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Environmental effects on cortical dendritic fields

I. Rearing in the dark

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Previous studies of the effects of visual deprivation in the cat have shown a number of anatomical, physiological (Baxter, 1961; Hellstrom & Zetterstrom, 1956; Cornwell, Sharpless & Kana, 1962; Rasch, Swift, Riesen & Chow, 1961; Wiesel & Hubel, 1963, 1965) and behavioral (Riesen, 1965) abnormalities in the visual system of animals reared either in the dark or in the light, while using various methods of occluding the passage of light into the eye. Anatomical studies have revealed striking alterations at the retinal (Rasch *et al.* 1961) and geniculate (Wiesel & Hubel, 1963, 1965) levels, but the search at the cortical level for morphological effects of visual deprivation in cat has usually proved fruitless. Some studies have shown changes such as diminished cortical weight in rats (Bennet, Diamond, Krech & Rosenzweig, 1964), decreased nuclear diameter in mice (Gyllensten, 1959), reduced numbers of dendritic spines in mice (Valverde, 1967), and deformed dendritic spines in rabbits (Globus & Scheibel, 1967). Others have shown no effect on dendritic fields in mice (Haddara, 1955) and rabbits (Goodman, 1932; Globus & Scheibel, 1967). The former study (Goodman, 1932) also failed to demonstrate any effect of dark-rearing on cortical thickness, extra-nuclear chromatin and nuclear size in Nissl stained material. Examination of visual cortex of cats has generally revealed no anatomical effect of visual deprivation (e.g. Wiesel & Hubel, 1965).

In addition to the traditional visual areas discussed above there have been reports of visual evoked responses recorded from posterior cingulate gyrus in cat by means of gross electrodes (Harman & Berry, 1965; Hughes, 1959; Ingvar & Hunter, 1955), but in view of the proximity of posterior cingulate gyrus to primary visual cortex the significance of these responses has been questioned by some as possibly being due to current spread. Recently, MacLean and co-workers reported single unit (Cuenod, Casey & MacLean, 1965) and degeneration studies (MacLean, 1966) in the squirrel monkey which indicated that there is a relatively direct projection from lateral geniculate to posterior limbic cortex. Although precise homologies between cat and squirrel monkey can not at this time be made, MacLean's data lend support to the earlier evoked response studies and raises the question of possible effects of dark-rearing on posterior cingulate gyrus.

The present investigation is a quantitative Golgi–Cox study of dendritic fields aimed at an examination of the effects of dark-rearing on visual cortex and on posterior cingulate gyrus in the cat.

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MATERIALS AND METHODS

In the current study cats were reared in the dark, from birth to the time of their sacrifice at 6 months. For each dark-reared cat a litter-mate was reared normally and sacrificed at the same time. There were three dark-reared cats and three normally reared cats. After sacrifice the brains were processed according to a modified Golgi–Cox method (van der Loos, 1959). Alternate sections of 40 μm and 100 μm were cut perpendicular to the pial surface. The 40 μm sections were counterstained with methylene blue to aid in cytoarchitectonic orientation. All measures reported here were taken from 100 μm sections. Cells measured were: (1) layer IV stellates of striate cortex, (2) layer II–III pyramids of posterior cingulate gyrus, and (3) layer V pyramids of striate cortex. The cells sampled from striate cortex were taken at the curvature of the posterior lateral gyrus where it passes from the dorsal to the medial surface of the hemisphere. Cells of experimental and control brains within these categories were selected at random with the restriction that the cell body be in the center of the plane of the section. Cells were traced using a camera lucida. Fifteen stellates and ten pyramids of each type were sampled from each brain. The stellate population was sampled (fifteen cells) a second time in one brain. A total of 225 cells was, then, drawn and measured. The brains were coded and their identity was not known until after the drawings and measurements had been completed. A sampling of cells was redrawn and measured blind to check reliability of the data.

Measures were taken both from the tracings and from the slides with a filar micrometer eyepiece. These measures included: length of dendrites of each order,* number of dendrites of each order, number of intersections of dendrites with a series of concentric circles centred around the cell body with the cell body in the bulls eye and the number of dendritic branchings found between successive circles (Eayrs, 1955, fig. 2). Lengths of each order of dendrite were measured between branching points by following meanderings of the dendrite.

