roof is not always found, so it cannot explain all the cases.

Kundrat⁽⁸⁾ looks to a defect in development of the middle cerebral vesicle as the cause of the malformations which characterize these cysts, and the microphthalmia which invariably accompanies them, and in several of his cases gross deformities in the brain structure were discovered. But there are many cases of microphthalmia on record where there is no defect in the brain and *vice versa*.

The walls of these cysts are usually composed of two coats, an outer one of fibrous tissue continuous with the sclerotic and an inner of more or less highly developed retina. In a case examined by Treacher Collins⁽⁹⁾ the inner coat was represented by bodies normally found in the granular layers of the retina, arranged in separate patches. In another case examined by the same author in which there were two cysts, these were formed by a continuous layer of branching cells and granular bodies. In van Duyse's case, described above, in all sections the internal layer lining the cystic cavity with the exception of nodules of local gliosis proved itself to be retina incompletely differentiated and inverted. The neck of the cyst was lined by folded retina (in four layers). He goes on to say that he described the case (brother of the present one) with

microphthalmia and retro-palpebral cysts on both sides. These cysts communicated with the interior of the eye and had the same lining as the above. Rindfleisch found an inner wall of the cyst composed of retina with its layers well developed, with pigmented epithelium, and an elastic lamina. The inner surface of the retina was directed towards the interior of the cysts.

I have shown that these retinal cysts are due to the extruded folds that lie in the mesoderm, having been surrounded by it, becoming shut off, and then going on to cyst formation. After being in this way shut off from the body of the bulb, active growth in the separated portion does not cease, but, up to a certain point, proliferation of the elements proceeds, with the result that the retinal elements more or less fully formed are found lining these cysts. This is what we find in the case under discussion.

Case No. 3.—The microphthalmic eyes to be described were removed from a new-born pig. There is no record of any other abnormality in the animal save the other eye which is also microphthalmic, and will be described as the next case. Both these eyes were sent to the Pathological Department of the Royal London Ophthalmic Hospital by Sir John Parsons, and I have to thank Sir John and Mr. Humphrey Neame for their kind permission to study and report these rare abnormalities.

There is no record as to which side the eyes belong so I am describing them as "A" and "B."

The antero-posterior length of the first specimen "A" is 13 millimetres and it is 8 millimetres in thickness. In contour it is markedly irregular. At the posterior pole there is a cord-like structure leaving the globe, which on first sight looks very much like the optic nerve. This is well shown in the diagram which represents one-half of the eye. Of the other half microscopic sections were cut. As shown in the figure, the cornea is replaced by a hairy dermoid, which is encroaching on the limbus on both sides. In the cavity of the dermoid cyst are numerous sebaceous glands and remains of fatty tissue. In the centre of the cavity of the globe is a white glistening mass of cartilage. The rest of the cavity is full of a dark structure which seems to be folded up embryonic retinal epithelium, mixed up with choroid and remnants of vitreous body. There is just a trace of lens seen anterior to the cartilaginous piece.

The sclerotic coat is continuous all round and there is no ectasia or cyst formation discoverable. In this specimen there is no sign of any coloboma of the choroid, etc.

Microscopic description.—The half eye was imbedded in celloidin and horizontal sections were cut and stained with haematoxylin and eosin.

The normal cornea is replaced by a dermoid growth which encroaches on the limbus on the left hand side in the slides. The corneal epithelium is replaced by a pavement epithelium, many layers thick, with numerous papillae which resemble those of the

CASE NO. 3.

Note corneal dermoid with fibrous tissue cord at the posterior end, also a piece of hyaline cartilage and dark structure in the cavity of the globe (epithelial retinal tissue).

skin. The hair follicles are seen surrounded by sebaceous glands, some containing hair roots. Next to the epithelium the cyst wall is composed of fibrous bundles arranged irregularly: the separate fibres are but poorly supplied with nuclei. The cyst wall that is interposed between the ocular cavity and the cyst itself, is only one-third of the thickness of the rest of the wall, and, of course,

has no epithelial covering. It resembles sclerotic in structure, and is different from the rest of the cyst wall. The cyst itself has no proper inner lining. In the lumen of the cyst there are some

CASE No. 3.

