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DEGENERATIONS FOLLOWING LESIONS OF THE RETINA IN MONKEYS.

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THE optic nerve, so-called, consists of centripetal and centrifugal fibres, of which the former are probably the more numerous. Of these, most are believed to be the axons of the ganglion-cells in the retina. If therefore, groups of the ganglion-cells are destroyed, we should expect to find the corresponding fibres of the optic nerve degenerated, and to be able to trace these fibres to their ultimate destinations in the brain. This line of research has hitherto received very scanty attention.

Falchi (1) in 1886, and Baquis (2) in 1889, made retinal lesions for the purpose of studying the reaction of the different retinal elements.

Pick (3) in 1895, destroyed circumscribed areas of the retina in a very large number of rabbits, and traced the degenerations in the optic nerves, chiasma and tracts. He arrived at the following conclusions:—"The fibres retain, throughout their whole course, both in the optic

nerve and in the optic tract, the same relative position ; the crossing in the chiasma occurs in regular sequence : first the innermost bundles of the optic nerve, and then successively those lying farther outwards ; definite parts of the transverse section of the optic nerve thus correspond to definite parts of the tract of the opposite side. To the lower parts of the optic nerve answer similarly the parts lying below in the tract ; to the inner parts of the optic nerve, the outer parts of the tract ; to the outer parts of the optic nerve, the inner parts of the tract ; as also it is probable that the upper parts of the tract correspond to the upper part of the nerve. In the chiasma, there is merely a decussation of fibres in the transverse direction, and not any rearrangement of them in the vertical direction. The topographical relations between the retina and the optic nerve can be defined thus :—The different parts of the optic nerve correspond in general to the similarly situated parts of the retina ; and in a similar manner, the relations between the retina and tract of the contralateral side are in accordance with the same arrangement."

As in the earlier researches of von Gudden, the small direct tract which exists in the rabbit seems to have escaped Pick's observation. Pick made one or two observations upon cats, with the same results.

Dean and Usher (4), independently, in the same year, arrived at similar conclusions with regard to the optic nerve in rabbits. They do not record any investigations of the chiasma or tracts. They also made a lesion between the disc and the macula in a monkey, and obtained degeneration in the papillo-macular bundle in the optic nerve. The degeneration was similar in distribution to that found in cases of toxic amblyopia, viz., a wedge-shaped area on the temporal side near the eye, becoming crescentic and nearer the centre of the nerve farther back, and finally central near the chiasma.

METHOD.

In my experiments operations were performed upon six monkeys. The pupils having been previously well dilated by the instillation of atropine, the animal was anæsthetised

with ether. The fundus was examined ophthalmoscopically to see that it was normal, and the conjunctival sac was washed out with weak solution of perchloride of mercury. A speculum was inserted, and the eye fixed by fixation-forceps, held by an assistant. A Graefe's cataract knife was then introduced into the eye 4 or 5 mm. behind the corneo-scleral margin, at either the nasal or temporal side, thus avoiding dangerous injury to the ciliary body, and minimising injury to the retina. The knife was passed across the eye through the vitreous to the opposite side, and the retina wounded there to the required extent, the position of the point of the knife being in some cases observed by the ophthalmoscope (direct method). The ophthalmoscope was especially used in lesions near the disc or macula. In other cases, the wound was made without ophthalmoscopic examination, the slight resistance encountered being sufficient to show that the retina had been reached. The exact position and nature of the wound were subsequently determined by ophthalmoscopic examination, which was repeated after an interval of a few days, and also shortly before killing the animal. The lesions were all investigated microscopically by a suitable section of the eye, *post mortem*, and were then prepared for microscopic examination. The results of the latter investigation have elicited several points which are of ophthalmological rather than neurological interest, and will be detailed elsewhere.

There was usually no loss of vitreous during the operation, but a small bead escaped in two cases, without, however, causing any untoward result. The wound of entrance healed with great rapidity in all cases. There was slight hyperæmia of the conjunctiva for a day or two, but this quickly passed off, and the animal looked perfectly normal.

The monkeys were chloroformed to death from a fortnight to three weeks after the injury. The brain was removed and placed in formol, the optic nerves being cut through immediately in front of the chiasma. The roofs of the orbits were then removed, and the optic nerves dissected free from the other orbital contents. Great care was taken

to preserve the accurate orientation of the nerves. The eyes were left *in situ* until the orbits had been dissected back to the foramina, so that the nerves were thus anchored at each end. The eyes, with the nerves attached, were then lifted out of the orbits and pinned out upon a piece of cork. They were then hardened in formol. When hardening was completed, the eyes were removed and examined. The nerves were pinned out, side by side, upon a piece of liver, and transferred, after thorough washing in running water, to Busch's solution. In this condition they were put through the alcohols and embedded in celloidin, the pins being removed after the celloidin had set. Small, fine, entomological pins were used. There was usually a slight reduction of osmium around the pin-holes, but this did not extend for any distance into the nerve, and the degenerations were determined from careful examination of many sections, and not from isolated ones. The sections were cut with a Jung microtome, every fifth (in some places, *e.g.*, the chiasma, more) being mounted and examined.

