Medicine. — *On the Time and Place of Experimental Myelin Degeneration in the Optic Pathways.* By R. G. MEADER [1]), Yale University, New Haven. (From the Neurological Laboratory of the University of Amsterdam. Director: Prof. Dr. B. BROUWER). (Communicated by Prof. B. BROUWER.)

(Communicated at the meeting of May 20, 1939.)

The time at which secondary degeneration of the medullated nerve fibers is first visible has been studied chiefly in the peripheral nervous system. Systematic examinations concerning this problem in the central nervous system are rare. SPIELMEYER (1929) summarized the knowledge in both fields. To that have been added more recently the observations of PARKER and PAINE (1934) on peripheral nerves and the extensive review of ROSSI and GASTALDI (1935) on both central and peripheral nerve fibers. The general concensus of recent opinion seems to be that in the fibers of the central nervous system as well as in those of the peripheral system, degeneration of the axis cylinder and of the myelin sheath in the distal stump begins at the lesion and proceeds toward the periphery of the nerve fiber. It seems worth while to make available the observations made on the time and place sequence of degeneration in the medullary sheaths of the optic pathways following enucleation of an eye.

Five rabbits were sacrificed at 96, 133, 180½, 232 and 279 hours, respectively, after enucleation of the left eye by Prof. Dr. W. P. C. ZEEMAN. The central nervous system was prepared by the Marchi method in the usual way. Projection drawings were made of the optic nerves, chiasma, tracts, corpora geniculata externa, and corpora quadrigemina antica. Details of granule distribution were filled in from microscopical observations. (See figs. 1, 2, 3).

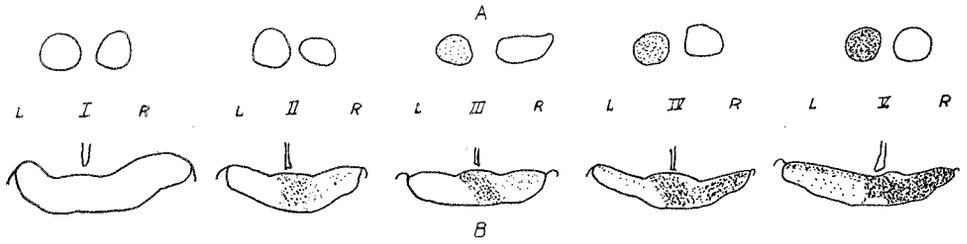

Fig. 1. Transverse sections through (*A*) the optic nerves and through (*B*) the caudal part of the optic chiasma of the rabbit, showing the amount of Marchi degeneration at successive periods after enucleation of the left eye. I. 96 hours, II. 133 hours, III. 180½ hours, IV. 232 hours, V. 279 hours.

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The general results may be summarized as follows: Marchi degeneration granules appear earliest (96 hours) in the more distal parts of the optic nerve fibers whose cell bodies have been removed. Between 133 and 180½ hours the portions of the nerve fibers nearest the lesion begin to show indubitable degeneration and the process reaches its height throughout the length of the fiber only after 279 hours.

