A NOTE ON TRANSNEURONAL ATROPHY IN THE HUMAN LATERAL GENICULATE BODY

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The phenomenon of atrophy in nerve cells after loss of their afferent connexions has been known for many years, but has been demonstrated unequivocally only in the lateral geniculate body, where it results from the degeneration and loss of afferents from the retina. It is shown by a diminution in the size of the perikaryon of the neurones, a somewhat variable loss of Nissl granules, a loss of intercellular neuropil (due to degeneration of fibres from the retina), and glial proliferation. Although often described in the older literature as a chromatolytic degeneration (*e.g.*, by Minkowski, 1920), it does not present the classical picture of chromatolysis and the usual description as an atrophy of the cells is the more appropriate.

Transneuronal atrophy has been described in situations other than the lateral geniculate body, *e.g.*, in the spinal cord of the monkey and man after posterior root section by Foerster, Gagel, and Sheehan (1934) but recent investigations (Cook, Walker, and Barr, 1951, and others) have failed to confirm these findings. An atrophy of cells scattered among many which were unaffected would be difficult to detect; this may well be the situation in the spinal cord and may account for the lack of confirmation. The lateral geniculate body, where all the cells receive their afferents predominantly and perhaps exclusively from the retina, might well show the process in its most obvious and easily detected form, and is clearly the region most suitable for its study.

There is much evidence to show that transneuronal atrophy in the lateral geniculate body differs in the rate at which it proceeds and probably also in the degree it reaches in different mammals. With the exception, however, of the work of Cook *et al.* (1951) in the cat and rabbit, it is difficult to make comparisons from the published accounts since quantitative methods have not been used to describe the degree of atrophy. It seems certain that the process is rapid and fulminating in primates, for changes are evident within seven days of section of the optic

nerve (Glees and Clark, 1941). In the cat Cook *et al.* found that changes first became noticeable in the second month, and in the rabbit that they were even slower in their development. In the cat the atrophy amounted to about 25% of the cross-sectional area of the cell, and did not increase up to 10 months after deafferentation (Cook *et al.*, 1951).

The normal primate lateral geniculate body, including that of man, has been studied extensively by quantitative methods (Balado and Franke, 1937; Clark, 1941; Chacko, 1948 and 1949) so that information about normal cell size, the total number of cells and their density is fairly complete. There appear, however, to be no similar studies of the cells in transneuronal atrophy, so that when a human specimen became available it seemed desirable that it should be investigated quantitatively. The primate lateral geniculate body is particularly suitable for this purpose since, owing to its laminar structure, normal and atrophic laminae are available side by side for comparison after unilateral enucleation of an eye, and any particular lamina which is atrophic will have its normal counterpart in the opposite lateral geniculate body.

The actual specimen was obtained between 36 and 40 years after eye enucleation, so that only the long-term results of the atrophy can be considered. After so long a period it is probable that a stable condition had been reached. The main purpose was to investigate the question whether a proportion of cells undergo complete dissolution as stated by Hechst (1933) and to estimate the percentage loss of size of the surviving cells (*a*) in the large-celled laminae 1 and 2, and (*b*) in the smaller-celled laminae 3 to 6. Both Hechst (1933) and Clark (1941) found that the large cells are less sensitive to deafferentation than those of medium size. Besides adding precision to this observation, quantitative methods might show other differences among the cells of the lateral geniculate body in their reaction to deafferentation. It is realized, of course, that few conclusions can be based on an examination of one

specimen, but material of this kind does not often become available, so that a record of the observations seemed justified.

Material

The specimen was obtained from a man who died at the age of 59 years after a thoracotomy for carcinoma of the lung; his left eye had been removed as a result of an injury received in the 1914/18 war. At necropsy a "few small areas of cortical atrophy" were noted as well as marked atrophy of the left optic nerve. There was no other evidence of disease or abnormality of the nervous system. The brain was fixed in formalin and both lateral geniculate bodies were embedded in celloidin, cut serially at 25μ , and stained with thionin. Good serial sections were obtained, cut approximately in a plane at right angles to the optic tract and therefore similar to the sections used by Chacko (1949) in her investigation of cell size in the normal human lateral geniculate body. A few sections were lost from the series cut from the right lateral geniculate body.