The results were tested for significance by means of an analysis of variance designed for the situation in which repeated measurements are taken on independent groups of subjects (Edwards, 1950). This analysis yields a summary table of the general form

Table 1

Source of variation	D.F. (when dendrite order is independent variable)	D.F. (when 18 μm circle or band is independent variable)
Between environment groups	1	1
Between animals in same group	4	4
Total between subjects	5	5
Between trials	4	11
Interaction: environment × trial	4	11
Interaction: pooled subject × trials	16	44
Total within subjects	24	66
Total	29	71

* First order dendrites: arising from cell body; second order dendrites: arising from first branching point; etc.

shown in Table 1. The trials component refers to dendritic order or 18 μm circle or 18 μm band for the various types of measurements. Statements about the significance of the data are based on the application of the F test to the interaction: environment × trial.

RESULTS

Layer IV striate stellates. Figure 1*a* shows the number of dendrites of each order for layer IV stellates of cortex of normal and dark-reared animals. For all orders of dendrites seen, the dark-reared animals are deficient in number of dendrites. This difference is significant beyond the 1 % level of confidence determined by the analysis of variance for repeated measures. The difference is relatively small in the first-order dendrites, greater for the second and third orders and less for the fourth and fifth orders (although in terms of percentage the latter would be relatively large).

The lengths of dendrites as a function of order are shown in Fig. 1*b*. There is no difference between the dark-reared and normally reared animals in average length of first- and second-order dendrites, but there is a considerable difference in length of the third-order dendrites. The average total length of all dendritic processes was 1251 μm per cell in the normally reared controls; in the dark-reared animals the length was 981 μm per cell or 78 % of control. This difference was significant beyond the 1 % level. The difference is presumably largely accounted for by the third-order dendrites.

The data on number of intersections of dendrites with concentric circles centred around the cell body are presented in Fig. 1*c*. The difference between these two curves is significant beyond the 1 % level. These data may be taken as an indication of complexity of the dendritic field at increasing distances from the perikaryon, and of opportunity to make connexion with other cells. The results suggest that the dark-reared animals are similar to the normals for about 36 μm (the first two concentric circles) from the centre of the cell body. Beyond this point the number of dendrites available for intersection falls off more rapidly in the dark-reared animals. This is due to a decreased probability of dendritic branching, and therefore fewer dendrites, in the dark-reared animals. The dendritic fields of both the dark-reared and normally reared animals appear to extend an approximately equal distance from the cell body, somewhat more than 210 μm.

Figure 1*d* describes the dendritic branchings in consecutive 18 μm bands around the perikaryon. Again, we see that in regions close to the cell body the dendrites of the dark-reared and normally reared groups branch in approximately equal numbers. It is only when the second 18 μm band is reached that the dendrites of the dark-reared animals start to show a deficiency in branching.

The data in Fig. 1*e* were obtained by dividing the length of all dendrites of each order by the number of dendrites of each order (for each group) to yield the average length of a single dendrite of each of the first five orders. First, we see the general phenomenon that dendrites of higher orders are, on the average, longer than dendrites of lower orders. Perhaps somewhat more surprisingly we also see that individual dendrites of dark-reared animals tend to be longer than those of their normally reared siblings. This finding, coupled with the approximately equal extension of the dendritic field from the perikaryon shown in Fig. 1*c*, suggests that the major effect