Note the typical appearance of the dermoid representing the cornea. The lens is displaced and tilted. There is no communication between the interior of the globe and the degenerated plug of tissue representing the optic nerve. Retinal elements are gathered behind the posterior lens capsule.

well developed sebaceous glands. Their acini are full of some faintly staining structureless material, probably epithelial debris and secretion. The lumen of the cyst is divided into compartments by fibrous tissue septa. The rest of the cavity is full of loose areolar tissue which contained fat in the living specimen. The cystic wall

interposed between it and the optic cavity may be regarded as representing the cornea. As already stated, it resembles sclerotic in structure, though only one-third its thickness. At the middle of the posterior surface of this altered cornea is a thick line of homogeneous structure, probably representing Descemet's membrane, but there is no definite posterior endothelium. At the extreme periphery on the right side the only remnants of the iris are attached to the posterior surface of the cornea. This is the pigmented epithelial line whose posterior border merges insensibly into the choroid. Its anterior border extends only a short distance past the limbus corneae. Of course, there is no anterior chamber or angle, and the spaces of Fontana, etc., are also absent. The writer could not see any trace of the venous channel (Schlemm's canal) in any section. The space between the posterior surface of the cornea and the capsule of the lens is reduced to a mere chink. The lens is on the small side in all the slides, and is tilted so that its right equatorial extremity reaches further forward than does the left. This point is not well shown in the figure, as the lens is more oval than that which the artist has drawn. It is enveloped by a capsule which is closely applied to it posteriorly, and to its right side, but on reaching its anterior surface there is an interval between it and the lens which increases as we pass on to the left hand side of the slides. Here the capsule is actually folded up. Between the capsule and the lens in this situation are found embryonic fibres of the lens in different stages of development. Some cells are degenerated and vacuolated. Retinal epithelium is adherent to the posterior surface of the lens capsule. The sclerotic is well developed and appears quite normal, save for the pigment that is scattered all through its thickness. It is prolonged as a cord posteriorly. The outer covering of this cord is scleral tissue which is lined on the inner surface by a layer of choroid intermixed with retinal epithelium. In this layer are found some blood-vessels. Internal to this is a space which resembles the vaginal space of the optic nerve. Inside this is a plug of homogeneous matter, due probably, to the hyaline degeneration of embryonic mesoderm and nervous structure; it stains evenly and shows no structural details. Its surface is full of haemorrhages. This plug or cord of structureless material passes inside the cavity which represents the vitreous space, and spreads out to fill the posterior quarter of that cavity. Its anterior end contains numerous haemorrhages and is lined by the choroidal pigment. This fact is very well shown in the diagram, and in none of the slides could I make out any communication between the interior of the globe, *i.e.*, the part lined by the choroid, and this plug of degenerated fibrous tissue. Choroid lines the sclerotic and consists of an irregular network of pigment epithelium, fibrous tissue, and blood-

vessels of all sizes, cut across in different directions. There is a slight attempt at the formation of a ciliary body on the right hand side in the slides. Here the depth of the choroidal structure is increased and from its anterior part is given off the thin line representing the iris which is adherent to the posterior surface of the cornea. Retina and remnants of the vitreous body are in the form of a solid mass filling the cavity of the globe, and immediately behind the posterior part of the lens capsule the embryonic retinal epithelium has the appearance of numerous tufts cut across in various directions; each of these has a central cavity filled by colloid matter that stains evenly and has no structural details. There is no suggestion of any pigmentation in this part of the slide. Posterior to the lens and about the middle of the cavity of the globe is a piece of hyaline cartilage cut across. It shows the usual structure, and is surrounded by embryonic retina. The rest of the cavity is full of embryonic undifferentiated retinal epithelium with haemorrhages in several parts and structureless colloid matter. In parts there are scattered amongst the retinal epithelium structures resembling malformed fibrous tissue. This seems to be prolonged forwards between the lens and ciliary process on the right hand side in the slides, and it appears that the dislocation of the lens in the opposite direction, is due to this.

