The Plasticity of the Mammalian Central Nervous System with Special Reference to New Growths in Response to Lesions

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The paper is a review of recent experimental work on plasticity of the central nervous system of mammals, particularly at the higher levels. They show a remarkable regenerative ability but this is effective only over very short distances, perhaps no more than 50 μm. It has to be appreciated that neuronal replacement does not occur from the very earliest age onwards.

Introduction

Soon after birth all generation of neurones ceases. Thereafter neuronal death takes over. We have the gloomy prospect of having inherited a brain that is progressively degenerating – at least in its neuronal population. In special areas remarkable death rates occur apparently as a regulative process for neuronal populations that grew in excess of needs in the intial neurogenesis. For example, Cowan [1] reports that in the isthmo-optic nucleus of the chick 27000 is reduced to 11000 in a few days and in the mesencephalic nucleus 4000 reduces to 1000. In the toad Hughes [2] and Prestige [3] find a great neuronal loss in the spinal cord particularly in the motor columns. The control of neuronal death is not known nor is the basis of sparing. Presumably the neuronal multiplication in the earlier stages results in an excess of neurones and far beyond the needs of the matured neuronal system, hence the control of population by death.
These are dramatic cases, but throughout the life of mammals and man there is a continuous neuronal death. Brody [4] reports that there is a continual loss of neurones in the male frontal cortex. For example the population at 40 years is reduced to half by 90 years. But fortunately, as we shall see, progressive death is not the whole story.

General Features

Let us first consider some general features of patterned connections between neurones. Fig. 1 gives a diagrammatic representation of impulse propagation through a series of neurones arranged formally in the characteristic manner of in-parallel and in-series. This model is of course tremendously simplified, but it does help to illustrate the manner of operation of assemblages of neurones in the central nervous system. In the diagram two of the neurones in column A are assumed to be excited and are in grey. Various axonal branches and their synaptic connections from neurones in column A to column B and so on to C and D are shown. By convention in this model it is assumed that summation of two synaptic actions is required to generate the discharge of an impulse from a neurone and so its activation is transmitted (see arrows) to synaptic terminals (grey knobs) on the neurones of the next serial column. In this way it can be seen that the exci-

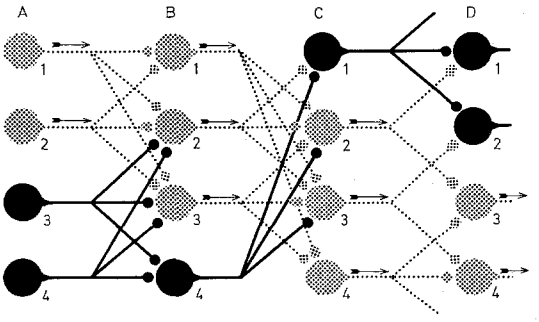

Fig. 1. Model of a highly schematic neuronal network to illustrate the simplest case of propagation along a multilane pathway. The synaptic connections of the twelve cells in columns A, B, and C are drawn, cells with impulses (note arrows) being shown light grey, while the silent cells are black. The assumption is that a cell fires an impulse if it is excited by two or more synapses (also light grey). Further description in text

* This paper was presented at the 25th Meeting of Nobel Prize Winners, Lindau, Germany, June 24, 1975.

Naturwissenschaften 63, 8–15 (1976)

tation of neurones A 1 and A 2 will result in the output of impulse discharges from neurones D 3 and D 4 but not from neurones D 1 and D 2. As already mentioned, Fig. 1 is an extremely simplified model because, firstly, it assumes a simple geometrical arrangement with columns of neurones in serial array, whereas there are known to be all manner of synaptic connections bridging such serial order, as for example from neurones of A column directly to neurones of columns C and D. Also there are many varieties of feedback controls via axon collaterals, and the consequent loop operation of large assemplages of neurones. Another serious deficiency in Fig. 1 is that no account has been taken of inhibition. Nevertheless Fig. 1 is of value because it gives a simple diagrammatic illustration of the way in which information is propagated from neurone to neurone, summation being required at each synaptic relay. Consequently there is the necessity for the in-parallel arrangement of neurones.

Some months after birth there is no formation of new neurones, and early in life the neuronal connectivities, such as those illustrated in Fig. 1, are grown. It will be appreciated that serious disabilities of the patterned operation would attend substantial losses of neurones if there was no compensation by regenerative or reorganizational processes.