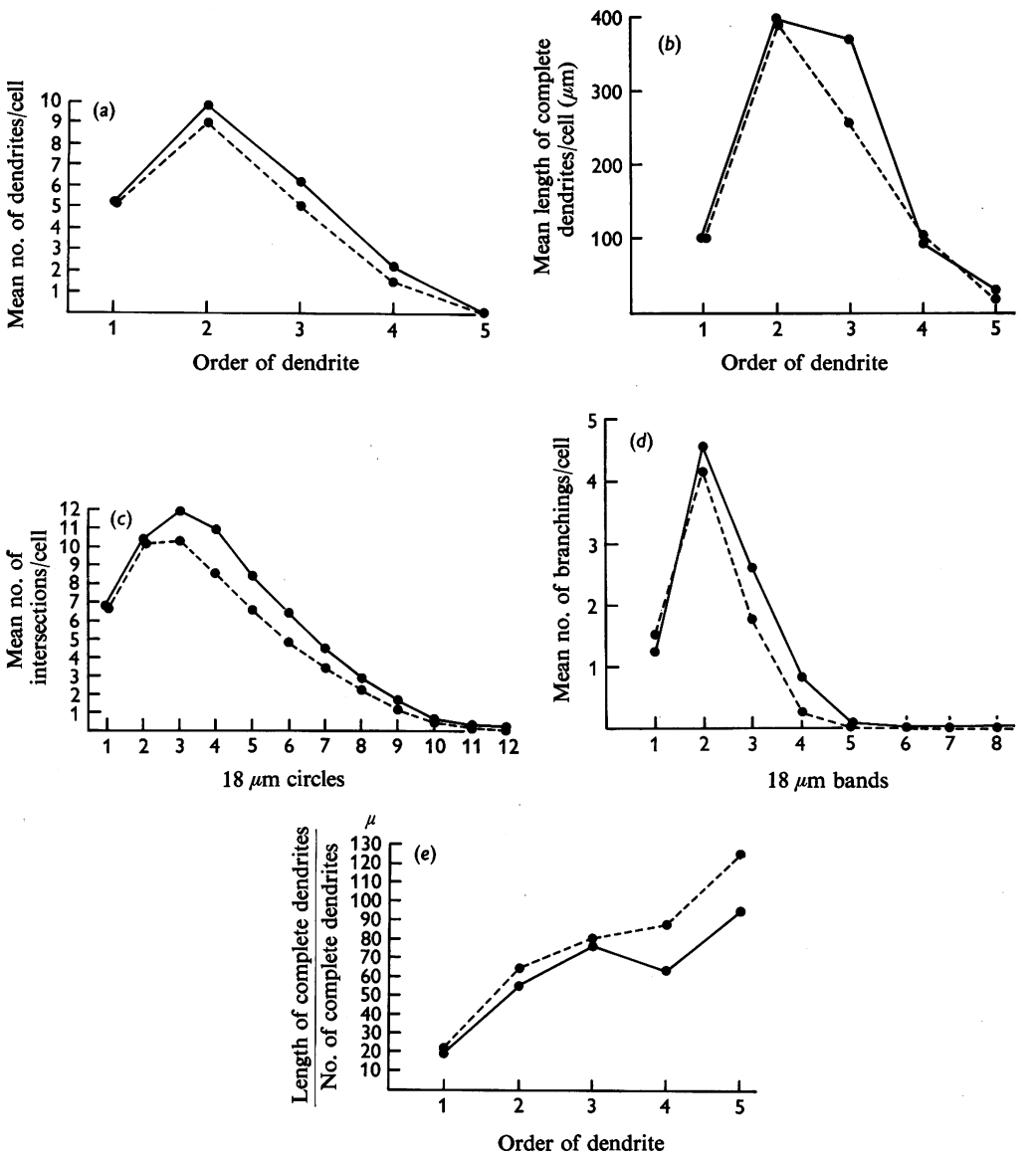

Fig. 1. Data from layer IV striate stellate sample. ——, Control; - - -, experimental. (*a*) Average number of dendrites per cell as a function of order of dendrite in normally reared and dark-reared cats. (*b*) Average length per cell of all dendrites of each order as a function of order of dendrite in normally reared and dark-reared cats. (*c*) Average number of intersections of dendritic processes with concentric circles centred around the cell body as a function of circle radius (in increments of 18 μm) in normally reared and dark-reared cats. (*d*) Average number of branchings of dendritic processes in concentric circular bands centred around the cell body as a function of distance of band from the cell body. Distance increments by 18 μm and thickness of each band is 18 μm. (*e*) Average length of individual dendrites per cell (in microns) as a function of order of dendrite in normally reared and dark-reared cats.

of dark rearing on the dendritic fields of these cells is to decrease the probability of branching. The individual dendrites of each order are longer in the dark-reared animals because they are less likely to be interrupted by a branching. It appears that it is this decreased branching, and its consequent decrease in number of higher order dendrites, that is responsible for the decrease in summed lengths of dendrites of various orders and in number of intersections, rather than any decrease in length of individual dendrites.