Observations

Histology.—Ordinary histological examination showed the expected atrophy in the first, fourth, and sixth laminae (heterolateral) and in the second, third, and fifth (homolateral), and also the characteristic large cells of laminae 1 and 2 and the medium-sized cells of laminae 3 to 6.

No detailed description is necessary since the general features of material of this kind are well known. Lipochrome was present in most cells, and about equally in those from normal and atrophic laminae. The accumulation of this material with advancing age seems to be unaffected by deafferentation. Nissl granules were present in the cells of both normal and atrophic laminae, but were less conspicuous in the latter, which contained a proportion of cells in which the cytoplasm was pale and almost completely devoid of basophilic particles. It was always possible, however, to find many cells in atrophic laminae which were normal in this respect. In laminae 1 and 2 the contrast between cells which showed only a diminution in size, and rather small, pale cells in which no Nissl material could be found, gave an impression that these laminae might contain two types of cell differing strongly in their reaction to deafferentation.

In the deeper laminae, 3 to 6, loss of size and of Nissl material seemed rather more marked than in laminae 1 and 2 but no impression of more than one cell type was given. When normal, the cells of these laminae are very uniform, and many of the apparent variations in size which can be seen result from the varying orientation of the elongated cell body relative to the plane of section; this orientation is generally with the longer axis at right angles to the plane of the lamina. There is some tendency for

cells to be arranged in clumps or glomeruli as noted by Taboada (1928) although this was not a very noticeable feature in the present specimen.

It should be added that apart from the changes in the cells characteristic of transneuronal atrophy and some increase in the number of neuroglial nuclei, no pathological changes of any kind could be detected.

Loss of Cells in Transneuronal Atrophy.—An approximate estimate of cell density in laminae 3 to 6 was obtained by counting the number of nucleoli which could be identified in an area of 0.56 mm.^2 in sections of each lamina; in each case a region from the central part of the lamina was selected for counting, *i.e.*, a region associated functionally with central vision. Since the sections were 25μ thick it was possible to calculate the number of cells/ mm.^3 for the regions counted, with the following results:—

Lamina	Normal Laminae (cells per mm.^3)	Atrophic Laminae (cells per mm.^3)
3	23,000	21,000
4	22,000	22,000
5	23,000	22,000
6	18,000	19,000

These figures are given to the nearest 1,000 and are of the same order of magnitude as those obtained by Chacko (1948) in the normal lateral geniculate body. They show that the cell density is approximately the same in the atrophic as in the normal laminae, and since each atrophic lamina appears considerably shrunken and therefore smaller in volume than the corresponding normal lamina on the opposite side, a proportion of the cells originally present must have disappeared. Unfortunately it was not possible to measure the total volumes of the laminae owing to the loss of some of the sections from one series, but a rough estimate of the relative difference in volume between normal and atrophic laminae could be made by comparing their areas in corresponding sections. Fig. 1 shows outline drawings of such sections in which the second, third, and fifth laminae, receiving uncrossed fibres, are marked in solid black. Planimetric measurements showed that the total area occupied by the normal laminae 4 and 6 (left) was 117.4 cm.^2 , and for the same laminae (atrophic) on the right, 57.4 cm.^2 . Laminae 3 and 5 (atrophic, left) gave a total area of 49.9 cm.^2 and on the right (normal) 94.7 cm.^2 . It appears, therefore, that the shrinkage in sectional area in atrophic laminae is about 50%, and, since the cell density is not substantially altered, about half the cells originally present must have disappeared. A similar estimate was not made from the large-celled laminae. These laminae had very indefinite boundaries and, particularly in the atrophic condition,