The neuronal population of about 10 thousand million constitutes but the raw material for the wonderfully organized communication system of the brain and it is in organization rather than in population *per se* that we have to seek for all the marvellous performance of our brains – not only in immediate intelligent or skilled responses but in all the richness of storage and retrieval that gives us memory and that more importantly gives each of us the self recognition of personal identity through all the vicissitudes of life.

Recovery from Brain Damage

Although lower vertebrates have long been known to exhibit remarkable recovery from brain damage, it has until recently been believed that the mammalian brain and spinal cord have almost lost that ability. There are of course remarkable examples of functional recovery after clinical lesions, which are generally attributed to the better utilization of the remaining areas of the brain. Undoubtedly there is immense redundancy in the neuronal connectivities of the brain, particularly at higher levels.

In the peripheral nervous system there is a fairly efficient regeneration. For example, as illustrated in Fig. 2, section of a motor-nerve fibre results in profuse branching from the central cut end (A). One or more sprouts grows along the channel constructed by the Schwann cells surrounding the peripheral dead fibre, and thus reinnervation of the muscle is accomplished (B). However, there is no such effective regeneration process in the mammalian central nervous system. A tragic example is given by the total failure of spinal-

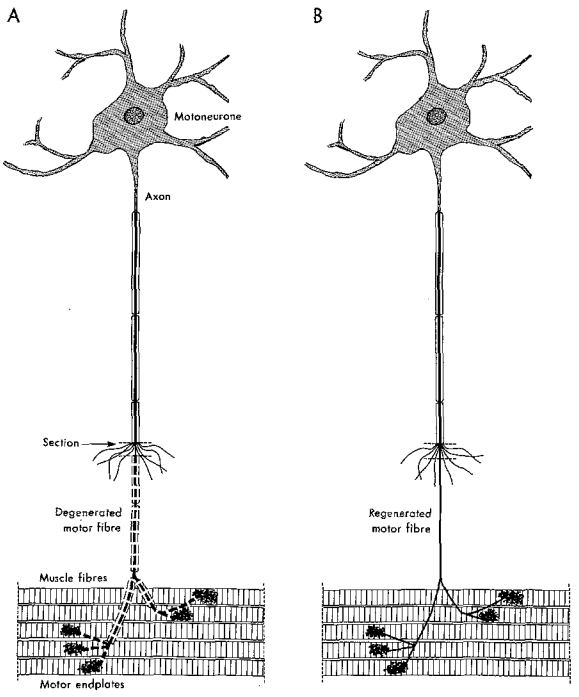

Fig. 2 A and B. Motoneurone with its axon passing as a myelinated nerve fibre to innervate muscle fibres. (A) Some days after section of the axon there is profuse branching from the central cut end and degeneration of the axon peripheral to the section. (B) Some weeks later one of the branches has traversed the pathway left by the degenerated axon and has reinnervated the muscle fibres

cord regeneration after its section in paraplegia. The cut ends of the nerve fibres attempt regeneration but lose the way and cannot track down the old pathways in the spinal cord, as they do peripherally. It seems that the inflammatory reactions of neuroglia at the site of the lesion impede the growth of the axonal branches, hence the resulting formation of knotted structures called neuromas.

Experiments on mammals confirm this failure of regeneration in the spinal cord after controlled lesions. For example, after spinal-cord transsection there is no reconstitution of communication in either direction across the gap. Furthermore, there is little readjustment or reorganization locally in response to specific lesions such as for example the crossing of peripheral nerves to muscles of antagonistic function. Sperry [5] reviewed the earlier work including his own experiments with monkeys, and later we ([6], Chapter 16) confirmed Sperry's negative results with but minor revisions. In this work of 10 – 15 years ago, the greatest changes that were disclosed consisted merely in a slight central reorganization that was little above statistical significance. For the most part, all that was shown was a random growth of connections having no functional meaning. Subsequent work by other investigators has confirmed this virtual absence of spinal-cord reorganization following controlled lesions. At the most there was a very limited sprouting with little physiological evidence for the establishment of new connectivities.

Experiments at Higher Levels

It can now be recognized that these attempts to discover effective neuronal regenerations in the spinal cord were in fact applied to an unfavourable region of the central nervous system. In the last few years at higher levels of the mammalian nervous system there have been experiments that are excellently designed and controlled. These experiments by many investigators have disclosed that lesions have resulted in a remarkable regrowth of synaptic connections in the brain stem and cerebral cortex, even in the adult mammal.