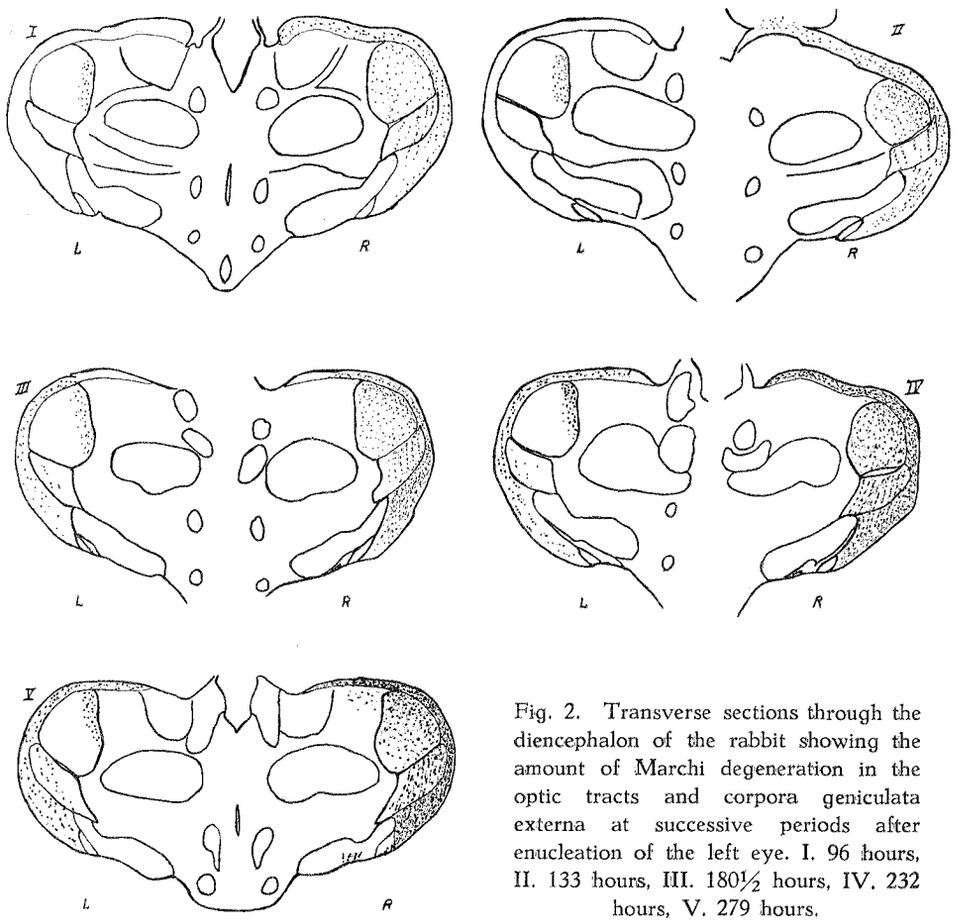


Fig. 2. Transverse sections through the diencephalon of the rabbit showing the amount of Marchi degeneration in the optic tracts and corpora geniculata externa at successive periods after enucleation of the left eye. I. 96 hours, II. 133 hours, III. 180½ hours, IV. 232 hours, V. 279 hours.

The detailed observations on each experimental animal are presented below. The number in brackets is that assigned to the series in the neurological laboratory of the University of Amsterdam.

96 hours after enucleation (B 621).

Degeneration granules are not to be seen in the optic nerve and chiasma, nor in the ipsilateral (left) tract. A few black grains in rows appear in the crossed (right) tract as it approaches and embraces the corpus geniculatum externum. In the dorsomedial nucleus of this latter body many fine

133 hours after enucleation (B 616).

The optic nerves are free from degeneration products but in the chiasma a few granules are evident among the interlacing bundles. Increasing numbers of larger grains appear in the right tract as it reaches the geniculate body. They tend to lie parallel to the course of the fibers. There is no clear degeneration in the uncrossed optic tract. The condition in the right and left lateral geniculate bodies is merely an accentuation of that seen after 96 hours. On the right side, the granules seem to be a bit more numerous in the lateral portion of the dorsomedial nucleus than in its medial portion, due in part to the larger granules present in the bundles of optic fibers that traverse that nucleus. The ventrolateral nucleus on the right shows similar but very few groups of granules in the fibers passing through it. There are none on the left. In the right corpus quadrigeminum anticum the number of large and small granules in the brachium conjunctivum and in the superficial fiber and cell strata has increased. Those in the cellular layer are chiefly of the small variety. The left colliculus and its brachium are not degenerated.

180½ hours after enucleation (B 617).

Large and small black grains are sharply distinctive of the left optic nerve (fig. 5) and are absent from the right. They are not numerous on the left, however, and most of the optic fibers appear to be still intact. In the chiasma, the grains form obliquely oriented rows in the region of the interlacing bundles. They are distributed throughout the right optic tract in short rows parallel to the normal appearing fibers. They become more numerous in the vicinity of the corpus geniculatum externum. The left tract contains granules which become larger and more numerous as it approaches the optic centers but they are never very prominent. In the corpora geniculata externa and in the right corpus quadrigeminum anticum (fig. 6) the only change from the earlier picture is the continued increase in the number of degenerating granules.

The fasciculus accessorius optici anterior (BOCHENEK) and the tractus peduncularis transversus on the side opposite the enucleated eye exhibit degeneration.

232 hours after enucleation (B 618).

The only change from the preceding series is the intensification of the degenerative process, that in the primary optic centers continuing to be more marked than that in the optic nerve. Degeneration in the left optic tract (uncrossed fibers) is clearly seen, being concentrated chiefly in the dorsal part of the tract.

279 hours after enucleation (B 620).