FIG. 1.—Outline drawings of the laminae in four corresponding sections from the right and left lateral geniculate bodies. The second, third, and fifth laminae, receiving uncrossed retinal fibres, are in solid black.

were very thin in many places. It is doubtful if outlines of the sections of these laminae could have been made with sufficient accuracy, and, owing to the scattered arrangement of the cells in many regions, cell counts from sample areas could have given very misleading results. From the general appearance there was no doubt that the atrophic laminae 1 and 2 contained considerably fewer cells than the normal. The cell loss was probably not very different from that estimated for laminae 3 to 6.

The Size of Surviving Cells.—The surviving cells in atrophic laminae were measured and compared with cells in normal laminae as follows. The sections were projected at a magnification of $\times 875$, and the outlines of cells drawn and their areas measured with a planimeter. In this way 90 cells (three samples of 30) were measured from each of six normal laminae and an equal number from six atrophic laminae. All samples were taken from the central parts of the laminae, and the criterion for the selection of a cell for drawing was the identification of a nucleolus within it. From the figures obtained the means and standard deviations for each lamina were calculated. The cell size is therefore expressed as a mean pro-

jection area in $\mu^2 \pm$ the standard deviation, and the results are given in Table I. Histograms have also been constructed (Fig. 2) showing the distribution of cell size, but for this purpose the results for the large-celled laminae 1 and 2 have been grouped together and the same has been done for the cells of smaller size from the four laminae 3 to 6.

The principal result from these measurements is shown quite clearly in Table I, namely that the large cells of laminae 1 and 2 which survive are reduced in mean size (measured as projection area) by from 30 to 35%, while the corresponding cells in laminae 3 to 6 show a greater reduction, varying between 40 and 52%. In all laminae the differences in size between the cells of the normal and atrophic laminae are highly significant, since these are in no case less than 10 times the standard error. That the size reduction is some 15% greater in laminae 3 to 6 than in laminae 1 and 2 is consistent with the previous observations of Hechst (1933) and Clark (1941) that the large cells are less sensitive to deafferentation than the smaller cells.

TABLE I
SIZE OF SURVIVING CELLS

Lamina	Normal Cells (Mean $\pm$ Standard Deviation)	Atrophic Cells (Mean $\pm$ Standard Deviation)	Difference	Difference %	Standard Error of Difference
1	460 $\pm$ 101	321 $\pm$ 89	139	30	14.0
2	430 $\pm$ 104	281 $\pm$ 93	149	35	14.7
3	289 $\pm$ 59	140 $\pm$ 34	149	52	7.2
4	280 $\pm$ 66	167 $\pm$ 41	113	40	8.2
5	316 $\pm$ 55	161 $\pm$ 39	155	49	7.1
6	298 $\pm$ 80	144 $\pm$ 33	154	52	9.1
1 + 2	443 $\pm$ 103	302 $\pm$ 93	141	32	10.3
3 to 6	296 $\pm$ 67	153 $\pm$ 38	143	48	4.1

The figures for mean size are all given in μ^2 and in each individual lamina (normal or atrophic) are based on measurements of 90 cells. The figures for laminae 1 and 2 combined are based on 180 and for laminae 3 to 6 on 360 measurements.

A number of smaller differences are also apparent from the figures. Some of these, such as the difference between laminae 1 and 2 in the size of the normal cells (460 as against 430 μ^2), are not significant in the statistical sense and may be ignored. The position is not so clear when the atrophic cells of laminae 1 and 2 are compared; the means differ by 40 μ^2 and this is about three times the standard error of the difference, a rather low level of statistical significance which could, however, indicate a real size difference between the two cell populations. Differences of a similar kind, and with about the same level of statistical significance, can be found between some of the other laminae. In the normal condition the mean sizes of the cells in laminae 3 and 4 are smaller than those of cells in lamina 5, while in the atrophic condition they are smaller in laminae 3 and 6 than in 4 and 5. While one cannot