This work at higher levels of the central nervous system can best be introduced by considering the fine work of Raisman and his colleagues on neurones of the septal nuclei in the diencephalon. As illustrated in Fig. 3, the septal nuclei provide ideal conditions for the experimental investigations [7, 8]. The two principal inputs to these nuclei are the fimbrial pathway from the hippocampus and the medial forebrain bundle (MFB) from the hypothalamus. The former input forms synapses almost exclusively on the dendrites of septal cells, while the latter input ends on both dendrites and somata (Fig. 3A).

After sectioning of either pathway in adult rats (3–6 months old) there was within a few days the usual degeneration and disappearance of the synapses formed by that pathway. Electron-microscopic observations revealed that the number of synapses was reduced almost to half. But some 30 days later the full population was restored. Convincing evidence was presented that this restoration was due to sprouting of the fibres of the other pathway, the sprouts growing to form new synapses that occupied the vacated synaptic sites, as is illustrated in Fig. 3B and C. In the electron micrographs it could be seen that some weeks after section of the MFB the fimbrial fibres occupied a considerable number of synapses on the somata of the septal neurones, as is illustrated in Fig. 3C. Conversely, after section of the fimbrial pathway, there was evidence that the fibres of the MFB sprouted to form many new synapses, which often had the double configuration shown in Fig. 3B. These new synapses would all be on the dendrites, which is the site of the vacated fimbrial synapses.

It appears that there has been a loss of the embryonic growth specificity, so that collaterals growing from the intact axons now heterotypically innervate synaptic sites originally reserved for and occupied by the other input. Raisman [7] regards this heterotypic regeneration of synapses as being functionally meaningless. Nevertheless, this regeneration is of great interest because it shows that axonal sprouting and synaptic formation can occur in the adult rat, but only at micro distances, perhaps no more than 50 µm. Raisman further suggests that this heterotypic regeneration may be aided by the chromatolytic reaction of the septal neurones that follows the inadvertent section of their axons in the initial operation. Since the axons of the septal neurones are in both the fimbria and the MFB, many would be sectioned in the initial operation. Two important negative findings are illustrated in Fig. 3B

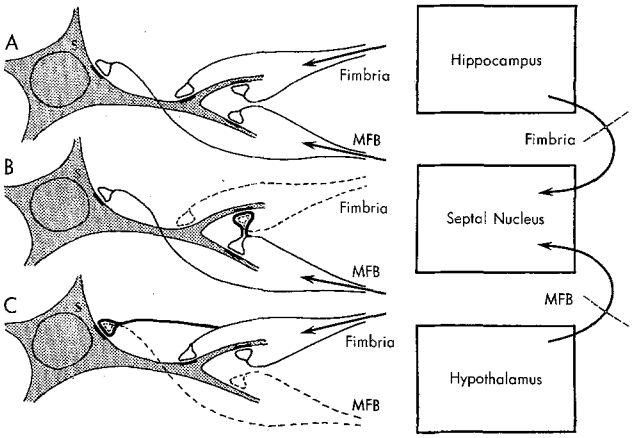

Fig. 3A–C. Schematic representation of synaptic connections to septal cells. (A) In the normal situation, afferents from the medial forebrain bundle (MFB) terminate in boutons on the cell soma (*S*) and on dendrites, and the fimbrial fibres are restricted in termination to the dendrites. (B) Several weeks after a lesion of the fimbria, the medial forebrain bundle fibre terminals extend across from their own sites to occupy the vacated sites, thus forming double synapses. (Degenerated connections: discontinuous lines; presumed plastic changes: heavy black line.) (C) Several weeks after a lesion of the medial forebrain bundle, the fimbrial fibres now give rise to terminals occupying somatic sites, which are presumably those vacated as a result of the former lesion (from [7])