The myelin degeneration is not yet at its height but the entire optic

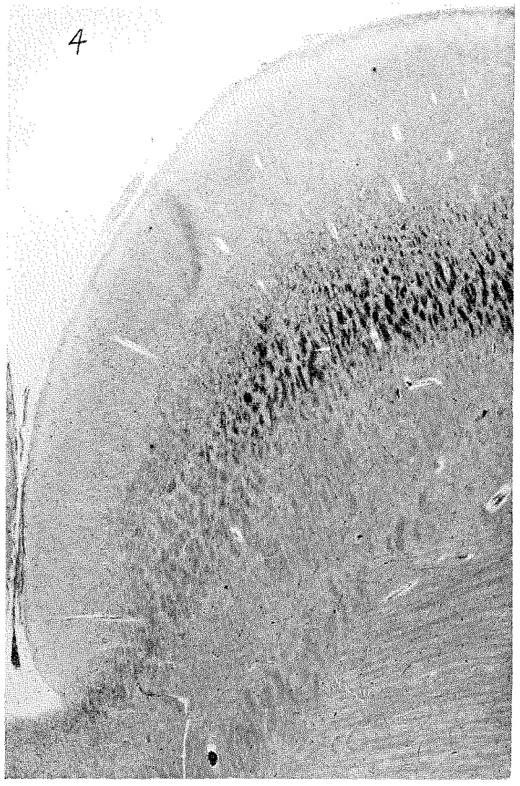
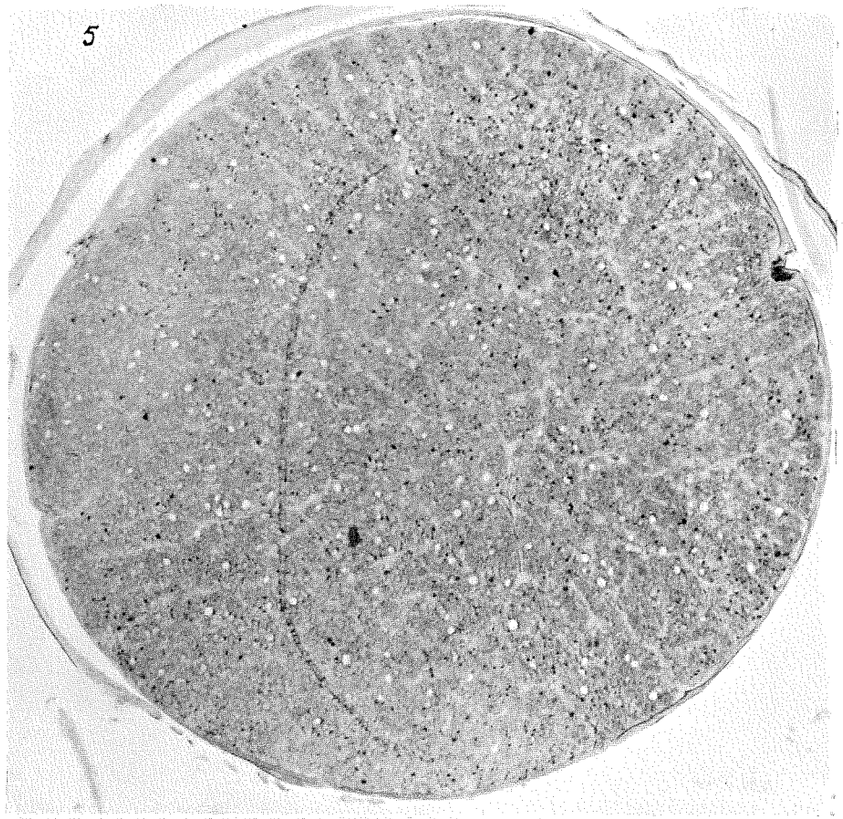
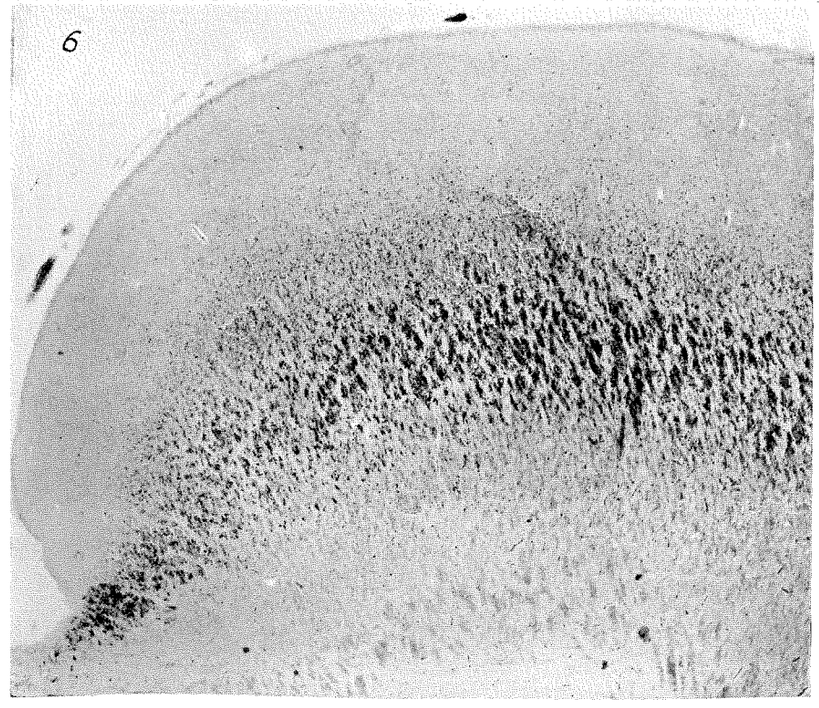