EXPERIMENTS.

Experiment I.—Rhesus. Right Eye.

October 16, 1901. A small lesion, about 2 mm. long, in a direction tangential to the disc, was made near the equator in the lower nasal quadrant. There was a little hæmorrhage; the area of pigmentary degeneration was very little larger than the lesion.

October 31, 1901. Killed.

The degenerations in the optic nerve are shown in the micro-photographs on Plate I. The degenerations in the optic nerve, chiasma and tracts are shown diagrammatically in figs. 1 to 8. (The outlines of the diagrams were all drawn with the Edinger Projection Apparatus, the details being filled in free-hand, under a higher power, only degenerations which could be traced along the nerve being drawn. The diagrams therefore represent what are believed to be the essential degenerations following the given lesion.)

Figs. 1 to 5 show that the main area of degeneration is wedge-shaped near the eye, the apex of the wedge being

PLATE I.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

towards the centre of the nerve, and the base at the periphery, the whole lying in the upper part of the inferior nasal quadrant. There are scattered degenerated fibres over the whole nasal side, and a few isolated ones upon the temporal side. In sections taken more posteriorly, behind the entrance of the central retinal vessels, the shape of the area occupied by degenerated fibres becomes more crescentic, but is still nasal. Fig. 6 is a nearly vertical (frontal) section of the

chiasma. It shows the fibres crossing, principally in the inferior or ventral part of the chiasma. Fig. 7 is a slightly more oblique section farther back, being in a direction downwards and forwards. The degeneration is therefore ventral and anterior. Fig. 8 is still more oblique, approaching the horizontal, so that only the extreme posterior part of the chiasma is shown, and the tracts are cut more or less

longitudinally. Very few fine dots of degeneration are seen in the chiasma and tract of the same side, the main area of degeneration being in the outer part of the contra-lateral tract. Farther back the fibres spread out over a larger area of the section of the tract, becoming diffuse as they approach their termination.

In sections passing through the bundles of the third nerve as they leave the brain in this monkey, some apparent degeneration was seen on each side. The same occurred to a less extent in the decussation of the fourth nerves. The interpretation of this and other anomalies will be discussed later.

Experiment II.—Jew. Left Eye.

October 30, 1901. A rather larger lesion, about 3 mm. long, was made in a direction tangential to the disc a little in front of the equator in the lower temporal quadrant of the retina. There was practically no hæmorrhage, and the pigmentary degeneration was limited to the lesion.

November 18, 1901. Killed.

The degenerations in the optic nerve are shown in figs. 9 to 11.

Figs. 9, 10, and 11 show that the main area of degeneration is on the temporal side along the whole course of the nerve. It is most marked, and is very dense in the lower temporal quadrant, being more or less wedge-shaped near the eye, and becoming rounder farther back. It tends to become more dorsal near the chiasma, but it is possible that may be due to slight error in orientation. As in I., there is some diffuse generation, most marked on the temporal side. The fibres lie principally in the dorsal part of the chiasma. Many degenerated fibres are seen crossing to the opposite tract. Farther back the fibres lie principally in the central part of the tract of the same side. Posteriorly, they spread out and become more diffuse. In a similar area of the tract of the opposite side, *i.e.*, dorsally and centrally in front, becoming broader behind, there are many finer black spots of degeneration.

The areas including the third and fourth cranial nerves were not sectioned in this brain.

Experiment III.—Bonnet. Left Eye.

November 20, 1901. A very small lesion was made upon the temporal side near the equator, just below the horizontal meridian. There was no bleeding. Macroscopically there was only a white dot at the site of the lesion.

December 7, 1901. Killed.

The degenerations in the optic nerve are shown in figs. 12 to 14.

It will be seen that the degeneration is almost limited to the inferior temporal quadrant, and is very slight. In the chiasma it is at first ventral and anterior in position, gradually tending towards the dorsal surface. In the tract of the same side it is central and dorsal at first, becoming more diffuse posteriorly. There are only a few scattered fibres degenerated in the contra-lateral tract. There was apparent degeneration in the bundles of both third nerves.

Experiment IV.—Rhesus. Right Eye.