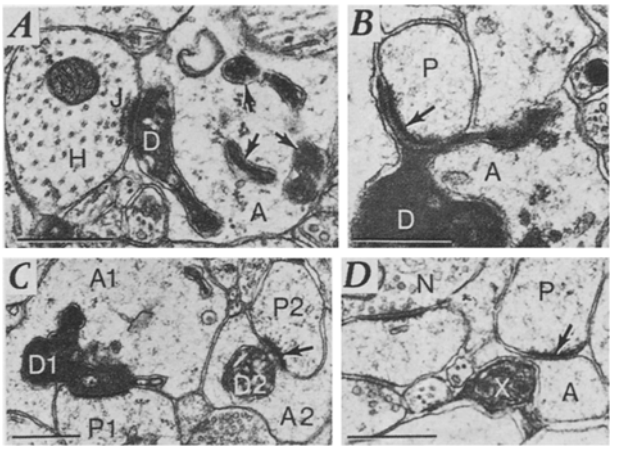

Fig. 4. (A) A dendritic shaft (*H*) containing microtubules is contacted by a degenerating axon terminal (*D*), surrounded by a reactive astrocytic process (*A*) which contains several phagocytosed fragments of degenerating axon terminal cytoplasm (arrows) containing recognizable synaptic vesicles. *J*, subjunctional bodies. Scale bars in all electron micrographs, 0.5 µm. (B) A spine-like profile (*P*) contacted at a well marked synaptic thickening (arrow) by a thin cytoplasmic protrusion from a degenerating axon terminal (*D*) the larger part of which is enveloped in a reactive astrocytic process (*A*). (C) A spine-like profile (*P1*) is contacted by a degenerating axon terminal (*D1*) surrounded by an astrocytic process (*A1*). A second spine (*P2*) with a marked "vacated" synaptic thickening (arrow) is apposed by an astrocytic process (*A2*) containing a fragment of degenerating axon terminal cytoplasm (*D2*). (D) A spine-like profile (*P*) with a marked "vacated" synaptic thickening (arrow) apposed by an astrocytic process (*A*) containing a dense fragment of degenerating cytoplasm of presumed axonal origin (*X*). *N*, part of an adjacent normal synapse (from [8])

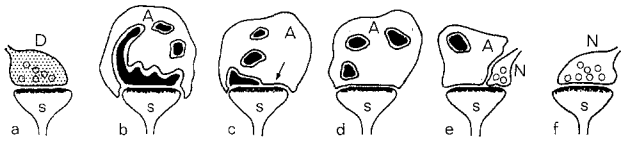

Fig. 5a–f. A schematic representation of some of the structures which have been found in apposition to dendritic spines in the septum during the period of the proposed collateral reinnervation. These configurations have been arranged in sequence from a to f in order to illustrate one possible series of changes which would result in reinnervation of the deafferented spine. (a) A degenerating axon terminal (*D*) lies in contact with the dendritic spine (*s*). (b) The degenerating terminal, now much darker and more shrunken, is surrounded by a swollen astrocytic process (*A*) which is indenting its surface and has partially engulfed two detached fragments of degenerating terminal cytoplasm (cf. Fig. 4A, B). (c) The reactive astrocytic process has now partially displaced (arrow) the degenerating terminal from the region of the synaptic thickening. (d) The displacement of the degenerating terminal from the synaptic thickening is now completed ("vacated synaptic thickening", cf. Fig. 4C, D). (e) The reactive astrocytic process is partially displaced from the synaptic thickening by a non-degenerating axon terminal (*N*) ("shared synaptic thickening"). (f) Complete reinnervation of the synaptic site by the non-degenerating axon terminal (from [8])

and C. Firstly, the sectioned fibres make only abortive growths and do not regenerate over the distances of millimeters along their degenerating pathways and secondly there is no evidence for development of new synaptic sites on the septal cells, there being merely heterotypic reinnervation of old sites.

Raisman and Field [8] have illustrated the manner in which the glial cells of the septal nucleus participate in the degenerative process. As illustrated in Fig. 4, the astroglia are specially concerned in the ingestion of the degenerating synapses, and at the same time they move in to occupy the vacated synaptic sites as described in the figure legend. The synaptic sites can be identified by the characteristic postsynaptic-membrane densities that remain after the synaptic knobs disappear. Westrum and Black [9] have reported a similar action of astroglia on degenerating synapses in the trigeminal nucleus.

In Fig. 5 Raisman and Field [8] give a diagrammatic illustration of the various stages in synaptic degeneration, namely ingestion by astroglia which then occupy the vacated synaptic sites until ejected by the new ingrowing synaptic terminals. This figure is important because it leads to the formulation of questions relating to the problems of sprouting and reinnervation of the synaptic sites. We may ask two questions: How is the sprouting initiated? How is the sprout guided to the vacated synaptic site?