FIG. 2.—Histograms showing the distribution of cell size in laminae 1 and 2 and laminae 3 to 6 in both the normal and atrophic conditions, those for laminae 1 and 2 being based on 180 and for laminae 3 to 6 on 360 measurements. The width of each column represents a range of $26\mu^2$, the height, the percentage of the measurements which falls within this range.

entirely ignore these differences, it is extremely doubtful if they have any biological significance. The cells, particularly in laminae 3 to 6, are fusiform or elongated and show an orientation roughly at right angles to the plane of the lamina in which they are situated. The plane of section therefore affects the projection area of a cell quite considerably. As far as could be judged, all sections used were cut in the same or similar planes, but the laminae have a somewhat complex curvature and small differences between the planes in which individual laminae are cut cannot be estimated or allowed for. Such differences are not random and might be large enough to account for the rather small differences in size which are under consideration. For this reason it was thought best to take no account of these differences for the purpose of the present paper, and to group all the large cells of laminae 1 and 2 in one class and the smaller cells of laminae 3 to 6 in another, as has been done in the last two lines of the table and in the histograms.

The histograms (Fig. 2) for laminae 1 and 2 show

an approximately normal distribution, with rather a wide scatter, but no clear evidence of bi-modality in either the normal or the atrophic condition. That of the normal cells shows that a fairly large number are rather small (less than $260\mu^2$) and there is a possibility that these represent a distinct element in the cell population of the laminae, although the alternative possibility that they are cells, the greatest cross-sectional area of which was not shown in the section under examination, cannot be definitely excluded. The histogram of the atrophic cells shows slight skewness to the right, indicating the persistence of a considerable proportion of cells the mean size of which is still close to normal, and these again may constitute a distinct group, less sensitive to deafferentation than the majority of the cells in these laminae.

In laminae 3 to 6 the histograms of both normal and atrophic cells show comparatively little scatter, and a close approximation to a normal distribution. The scatter is considerably less for the atrophic cells, and the evidence of the histograms as well as the

figures given in Table I confirm the general opinion that the cells of laminae 3 to 6 form a substantially uniform population, all reacting similarly to the loss of afferents from the retina.

Discussion

The main purpose of this paper has been to record quantitatively some of the features of transneuronal atrophy in the human lateral geniculate body, and few conclusions can be based on the findings until further data are available. Essentially, what has been described are the end-results and it would be necessary to have similar observations after shorter periods before precise and detailed comparisons with the process in other mammals can be made.

The primary cause of transneuronal atrophy is the degeneration of afferents from the retina. It is reasonable to suppose that its rate and extent will vary with their number and that the presence of afferents from other sources which remain functional would reduce the atrophy or prevent it from occurring. Judging from the percentage loss of cell substance, the cells of laminae 3 to 6 are considerably more sensitive than the large cells of laminae 1 and 2 to loss of retinal afferents, and it may be that it is in the deeper laminae only that the cells have an exclusive relationship to afferents from this source and from one eye only. While there is no doubt that lamina 1 receives mainly crossed fibres and lamina 2 mainly uncrossed, none of the evidence available excludes the possibility that lamina 1 may receive a few fibres from the eye of the same side and lamina 2 from the opposite eye. An arrangement such as this could account for the smaller degree of cell atrophy and the persistence of many cells of apparently normal size in these laminae; the existence of afferents not of retinal origin at all could have the same effect.

There are, of course, other possibilities. Large cells may be intrinsically less sensitive to deafferentation than small ones, but this raises the general question of the relative dependence of nerve cells of different types on their afferent connexions, a subject about which virtually nothing is known.