January 13, 1902. The lesion was larger, about 3 mm. long, in this retina. It was on the temporal side, a little behind the equator, and extended above and below the horizontal meridian. There was slight hæmorrhage, and, *post mortem*, there was an oval area of pigmentary degeneration, with axes of about 4 mm. by 3.5 mm. The retina was firmly adherent to the choroid over this area.

February 1, 1902. Killed.

Figs. 15 to 17 show the degenerations in the optic nerve.

It is seen to be diffused over the whole temporal side of the nerve, without any special area of concentration. In the chiasma it occupies the central and dorsal parts. There is no degeneration in the ventral part. In the tract of the same side the degeneration is arranged much the same as in II., but more fibres are affected. There is a finer, scattered degeneration in the contra-lateral tract.

The third and fourth nerves were not cut.

Experiment V.—Rhesus. Left Eye.

January 14, 1902. A small lesion was made between the macula and the disc, but at a slightly lower level. It was rather

deep, injuring the choroid and sclera, and there was some hæmorrhage.

January 28, 1902. This monkey died in the morning; it was dissected about two hours afterwards.

Fig. 18 shows the distribution of the degeneration in the anterior part of the nerve. Posteriorly it became more central. It occupied the central part of the chiasma, and continued central, and rather dorsal in the anterior part of

the same tract, becoming more diffuse posteriorly. There was a large amount of degeneration considering the small extent of the lesion. This was probably due to its proximity to the disc and its situation in the neighbourhood of the macula. There was fine degeneration in the contra-lateral tract, the fibres crossing in the central part of the chiasma.

There was apparent degeneration in the bundles of both third nerves.

Experiment VI.—Rhesus. Left Eye.

January 25, 1902. A lesion, 2mm. long, was made in a direction down and out, starting 2mm. down and out from the fovea centralis. There was considerable hæmorrhage into the vitreous.

February 15, 1902. Killed.

Fig. 19 shows the distribution of the degeneration in the posterior part of the nerve.

In the anterior part of the nerve it is most marked on the temporal side, especially just below the horizontal; but there is also a considerable amount of degeneration over the whole area of the section. It is chiefly central in the anterior part of the chiasma; in the posterior part, where the sections are more oblique, *i.e.* about half way between vertical and horizontal, it occupies a crescentic area at the periphery of each side with a connecting band in front. In this situation, therefore, the degeneration tends to become dorsal and external. Farther back, at the commencement of the tracts, there is degeneration in the central, and slightly dorsal parts on each side; and this becomes diffused over the whole tract still more posteriorly.

There is apparent degeneration in the bundles of both third nerves (Plate I., fig. 5).

REMARKS.

(1) *The optic nerve on the side of the lesion.*—My experiments on the monkey agree, upon the whole, with the previous observations of Pick, and of Dean and Usher upon rabbits. They also afford some confirmation of the experiment of Dean and Usher upon a monkey, and of the results arrived at by pathological investigation of cases of toxic amblyopia, in which the papillo-macular bundle is particularly involved. [Samelsohn (5), Nettleship (6), Vossius (7), Uhthoff (8), &c. (9), and especially a very important case reported recently by Birch-Hirschfeld (10).]

Pick's statement, quoted above, holds good as a general conclusion, so far as it refers to the optic nerve. I have invariably found some diffuse degeneration, and this is scarcely to be wondered at. The lesion made by the point

of a Graefe's knife is minimal, probably much less than by the point of a galvano-cautery. At the same time, in dealing with such a delicate structure as the retina, it is not surprising if the injury is not absolutely localised. It is only rarely possible to effect one's purpose without injury of the choroid or even the sclerotic, and it is impossible to entirely avoid the retinal vessels. A slight amount of hæmorrhage into the vitreous usually occurs, and the mere passage of the narrow knife across the eye must lead to reactive changes, probably accompanied by transient shrinking of the vitreous, which may well interfere with the nutrition of ganglion-cells in other parts of the retina.

As might also be expected, the nearer the lesion is to the optic disc, the greater is the resultant degeneration, for not only are the ganglion-cells destroyed, but the axons of ganglion-cells over a large peripheral area are also cut through. The experiments of Baquis and others afford no evidence of regeneration in these fibres, and as they belong strictly to the central nervous system, it is inherently improbable. Moreover, the time allowed is probably too short.

The very definite course of the macular fibres, which do not follow the law which Pick has stated, must cause some dislocation of the other temporal fibres; but the method is not sufficiently accurate to elucidate this point. It may possibly be settled in the future by pathological observations.

One slight modification of the general law as to the localisation of the fibres may be noted, viz., that in the posterior part of the nerve as it approaches the chiasma, the nasal fibres tend towards the ventral side, and the temporal fibres tend towards the dorsal side.