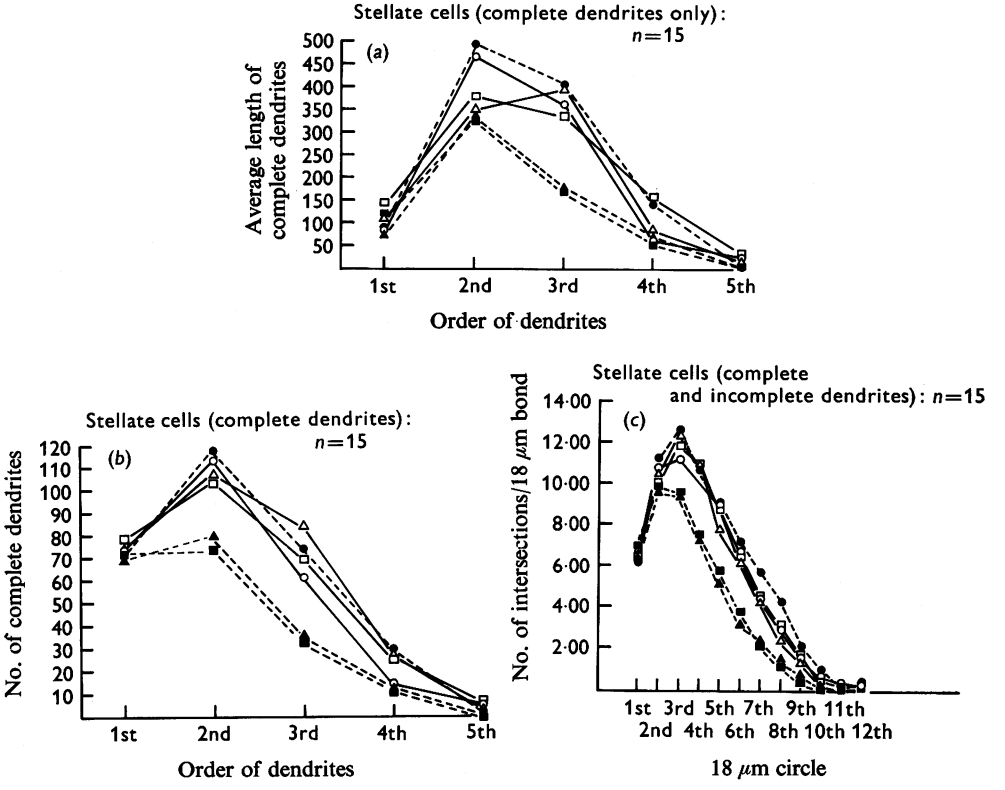

Fig. 2. Data from individual brains of layer IV striate stellate sample. Control: △, brain A; ○, brain B; □, brain E. Dark-reared: ▲, brain C; ●, brain D; ■, brain F. (*a*) Average length per cell of all dendrites of each order as a function of order of dendrite. (*b*) Average number of dendrites per cell as a function of order of dendrite. (*c*) Average number of intersections of dendritic processes with concentric circles centred around the cell body as a function of circle radius.

It is additionally instructive to look at the measurements of each individual brain that have gone to make up the preceding group data. Data from individual brains are presented in Fig. 2 showing length of dendrites of each order, number of dendrites of each order and intersections. In these graphs the data from the three control brains tend to fall together as do the data from two of the three brains of dark-reared animals. Brain D of the dark-reared group, however, consistently falls with the control group. In an attempt to determine whether this was a sampling artefact, another sampling of fifteen layer IV stellates was taken from striate cortex of brain D.