Fig. 4. Photomicrograph of the medial part of the right corpus quadrigeminum anticum 96 hours after enucleation of the left eye. Cross-section. Marchi stain.

Fig. 5. Photomicrograph of the left optic nerve 180½ hours after enucleation of the left eye. Cross-section. Marchi stain.

Fig. 6. Photomicrograph of the right corpus quadrigeminum anticum 180½ hours after enucleation of the left eye. Cross-section. Marchi stain.





pathway of the first neurone is involved. The left optic nerve, the crossing fibers of the chiasma, and the right optic tract, lateral geniculate body and anterior colliculus are all loaded with large and small black granules. The right fasciculus accessorius optici anterior (BOCHENEK) and tractus peduncularis transversus are affected in a similar way. The degenerated fibers in the ipsilateral (left) optic tract are few and lie chiefly in the dorsal part of the tract. Those in the left corpus geniculatum externum are confined to the medial part of its dorsomedial nucleus except for the fibers of passage in the ventrolateral nucleus. There is no degeneration in the left corpus quadrigeminum anticum.

Discussion.

It is clear that within the optic pathways of the first neurone in the rabbit, degeneration of the medullary sheaths can be recognized in Marchi preparations 4 days after enucleation of the eye, but only at the distal end of the fiber, i.e., in or near the terminal centers. Degeneration in the proximal part of the fiber, i.e., in the optic nerve, can be recognized 7½ days after operation. It is to be noted, also, that degeneration of the fibers in the uncrossed optic tract is not clearly recognizable until nearly 10 days have passed, considerably later than in the crossed tract (5½ days).

The first mentioned results are somewhat surprising in the light of the studies made on the time and place of appearance of degeneration in the medullary sheaths of severed peripheral nerves. It was stated by HOWELL and HUBER (1892) and confirmed by MÖNCKEBERG and BETHE (1799) and ROSSI (1912) that the first evidences of myelin segmentation appear on the 4th day after operation. These observations, however, were made on the proximal part of the distal stump near the lesion. Although I found Marchi granules in the optic fibers 4 days after enucleation, they were situated, not at the site of the lesion, but near the other end of the fiber. Since the preparations do not contain the portion of the optic nerve immediately next to the lesion, nothing can be said on that point. If Marchi granules were present, however, they must have been restricted to the first few millimeters of the transected nerve that were not removed with the brain. Only after 7½ days were any granules found in the most rostral sections close to the region of the lesion, a finding in partial agreement with SPIELMEYER's statement (1929) that Marchi degeneration begins about 8 days postoperatively. SPIELMEYER made no distinction, however, between the myelin degeneration of the proximal and distal parts of the distal stump. The only clearcut study of the direction and rate of myelin degeneration was made in the peripheral (lateral line) nerve of a fish (Ameiurus) by PARKER and PAINE (1934). Although their report indicates that the distal stump of a severed nerve undergoes myelin degeneration from the lesion toward the periphery at a rate of approximately 3.1 cm

per day at a temperature of 18° C, it is hardly comparable with these observations on the central nervous system of a mammal. The disagreement with regard to the direction of degeneration may be due to the difference between central and peripheral nerve fibers or between mammals and fishes. So far as I have been able to find out, there have been no similar studies made in mammals. ROSSI and GASTALDI (1935) studied the degeneration and regeneration of the optic nerve in rabbits, but they used only silver preparations, in order to follow the changes in the axis cylinders. SPIELMEYER (1929) mentioned in a footnote a case of optic nerve disease in man in which the nerve itself was free from degeneration products while the tract still contained a rich supply of them. He interpreted the condition as one in which the degeneration products had been already resorbed from the nerve because of its better circulatory relations due to its many septa, whereas the more compact tract still retained them. He gave no data concerning the duration of the injury or the condition of the optic centers. In view of the observations reported here, it seems possible that the nerve showed no degeneration products because they had not yet been formed there.