(2) *The optic nerve on the uninjured side.*—Both Pick and Dean and Usher, observed signs of degeneration in the nerve of the opposite—uninjured—side. This observation I am obliged to confirm. It may be mentioned at once that degeneration in my sections was limited to the visual paths, i.e., there was no trace of it in other parts of the brain, actually forming parts of the sections, and therefore subjected to identically the same method of preparation.

PLATE II.

FIG. 1.

FIG. 2.

In all the specimens it was a diffuse degeneration, usually without very definite areas of concentration, and always considerably less than on the injured side. The degeneration could be traced throughout the length of the nerve, and such concentration of fibres as occurred retained its relative position in all the sections. As a rule this was on the homonymous side of the nerve, as compared with the side of the lesion. Thus in Experiments II., IV., and V., with temporal lesions, the degenerated fibres were principally upon the external sides in both nerves. In Experiment III., with a very small temporal lesion, there were very few degenerated fibres in the other nerve. In Experiment VI. the degeneration was diffuse. In Experiment I. it was also diffuse, but there were a good many degenerated fibres upon the outer side of this nerve, although the lesion was nasal.

I must confess to scepticism when reading of these degenerations in the papers of previous observers, which was only allayed when I found that it was a constant result in my own experiments. One is naturally led to doubt whether it is not due to some error in technique; but the earlier observations were made with the original Marchi method, and in my experiments all the degenerations were limited to visual paths. Professor Schäfer has pointed out the necessity of getting rid of all traces of formol before placing the specimens in the osmic acid mixture, and this I was careful to do by thorough washing in running water. That the appearances are exactly those of degenerations is shown by the illustrations under a high power in Plate II., one of which is taken from the nerve on the side of the lesion, and the other from the opposite nerve.

There is one pathological examination on record which affords some support to this result. Kellermann (11), in a case of old-standing atrophy of the left optic nerve, found a small tract of degeneration in the right nerve, ventro-lateral near the eye, becoming central near the chiasma, and therefore running in the course of the macular bundle. No abnormality of vision was noticed during life, and the central vessels entered the nerve at the inner and lower part (this is not invariable), so that the bundle ran independently of

them. Kellermann attributes the degeneration to compression of the fibres in the chiasma, due to shrinking from atrophy of the fibres of the left nerve. Hebold (12), in a similar case, using Pal's method, found the nerve sound; but the method is not sufficiently sensitive for the purpose. Deutschmann (13), Henschen, and others have also been unable to demonstrate degeneration in pathological cases.

Kellermann's explanation of degeneration in the nerve of the uninjured side is very improbable; there is no evidence in its favour, and much of a general nature against it. Usher and Dean suggest that fat may be removed from the degenerated nerve and carried by lymphatics and deposited in the opposite nerve. This suggestion is equally far-fetched. We are forced to conclude that the degeneration is a genuine one, and, if so, what is the nature of the fibres involved? It is not probable, as Usher and Dean point out, that they are concerned in the pupillary reflexes, as these reflexes remain absolutely unimpaired. We are forced to conclude that they belong to some form of inter-retinal fibres—a reversion, in a sense, to the old inter-retinal tract (commissura arcuata anterior of Hannover, vordere Bogen commissur of Stilling). Ramon y Cajal (14) has demonstrated, by the methylene blue method in rabbits, a division of the optic fibres, and Kölliker discovered an isolated example in a human embryo. Bernheimer (15) was struck by the variety in the size of the fibres in the chiasma, so that it appears in many places as if the larger fibres divided. It is not improbable that the degenerated fibres in the nerve of the uninjured side are collaterals, and that they are distributed to physiologically corresponding parts of the opposite retina, possibly inducing chemical changes in the visual substances or movements in the cells, and so afferent impulses which subserve a modified type of binocular vision. This, however, must be left for further investigation.

(3) *The optic tracts*.—In all cases there was degeneration in both tracts. This may be explained partly by the diffuse injury which probably always results from the lesion, and which is manifested by diffuse degeneration in the nerve. I do not think that this accounts for it entirely. There are

apparently more fibres degenerated in the tracts than in the nerve, and we are here even more powerfully forced to the conclusion that division of the fibres occurs. Most of the experiments were purposely temporal lesions, in order, if possible, to obtain a pure degeneration in the homolateral tract. In these cases the degeneration in the contra-lateral tract usually showed smaller black globules, as if less myelin was present. Probably these were finer fibres—in fact, collaterals.

(4) *Apparent degeneration in third and fourth nerves.*—I do not think that this was a true degeneration, but an artefact similar to that obtained by Marchi in some of his early experiments.

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