Let us study each of these abnormalities separately.

Corneal Dermoid

Mitvalsky⁽¹⁰⁾ who studied this subject very carefully gives the following figures. Out of 75 cases on record 90 per cent. were typical, that is, they were not anatomically connected with the lids, and in the majority of these the growth was situated at the corneoscleral junction. In 5 out of these 65 the tumour was entirely corneal and in 10 entirely scleral. In some, conjunctiva was replaced by tumour tissue, in others it covered the growth, but in most instances a portion of the growth was apparently covered by conjunctiva, while the rest exhibited on the surface a pavement epithelium, papillae, hair follicles, and fine hair; sebaceous glands were common, but sudoriferous glands rare. According to the above writer the cystic form or closed dermoid is never met with in the eye.

The specimen above described is, of course, a typical dermoid. It is mainly corneal though it encroaches on the limbus. There is no trace of any normal corneal epithelium, but instead it is covered by a pavement epithelium, papillae, hair follicles and well formed hair. Sebaceous glands are well formed and the lumen of the cyst is full of fat and loose areolar tissue. On going through

the literature on the subject the writer is unable to find another case that showed all these points so distinctly and where the dermoid tumour was of such dimensions.

The tilting of the lens requires special mention. In the present case I cannot find any distinct cause for this displacement of the lens, save the fact that the embryonic retinal tissue seems to be adherent to the capsule on its posterior part, especially on the left side; then the embryonic fibrous tissue seems to be adherent to this part of the retina, and is continued on towards the back of the cornea between the lens and remnants of the ciliary body on the opposite side, which may possibly explain the present phenomenon.

Mayou⁽¹¹⁾ described a case in a child who was born at the seventh month. There was atypical fibrous development in the vitreous space, which had caused a backward dislocation of the malformed lens, with under-developed ciliary processes.

Treacher Collins⁽¹²⁾ described a case in a microphthalmic eye where the lens was held back by the fibrous tissue in the centre of the vitreous body; the suspensory ligament of the lens was stretched and attached to elongated ciliary processes. Retina in this case was much folded.

Carl Hess⁽¹³⁾ described a case of a microphthalmic eye in a child, aged three years. The measurements of the globe were 10 millimetres in all diameters; sclerotic, choroid, and retina were normal. There was a small coloboma of the iris. A process almost as large as the optic nerve came forwards in the vitreous cavity. This consisted of hyaloid artery with loose connective tissue containing mostly spherical nuclei and a few spindle-shaped elements. It decreased in size towards the centre of the vitreous to increase again further forwards becoming more fibrous in character as it reached the lens. It spread over the posterior capsule as a thick vascular membrane and passed as a delicate band round the equator of the lens through a coloboma of the iris into the anterior chamber. Here it split into two portions, one of which spread over the anterior capsule and was directly connected with the iris, and the other turned downwards to unite with sclerotic and choroid in the position of Fontana's spaces. The ciliary body, otherwise normal, was pushed away from the lens and bent towards the vitreous, at the place where this band came in relation to it, and the lens itself was dislocated in the contrary direction. No signs of any inflammatory processes were present. The cases quoted above would suggest that the dislocations of the lens that are present in microphthalmic eyes are usually due to some defect in the development of the vitreous body.

The piece of cartilage.—This piece of cartilage as described above is surrounded by the retinal elements, and on dissecting half the eye a note was made that this cartilaginous nodule is pushing the retinal elements from behind so that it has got inside the retina which is folded all round it. There are three possible sources for the development of cartilage in microphthalmic eyes.