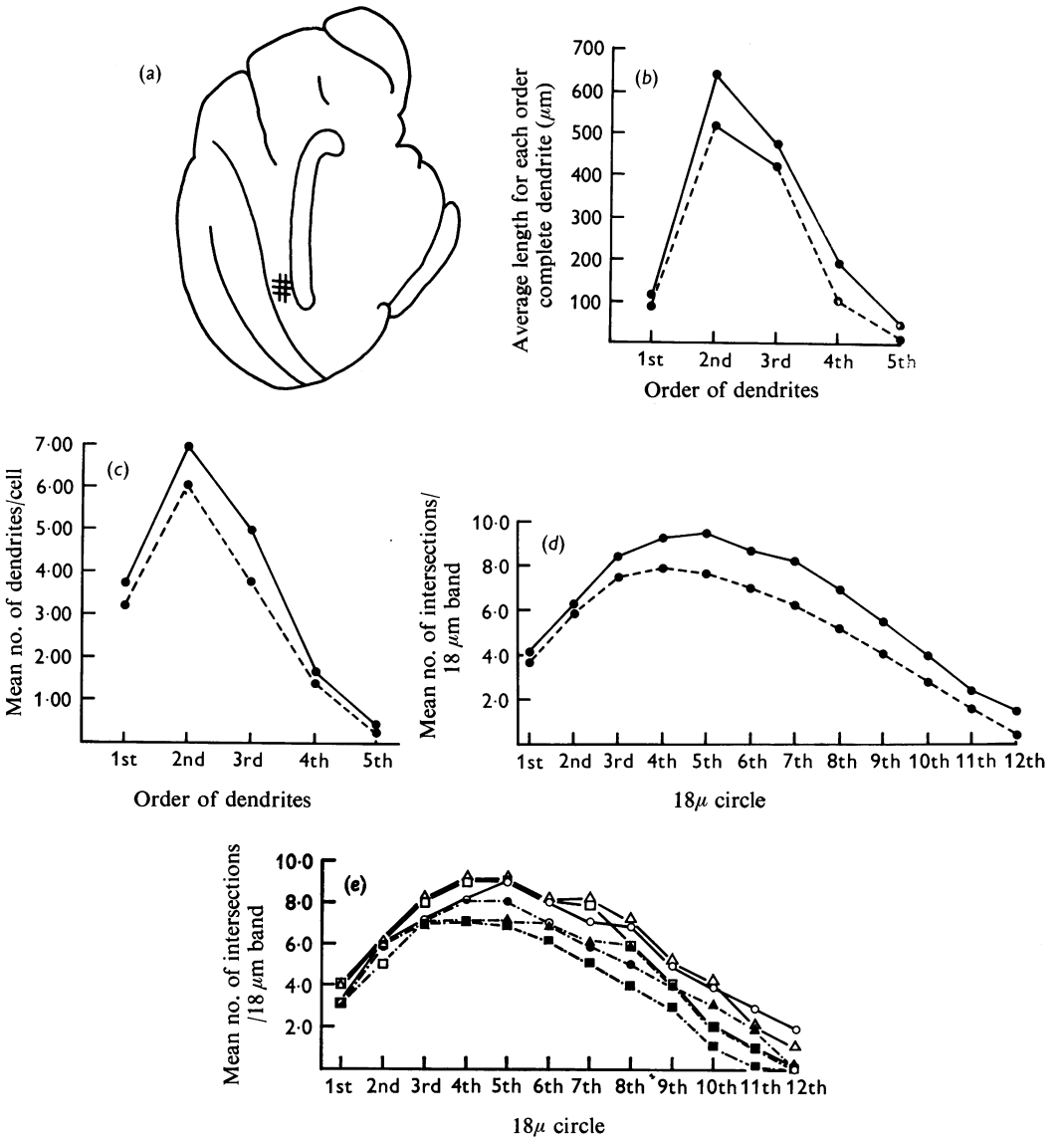

Fig. 3. Data from cingulate gyrus sample, *b–e*: ——, brain A, B, E (control); - - -, brain C, D, F (experimental). (*a*) Medial surface of cat cerebral hemisphere. Cross-hatching indicates region from which cells were taken to form the posterior cingulate gyrus sample. (*b*) Average length per cell of all dendrites of each order as a function of order of dendrite in normally reared and dark-reared cats. (*c*) Average number of dendrites per cell as a function of order of dendrites in normally reared and dark-reared cats. (*d*) Average number of intersections of dendritic processes with concentric circles centred around the cell body as a function of circle radius (in increments of 18 μm) in normally reared and dark-reared cats. (*e*) Average number of intersections of dendritic processes with concentric circles centred around the cell body as a function of circle radius. Data from individual brains. Control: △, A; ○, B; □, E. Experimental: ▲, C; ●, D; ■, F.

The measurements derived from the second sampling persisted in remaining essentially in the same range as the control values, suggesting that the behaviour of brain D represents a real phenomenon.

Cingulate gyrus pyramids. Similar measurements of cells in posterior cingulate gyrus of these brains were also made. Sixty pyramidal cells were sampled from pos-