The only other quantitative investigation of transneuronal atrophy is the one already referred to by Cook *et al.* (1951) in the cat. Since they found a 25% decrease in cell size, with no loss of cells, it seems that the atrophy is far less severe than in man and presumably in other primates. This is certainly the case where only the deeper laminae, 3 to 6, are considered. It must be remembered that the longest survival period for which there is information in the cat is 10 months. The authors state, however, that the degree of cell atrophy did not alter appreciably after the 63rd day, so there is reason for assuming

that a stable condition had been reached. It is therefore unlikely that, whatever the survival period, the atrophy would go as far as it does in man in the smaller-celled laminae, although comparison of specimens where the atrophy has proceeded for approximately equal periods is obviously desirable.

In the large cells of laminae 1 and 2 the decrease in size of between 30 and 35% is not so very different from the 25% observed in the cat, in spite of the very much longer survival period in the human specimen. This resemblance between the reaction of the large cells in man and of the cells in the pars dorsalis A of the lateral geniculate body of the cat which were studied by Cook *et al.* suggests a neurological similarity. It is possible that in the cat the cells studied are not related exclusively to crossed retinal fibres, although, as with the large-celled elements in man, if both eyes supply afferents to these cells the contribution from one must be very small. As Clark (1941) has pointed out, the segregation of the large cells is a very characteristic feature of the primate lateral geniculate body, but the chief progressive feature may be the development of the deeper laminae with smaller cells, each having an exclusive relationship to one eye or the other.

A feature of the atrophy in the human lateral geniculate body which has not been observed in other mammals is the very striking loss of cells (about 50%) in the affected laminae. This may be due to the fact that in animal experiments the survival periods have all been comparatively short, but in any case it seems unlikely that the death and disintegration of a cell can be due directly and solely to the loss of afferents. If this were so it would be very difficult to see why one cell should survive with no change but some diminution in size, while other and adjacent cells are so much more severely affected. It does not seem probable that so marked a difference of reaction could result from differences in afferent connexions. It is more likely that the death of a proportion of the cells is a secondary result of the shrinkage which occurs, itself due in the first place to the loss of retinal fibres. The overcrowding of cells, with the increased concentration of metabolic products which this implies, might be expected to result in the survival of only a definite and limited proportion, and it is of interest that the cell density does in fact remain about the same as it is in the normal lamina. The more extreme and long-term results of transneuronal atrophy cannot necessarily be taken as evidence relevant to questions about the number or source of afferent connexions.

The last point which needs comment concerns the size of the cells in the normal laminae. The smaller cells of laminae 3 to 6 are about two-thirds the size of the large cells in laminae 1 and 2; Chacko's

figures (1949) show a very similar relationship. She, however, was able to show also that there was a size gradient in laminae 3 to 6, the cells becoming progressively smaller in passing further from the surface. The differences were small but "in practically all instances, statistically significant". She found also that the crossed laminae contained significantly smaller cells than the uncrossed. None of these differences was apparent in the present specimen where the main purpose was to investigate the larger differences between the normal and the atrophic cells. Reasons have been given why the few smaller differences found among the normal cells are probably not biologically significant. It is possible that measurements from larger samples of the normal cells would have given results similar to those obtained by Chacko, but there is no doubt that the investigation of small differences of this kind in the normal lateral geniculate body requires more extensive material than a single specimen in which half the laminae are atrophic. The present results, therefore, while they provide no confirmation of Chacko's findings, do not make them any the less reliable.

Summary

In transneuronal atrophy of the human lateral geniculate body it is found, as a long-term result, that about half the cells in the affected laminae are lost after enucleation of one eye. The surviving cells

show an atrophy (measured as a diminution in projection area) of about 32% in the large-celled laminae 1 and 2 and about 48% in laminae 3 to 6.

These results are compared with similar quantitative observations made by Cook, Walker, and Barr (1951) in the cat, and the differences discussed. It is suggested that the difference in the reaction between the large-celled laminae 1 and 2 and laminae 3 to 6 in man may mean that only the latter have an exclusive relationship to one eye or the other and that the presence of these laminae (3 to 6) is the main progressive feature of the primate lateral geniculate body.

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