(1) Most commonly it is due to an atypical development of the embryonic mesoblast that goes to form the vitreous body.

(2) It may be an atypical development of the mesoderm that forms the choroid and sclerotic and may push the retinal elements from behind, which get folded over it, and thus in a section the cartilage is surrounded by embryonic structure. This is what I think has occurred in the present case.

(3) It may develop in a fibrosed part of the retina, but this implies first of all intrauterine endophthalmitis, and fully formed blood-vessels; a condition not proved to occur. This question of cartilage in the vitreous cavity will be further discussed in connection with the next case which has two cartilaginous nodules present.

Undifferentiated embryonic retinal elements.—As stated in connection with Case No. 2, for the proper development of retinal elements there must be enough space for them to spread. In microphthalmic eyes on account of the atypical development of the embryonic mesoderm that goes to form the vitreous body, there is very little space for the retina to spread out, with the result that it gets folded and forms tufts that are mostly situated near the posterior surface of the posterior lens capsule. The next specimen to be described exhibits this deformity in a still more advanced form, and I will discuss the further facts in connection with it. On account of the absence of the ganglion cells of the retina and their axis cylinders, the optic nerve fibres, the hypoplasia of the optic nerve is easy to understand. In the present specimen the optic nerve and sheath are represented by the plug of colloid matter well shown in the figure and described above. It is impossible to make out any structure in it save some haemorrhages. It may be that it is degenerated glial elements or again it may represent the fibrous cord which originally held the arteria centralis. The axis cylinders of the ganglion cells of the retina are really neurons of the second order so that the optic nerve is not like any other cranial nerve. The neurons of the first order are the elements uniting the rod and cone layer to the ganglion cells. Its development proceeds from the cavity of the globe towards the brain, *i.e.*, the axis cylinders of the ganglion cells of the retina as they grow are gathered together and leave the eye as the optic nerve. As regards the development of their myelin sheath, this is derived from the brain (Mayou⁽¹⁴⁾).

**Case No. 4. Second Eye from the same animal as
Case No. 3**

The eye is distinctly smaller than the previous specimen. There is an obviously small cornea, which is quite flat instead of being

CASE NO. 4.

Note absence of lens and pupillary opening. The anterior chamber is a mere slit. The coloboma of the ocular membrane is shown in the lower part of the figure (left side).

convex anteriorly. In circumference it is greatly reduced, being one-eighth of the circumference of the globe. The eye was cut into two halves as usual; one half was kept as a museum specimen; of the other half sagittal sections were cut serially.

The museum specimen shows defective sclerotic posteriorly. There is no sign of optic nerve present. On one side, which I

take to be the infero-medial, the sclerotic is represented by a very thin lining of fibro-muscular tissue. It is bulged outward by a plug of the contents of the globe that is protruding through the defect in the choroid and sclerotic at that place. There is a small

CASE NO. 4.

The cornea is shown on the left side in the diagram. Note coloboma of choroid and ectasia of sclerotic in the lower part of the diagram. There is a piece of cartilage in the vitreous cavity.

plug resembling the contents of the globe that lies outside the cavity altogether. The globe itself is very irregular in shape. Inside the cavity of the globe one can see a piece of hyaline cartilage. There is no trace of any lens discoverable. There is an obvious gap in the choroid on what I take to be the infero-medial surface. On the opposite side to this gap there are two

pockets formed in the sclerotic and choroid which contain structures resembling the folded up retina, like that found in the cavity of the globe. The retina is folded up and gathered into a mass that lies in the middle of the cavity. During the dissection of the half of the globe a note was made that a plug of fibrous tissue is uniting the ectatic sclerotic to the piece of cartilage that has been described above as lying nearly in the middle of the globe.

The thickness of the sclerotic varies. It is at its maximum at the limbus and a short distance away from it; as has already been stated, it is very defective posteriorly.