In the rabbits investigated, the full Marchi picture could not be obtained until later than 279 hours although there were great numbers of degenerated fibers present throughout the entire optic pathway of the first neurone as early as 233 hours. This observation is in approximate agreement with SPIELMEYER (1929) who considered the high point of the Marchi stage to be about the 12th day. ROSSI and GASTALDI (1935) found a gradual increase in the formation of myelin ellipsoids in the optic nerve of the rabbit during the 4th to the 10th days, after which time that phase of the process was completed. In order to secure the full degeneration, it seems safest to allow at least 12 days to elapse after operation.

The gradual increase in the intensity of the Marchi staining depends in part upon the increase in the number of fibers undergoing degeneration. According to MÖNCKEBERG and BETHE (1899), the finer medullated fibers of a peripheral nerve degenerate more slowly than the coarser ones. They believed, also, that sensory fibers break up faster than do motor fibers. My preparations confirm the increase with time in the number of Marchi granules at any given level of the optic tract but it is not clear whether the larger fibers are the first to go or not. It might be argued that since the granules appear earliest in the terminal centers where the fibers are finely medullated, it is the finer fibers which disintegrate first. That is only part of the story, however, for in the colliculus anterior at the earliest stage are found larger myelin ellipsoids, also, supposedly from thicker medullary sheaths. It seems likely, therefore, that the degeneration here is more a factor of distance from the proximal part of the fiber than of fiber size, for both large and small fibers are involved.

The earlier recognition of degeneration in the crossed fibers of the optic tract than in the uncrossed fibers may be due to one or both of two factors.

There may be a true differential in the time of their reaction to separation from their cell bodies which might rest upon a difference in the size of the crossed and uncrossed fibers, or upon some other unrecognized difference. It may, also, be that degeneration occurs just as soon in comparable fibers of the two sides but that the uncrossed fibers are so few in number and so diffused among the normal crossed fibers from the uninjured side that they are not recognizable and are considered artefacts until a sufficient number of granules have formed to make their relationships clear.

Summary.

1. Marchi degeneration granules are visible in the contralateral anterior colliculus, in both external geniculate bodies and in the distal parts of the contralateral optic tract 96 hours after the enucleation of one eye in the rabbit. They are clearly recognizable in the severed optic nerve 180½ hours after the operation. The full Marchi picture appears only after more than 279 hours.

2. The degenerative process takes place at an unequal rate in the fibers of the optic pathway. It is recognizable earlier in the crossed optic tract than in the uncrossed bundle. In the crossed tract, moreover, there is an increase in the number of Marchi granules at any one level proportional (within limits) to the postoperative survival of the animal.

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BERICHTIGUNG

zur Mitteilung von W. P. POSTMA: *Einige Bemerkungen über den Einfluss der Nitratreduktion auf die Atmung der Wurzeln*

in Proceedings Vol. XLII, N°. 2, 1939.

A. Tabelle III (Seite 184) soll heissen:

1. Reihe: Avena-Pflanzen, gezüchtet im Licht auf KNOP-Lösung ohne N. Analysiert nach 3, 7 und 11 Tagen.

2. Reihe: Avena-Pflanzen 3 Tage gezüchtet auf KNOP-Lösung ohne N, dann weiter auf KNOP-Lösung. Analysiert nach 7 und 11 Tagen.

Die Zahlen geben mg N in je 100 Pflanzen an.

	KNOP ohne N			KNOP		
Analysiert nach	Lösl. N	Eiweiss-N	Gesamt-N	Lösl. N	Eiweiss-N	Gesamt-N
3 Tagen	18.8	30.4	49.2			
7 Tagen	12.9	26.2	39.1	13.2	44.3	57.5
11 Tagen	13.4	19.1	32.5	7.1	56.4	62.5

B. Seite 185, Z. 9—14 ist folgendermassen zu lesen:

Pflanzen	auf	destill.	Wasser	je	Stunde	0.029	m.mol. CO_2
„	„	—N	—Glukose	„	„	im Mitt. 0.031	„
„	„	+N	—Glukose	„	„	im Mitt. 0.040	„
„	„	—N	+Glukose	„	„	0.059	„
„	„	+N	+Glukose	„	„	0.360	„