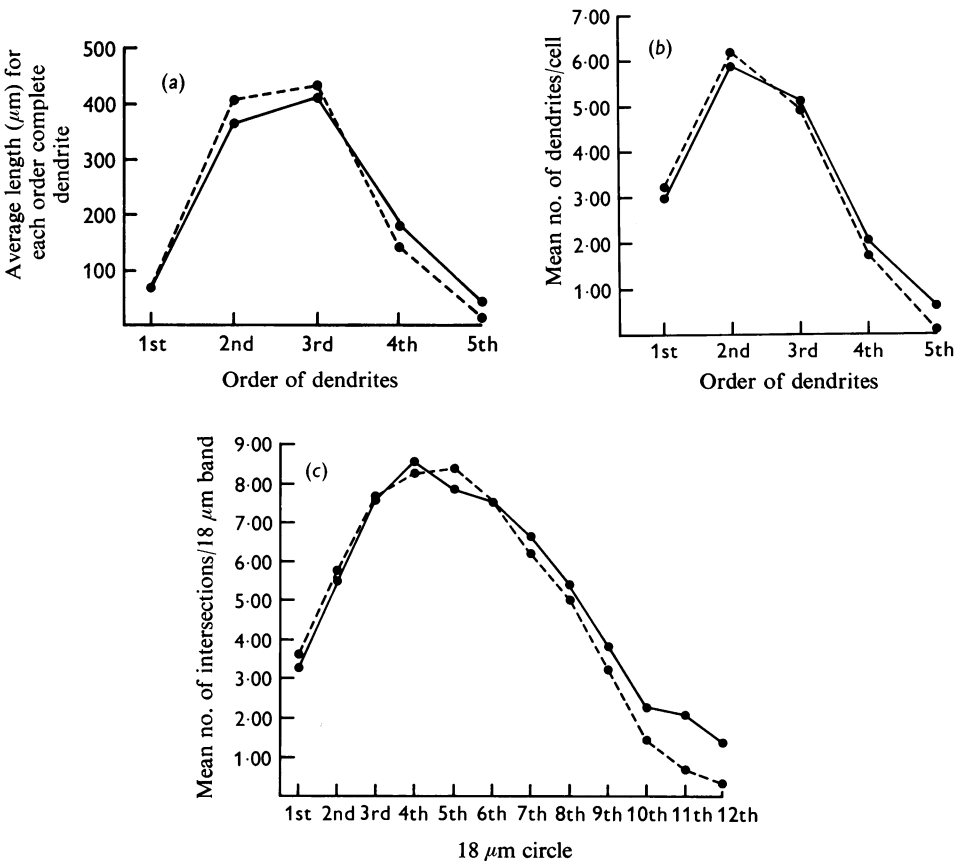

Fig. 4. Data from layer V striate pyramid sample. ——, Brain A, B, E (control). - - -, Brain C, D, F (experimental). (*a*) Average length per cell of all dendrites of each order as a function of order of dendrites in normally reared and dark-reared cats. (*b*) Average number of dendrites per cell as a function of order of dendrite in normally reared and dark-reared cats. (*c*) Average number of intersections of dendritic processes with concentric circles centred around the cell body as a function of circle radius (in increments of 18 μm) in normally reared and dark-reared cats.

terior cingulate gyrus of the same brains reported on above (ten cells for each brain). The region from which cells were sampled is shown in Fig. 3*a*. The cells chosen were 400–500 μm beneath the pial surface. The same measurements were taken in the same manner as described above for the layer IV striate stellates. The results are presented in Figs. 3*b*–3*d*. In each of these graphs the differences between the dark-reared and normally reared groups are significant beyond the 1 % level (repeated

measurement analysis of variance). The data shown represents only the basal dendritic fields of these cells. The general statement can be made that these data show effects of dark-rearing similar to those seen in layer IV striate stellates. In addition, the magnitude of the effect is similar in both cell types, if not somewhat greater in the posterior cingulate gyrus pyramids. One graph of data from individual brains showing intersections with concentric circles (Fig. 3*e*) illustrates the degree of individual variability in these cingulate gyrus data and also shows that these cingulate cells did not resist the effects of dark-rearing in brain D as did the layer IV striate stellates.

Layer V striate stellates. The question to be next asked is whether these deficiencies in dendritic fields are a general effect of dark-rearing seen throughout the whole cortex. An answer is suggested by the results obtained from making similar measures of length and number of dendrites and intersections with concentric circles of a group of sixty pyramidal cells from layer V of striate cortex. Figs. 4*a–c* show the results of such measures, and lead us to the conclusion that these cells are, in comparison to the other cell types measured, affected relatively little by the dark-rearing. In these graphs the differences between the dark-reared and normally reared groups fail to reach significance at the 5 % level. Apparently rearing in the dark under the conditions of this study does not produce a generalized deficiency in cortical dendritic fields.