Microscopic description.—The slides to be described are stained with haematoxylin and eosin:

Cornea.—This is comparatively small in circumference, and, as already stated, is flat instead of being convex anteriorly. The corneal epithelium appears to be quite normal; it is seven cells thick. The cells are of pavement type anteriorly, but as one traces them further back they get more and more elongated, until we get to the line of cells next to the substantia propria, which are cylindrical.

There is no Bowman's membrane present. Substantia propria consists of the usual structure, that is, bundles of corneal lamellae arranged in a regular manner; the spaces between these lamellae are well marked. Posteriorly about the middle of the cornea Descemet's membrane can be made out. This seems to be lined by the posterior endothelium. There is an abrupt change in the structure of the corneal lamellae as we reach the limbus. The anterior chamber is a mere slit-like opening between the imperforate iris and posterior surface of the cornea. On one side of the slide the iris is adherent to the back of the cornea. The normal structure of the angle of the anterior chamber is wanting, that is to say, there are no spaces of Fontana, etc. The iris on the right hand side of the slide is composed of two distinct parts. The part adjacent to the remnants of the ciliary body is of great thickness and has a well-developed posterior pigmented epithelial layer (*pars iridica retinae*). Anteriorly the pigmented stroma cells are condensed to form another pigmented layer, which on a superficial examination resembles the posterior one, but under a high power has proved to be just a condensation of the pigmented stroma cells. Between the two layers above described are numerous blood-vessels of different sizes cut across in different directions. They have fairly thick walls and some of these contain blood corpuscles in their lumen. The stroma itself is composed of loose fibrous tissue and of chromatophores. The part further away from the ciliary body is very thin as compared with the part above described. It is composed of the same two layers, anterior

and posterior, of pigmented cells. Between these two layers in all slides there is a mass of red blood corpuscles that have gone on to hyaline degeneration, but the structure can still be made out. This part of the iris is adherent to its fellow on the opposite side. The iris on the other side is very rudimentary. As stated above, one part of it is adhering to the back of the cornea, while the other part dips backwards in between the embryonic retinal tissue. The ciliary body is represented on both sides by an irregular network of finger-like processes which are lined on the inner surface by pigment epithelium and contain in their lumen various amounts of fibrous tissue and colloid material. The choroid is very irregular in thickness in different parts of the slides. It is defective on the infero-medial side, *i.e.*, there is a coloboma of the choroid at this spot. Its normal structure is best seen where it lines the two diverticula situated opposite the colobomatous area. Here its innermost layers are composed of pigmented cells arranged in a regular manner resembling palisade epithelium, but the cells in the present case are more rounded. Exactly opposite the colobomatous area the choroid dips into the cavity of the globe in a long finger-like process; its end is directed towards the colobomatous area. From the slides it appears as if the fibrous tissue that is uniting the ectatic sclerotic with the cartilaginous pieces is prolonged forward to be adherent to the extremity of this choroidal incursion, and that it is dragging the choroid towards the colobomatous area at this spot. In structure the choroid is composed of blood-vessels of different sizes: some of these contain blood cells in the lumen, chromatophore cells and fibrous tissue. There is no lamina suprachoroidea discoverable.

The retina and the vitreous body.—As already stated the retina is folded up in a mass in the centre of the cavity of the globe and is very abundant just behind the iris to which it is adherent. In structure it is composed of embryonic retinal epithelial cells that line the sides of the finger-like processes, the lumen of which is full of colloid matter. These are cut across in various directions and give a very complicated picture. In the middle of the slides the retinal epithelium gives an appearance like that of the rosettes of a glioma. There are concentric layers of epithelial cells arranged round a cavity which contains blood cells. The vitreous body is represented by ill-developed embryonic fibrous tissue, and opposite the coloboma of the choroid are two nodules of hyaline cartilage. These cartilaginous nodules are united to the ectatic sclerotic by fibrous tissue containing retinal epithelium in places. In the cavity of the globe are found some haemorrhages. The two pockets described above are lined by the choroid, as already stated, and contain in their lumen huge masses of red blood cells with a few polymorphs.

The coloboma of the ocular floor.—Its size is different in various slides. If we trace it from the periphery towards the centre, in some slides it is not present at all; then in the innermost slides it is nearly one-seventh of the circumference of the globe. The ectatic sclerotic opposite the colobomatous area is very thin indeed. All these details are very well shown in the accompanying figure.

The important point to note is the fibrous tissue cord that seems to be uniting the cartilaginous pieces to the defective sclerotic and is prolonged forwards to be attached to the finger-like incursion of the sclero-choroidal tissue which it is dragging towards the coloboma.

There is no trace of any lens discoverable in any of the slides.

In this microphthalmic eye there are the following interesting points for discussion :

Absence of the lens.—This may be either due to absorption of the foetal lens or to its non-formation. In the case described by Hermann Becker and quoted above, there was no lens discoverable. Although Becker admits that the foetal lens may disappear completely, he believes that no lens was formed in his case, because if such had ever existed a pupillary opening must have been produced, unless of course the lens had developed in some other position and of this he could find no evidence. Mayou⁽¹⁴⁾ describes a case of a child born at the seventh month who lived for twenty-four hours. He says : "In the right eye the condition represents what I take to be the failure in the secondary optic vesicle or lens to hit off the primary outgrowth from the fore-brain, with the result that the lens lies below the primary optic vesicle, the two layers of which have not come together since they have become distended to form a cyst, the anterior end of which lies in front and to the inner side of the lens. It is clear from this case that lens sometimes develops in other positions than the interior of the optic cup."

In the present case I believe there was no lens formed at all, otherwise one would expect to find a pupillary opening and some trace of an anterior chamber.

Coloboma of the membrane of the optic floor with ectasia of the sclera in that situation.—These colobomata are undoubtedly due to the defective closure of the choroidal fissure (foetal cleft). This cleft, as already stated, is formed simultaneously with the formation of the secondary optic vesicle and invagination of the lens. It is ventral in position and extends back a short distance in the pedicle. The cleft soon closes, but there is delayed retinal pigmentation at this spot (sixth week in man). When the eyes are gradually pushed from the lateral to the medial position, there is no rotation, so that the choroidal fissure still occupies the ventral position (Chievitz⁽¹⁵⁾). It is extremely rare to meet with an atypical

choroidal coloboma, though it does occur, and two choroidal colobomata may occur in the same eye. This is explained by the occasional occurrence of a double foetal cleft. A case of this kind was described in a calf embryo by van Duyse. As to the causes of the defective closure of the foetal fissure there are three different theories, *i.e.*,

- (1) Mesoblastic theory.
- (2) The retinal theory.
- (3) The lenticular theory.

The lenticular theory which ascribes the defect in the closure of the foetal fissure to the abnormally big size of the lens, which fills up the cavity of the globe cannot operate in the present case on account of the absence of the lens. The second theory that ascribes the whole phenomenon to an undue proliferation of the retinal elements does not explain all the facts, and so I am leaving that out of discussion. In my mind the mesoblastic theory, as stated, explains all the facts very satisfactorily. v. Hippel's⁽¹⁶⁾ experiments (quoted by Sir John Parsons) are very interesting in this connection. According to this writer the edges of the foetal cleft are separated by a narrow band of vascular mesoderm which increases in size. The cells in the lips of the cup are absolutely normal. As the development proceeds a struggle between these two tissues ensues; if the vitreous is normal then the retina spreads out without folding; if it is diminished the retina is folded and endeavours to find space by overlapping the edges. If the vitreous is very small, folding of the retina becomes much pronounced. As explained while discussing Case No. 3 the amount of vitreous depends on the intruded mesoderm; if it is dense very little vitreous is formed and *vice versa*. This theory seems to explain all the facts found in colobomata of the choroid and retina.