DISCUSSION

Structural alterations have previously been demonstrated at various levels of the visual system after rearing either in the dark or with the eyes occluded. At the retinal level there is a clear species difference with cell loss in the ganglion cell layer of chimpanzees reared in the dark (Chow, Riesen & Newell, 1957), while loss of ganglion cells has not been found in the cat (Riesen, 1965). There have, however, been described a number of other changes in the cat retina after rearing in the dark including: reduction in thickness of the inner plexiform layer, lowering of cytoplasmic and nucleolar RNA and protein in neurons from the multipolar, bipolar and receptor cell layers, and a significant reduction of mean nucleolar volume and cytoplasmic cross-sectional area of ganglion cells (Rasch *et al.* 1961).

At the geniculate level monocular or binocular deprivation by lid suture or translucent occluder just before normal eye opening (Wiesel & Hubel, 1963, 1965) produced in cat reduction in size of cell bodies and nuclei, 'lack' of Nissl substance and reduction of the volume of the space between cell bodies. The changes were less severe when deprivation was by translucent occluder rather than lid suture, and they were also less severe when deprivation was initiated at a later age. These authors comment that 'no obvious histological changes were seen on simple inspection of Nissl or myelin sections of retina, optic nerve, superior colliculus or cortex' (Wiesel & Hubel, 1965).

There is little doubt that the effects of rearing otherwise normal cats in the dark produces relatively slight morphological changes at the cortical level, compared to those produced at lower levels (Riesen, 1966), some hormonally induced changes in cortex (Zamenhoff, Mosley & Schuller, 1966), and those marked changes seen in cortex during normal development (Eayrs & Goodhead, 1959).

The recent failure of Globus & Schiebel (1967) to produce evidence of change in

dendritic branching or length in rabbits reared in the dark from birth to 30 d may be related to a number of aspects of their study. The species dealt with may not respond to dark-rearing in the same manner as cat. Although the rabbit cortex matures earlier than cat cortex the relatively short duration of dark-rearing may be of significance in terms of effect on dendritic fields. In addition these authors examined their sample of cells under low power without tracing them (A. Globus, 1967, personal communication), so that the measures obtained may be contaminated by dendrites of other cells, and lengths were estimated by determining intersections with concentric circles in an eyepiece graticle rather than by direct measurement. Also, the number of cells dealt with per animal was smaller (10 layer IV stellates, 20 from all layers) than in the present study.

In view of the relatively slight effects of dark-rearing on cortical morphology shown here it is not surprising that earlier Nissl and myelin studies have not shown evidence of deficits in cat striate cortex after visual deprivation. It appears that methods that stain the dendritic tree combined with careful quantification are best suited for demonstration of the relatively subtle cortical changes produced by rearing in the dark. The Globus & Schiebel (1966) studies of spines, the work of Jones & Thomas (1962), and the results of the present study suggest that the examination of dendritic fields or spines may offer a method of tracing pathways after lesions, deprivations or other manipulations. The tedious nature of present means of making such studies serves as a limit to such an approach, but more automated methods using scanning techniques are clearly within sight.

The average dendritic length of 1251 μm per control cell found in our study is smaller than that derived from the data of Sholl (Sholl, 1953) for five stellate cells in visual cortex. This difference is partially accounted for by Sholl having cut thicker sections (100–200 μm). In the present study all sections were cut at 100 μm in order to make possible examination of the entire section under oil so that ambiguities could be resolved. Sholl, however, also reports more first order dendrites per stellate cell (6·8) than were seen in control stellates in the present study (5·2). This difference cannot be easily explained by differences in section thickness. Two other factors may be considered: (1) the unreliability of using for comparative purposes a mean based on five cells, and (2) the possibility that there is a true population difference between Sholl's cats and the cats used in the present study.

It is possible to correct the lengths measured for the flattening involved in projecting the three-dimensional dendritic field on to two dimensions. This correction factor was empirically determined by measuring a sample of fifteen cells in both two and three dimensions. The three-dimensional measures were obtained by including readings of the fine focus adjustments in the calculation of length. The ratio between the two- and three-dimensional measures was found to be 2·46, which served as the correction factor. When this correction factor was applied, a total dendritic length of 2413 μm per cell was calculated for the dark-reared animals and 3077 μm for the controls. The correlation between the two- and three-dimensional measures was $+0{\cdot}87$, $P < 0{\cdot}01$.

The authors are unable to suggest any factor in the procedure that would account for the difference between brain D and other brains in the experimental group. Other workers have also called attention to differences in the way dendritic systems of

individual animals react to experimental treatment (Globus & Schiebel, 1967; Valverde, 1967, personal communication). The available data, then, suggests that neuronal systems deprived of input or stimulation show a greater variability in quantitative aspects of their dendrites than do their normal controls. It is tempting to speculate that stimulation tends to drive neuronal systems toward some common point, whereas lack of stimulation allows greater manifestation of genetic variability.