Cartilaginous nodules which are present.—It is clearly seen from the diagram and slides that the cartilaginous nodules are arising as atypical development of the intruded mesoderm that goes to form the vitreous body. In this connection work done by Carl Hess is very important. One of his cases where the lens was pushed on one side has been quoted above while discussing Case No. 3. That showed an atypical development of vitreous with choroido-retinal and iridic colobomata. There was no sign of any inflammatory process present. Case No. 2 in his series represented bilateral microphthalmia. The lenses in both eyes were fixed against the ocular tunics in close proximity to the optic nerve. There were colobomata present as in the other case. Connective tissue bands were present in the vitreous. The Case No. 3 was again a bilateral microphthalmia in a prematurely born child. Vitreous was pierced by a band of fibrous tissue surrounding the

hyaloid artery forming the capsule of a dislocated irregularly shaped and cataractous lens and proceeding forwards in the anterior chamber to join the corneo-scleral border. Its anterior portion contained hyaline cartilage. The right eye contained a similar piece of cartilage. Other cases of atypical development of the vitreous have been quoted above (Mayou, etc.).

Let us take the last interesting feature of this case, *i.e.*, the undifferentiated embryonic retinal tissue portions. As stated above the mal-development of the retina is the result of defective vitreous cavity. The appearance of rosette formation is really due to folds of retinal elements having been cut across in different directions. It is quite a common occurrence in microphthalmic eyes. Cases have been described by Greeves⁽¹⁶⁾ and others.

In the second case described by Greeves in a patient, aged 4½ years, the right eye had been much smaller than the left since birth. There was no history of any eye trouble. The retina was gathered into a mass in the centre of the globe. In some parts an appearance of rosettes was produced by a section across the convolutions. Lens in this case was represented by a shrunken mass of capsule lying in the centre of the pupillary area.

Summary

I have described above four cases of microphthalmia representing different stages at which the arrest of normal development has taken place. In all these cases aberrant development was present. There are two main theories to explain this abnormality. Deutschmann⁽¹⁷⁾ attributes all congenital abnormalities to intrauterine inflammation. This may operate in cases of atypical colobomata of the iris and of anterior staphylomata, but it has never been proved to have occurred in cases of microphthalmia. There is no suggestion of any inflammation in the cases described above. Hess describing four cases of microphthalmia, to which reference has already been made, came to the same conclusion. In none of his series of cases was there a suggestion of any inflammation.

The second theory attributes this abnormality to an arrest of normal development. Any deleterious agent might be expected to act injuriously on delicate foetal structures. In this connection Ochi's⁽²⁰⁾ experiments are interesting. He employed four methods :

- (1) Salt solution injected near the blastoderm.
- (2) Distilled water injected near the blastoderm.
- (3) Air injected near the blastoderm.
- (4) Mechanical disturbance.

By these means he obtained microphthalmia in 26 cases.

There is strong evidence that in Case No. 1 of our series fright has been the operative cause. First cessation of the menses usually corresponds to about three weeks' gestation and this is the time when the optic vesicles are being formed as a pair of hollow diverticula from the lateral aspects of the fore-brain. This coincides with the time when the girl first realized her condition, and the consequences associated with it. Naturally, her whole nervous system is upset with this sudden shock, and it is quite conceivable that this acts deleteriously on the developing embryo with its maximum effect on the most delicate structure, that is, the primary optic vesicle. It may be that no primary optic vesicle is formed at all or that its future development is arrested. Probably in other cases some such agent as an injury, change in pressure, chemical poison, etc., has been operative.

Consanguinity is sometimes blamed as the cause of these abnormalities. Cases of anophthalmia have been described by H. Triepel⁽¹⁸⁾ and Cecchelto⁽¹⁹⁾, and microphthalmia by van Duyse, but of course, this is not always found.

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