There does not seem to have been a failure to produce *any* effect on brain D since measures derived from another cortical region (posterior cingulate gyrus) of brain D show an effect of dark-rearing more similar to that seen in the brains of the other dark-reared animals.

The exploration of posterior cingulate gyrus made in the present studies demonstrates an effect of rearing in the dark outside traditional primary visual cortex. This effect on cingulate gyrus cells may be considered to complement studies demonstrating evoked responses to photic stimulation recorded from posterior cingulate gyrus (Harman & Berry, 1965; Hughes, 1959; Ingvar & Hunter, 1955). The similar magnitude of effect seen in layer IV striate stellates and in the cingulate gyrus cells raises the question of whether these two cell populations may be a similar number of synapses removed from the periphery. Whether or not rearing in the dark produces effects on dendritic fields similar to those demonstrated in this study in still other cortical regions remains a matter for speculation. Gyllensten, Malmfors & Norllin (1966) have, however, shown that rearing mice in the dark will ultimately result in hypertrophy of cells in auditory cortex, manifested as increased volume of internuclear material and increased diameter of cell nuclei.

The finding that dark-rearing affects the cells of layer IV in striate cortex and not those of layer V is in agreement with the findings of Gyllensten (1959) of decreased nuclear diameter of cells in layers II to IV of visual cortex of dark-reared mice with no significant changes found in the infra-granular layers. Studies using the Golgi methods (Cajal, 1911; Lorente de No, 1949; Polyak, 1957) and terminal degeneration studies (Nauta, 1954) suggest that the fibres from specific thalamic relay nuclei terminate in the middle cortical layers (IV and lower III) and not in other cortical layers. The interesting issue of whether this statement holds true for the supragranular layers and its relation to effects of dark-rearing on these layers (e.g. Valverde, 1967) is beyond the scope of the present paper.

The experimental manipulation of neuronal dendritic fields has been accomplished in the past by surgical intervention within the nervous system (Jones & Thomas, 1962) and by variation of the chemical milieu of the nervous system (Eayrs, 1955). The extensive studies of Eayrs (1955) showed deficient dendritic fields in the sensori-motor cortex of rats made hypothyroid by daily administration of methyl thiouracil starting at birth. In Eayr's study the differences reported are of greater magnitude than those reported here. By injecting growth hormone (purified bovine somatotrophin) into pregnant rats during the 7th to 19th d of gestation, Clendinnen & Eayrs (1961) produced in the off-spring a significant increase of approximately 22 % in the mean number and length of dendrites in layer III of the cerebral cortex. Behavioral tests showed slightly earlier appearance of placing and righting reactions, and more rapid learning at 85 days and after. These data clearly support the view that increasing probabilities of neuronal interactions may be directly related to behavioural adaptability.

In the Jones & Thomas (1962) study, resection of the olfactory bulb in adult rats led to changes in the apical dendritic fields of pyramidal cells in the plexiform layer of prepyriform cortex similar to some of the changes reported in this paper. That these results were obtained in adult rats is of interest since the deficits reported by Jones & Thomas presumably represent a regression of previously formed dendritic fields rather than what is assumed to be a failure to develop reported in the present study.

SUMMARY

These data show that layer IV stellate cells in primary visual cortex of cats reared in the dark have a smaller dendritic length as well as fewer dendrites in comparison to their normally reared litter-mates. In addition, there are fewer intersections of dendrites with concentric circles around the perikarya of these cells in the brains of dark-reared animals. These deficiencies appear to be due largely to a decreased probability of dendritic branching. That portion of dendritic field that lies close to the cell body appears to be little affected by dark-rearing compared to dendrites more distant from the cell body. Similar decrements in dendritic fields were also shown in pyramids sampled at a depth between 400 and 500 μm below the pial surface in posterior cingulate gyrus. No significant effect of dark-rearing was seen in layer V pyramids from striate cortex.

These findings demonstrate that environmental manipulation can affect the structure of the intact brain. Even when there is a degree of dependence on innate organization as has been shown for visual cortex by Hubel & Wiesel (1963) certain components of an intact central nervous system may fail to develop in a normal fashion as a consequence of disuse or decreased input.

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