Sprouting at Vacated Sites

The synaptic regeneration to septal neurones gives very clear documentation of the remarkable ability of presynaptic nerve fibres to sprout and reconstitute synaptic contacts at vacated sites. It has been suggested by Raisman and Field [8] and Watson [10] that glial cells may provide the guidelines for the newly growing fibre in the same way as Rakic has demonstrated for

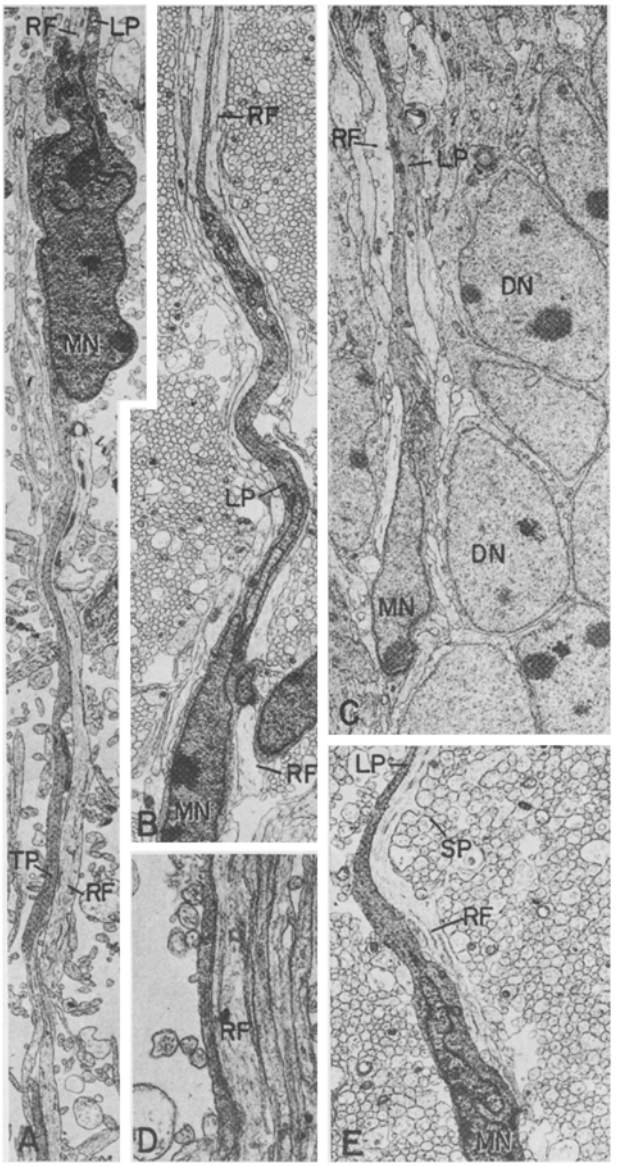

Fig. 6. (A) Migrating neuron (*MN*) whose leading process (*LP*) and trailing process (*TP*) are aligned with a radial fiber (*RF*). Intermediate zone of 97-day fetus (×3000). (B) Similar cell in 81-day fetus. The leading process (*LP*) becomes very attenuated at the top of the picture (×3000). (C) Cortical plate: migrating neuron (*MN*), its leading process (*LP*) aligned with a radial fiber (*RF*), bypasses more mature deep neurons (*DN*) on the way to the more superficial layers. 81-day fetus (×3000). (D) Contiguous processes of several migrating neurons aligned along a radial fiber (*RF*) in the intermediate zone of a 97-day fetus (×8000). (E) Leading process (*LP*) of a migrating neuron (*MN*) closely follows the contour of the curved radial fiber (*RF*). The radial fiber emits a spiny process (*SP*) on the side away from the contact with the migrating neuron. 81-day fetus (×3400) (from [11])

glia in the initial process of neurogenesis in the monkey. Rakic [11–13] has shown both in the cerebrum (Fig. 6) and in the cerebellum (Figs. 7 and 8) that the glial filaments run as long parallel strands at right angles to the surface. The electron-microscopic records (Fig. 6) show conclusively that in the developing cerebral cortex the embryonic neurones (MN) glide along these strands (RF) in a very intimate association with a separation of about 200 Å, there being a leading

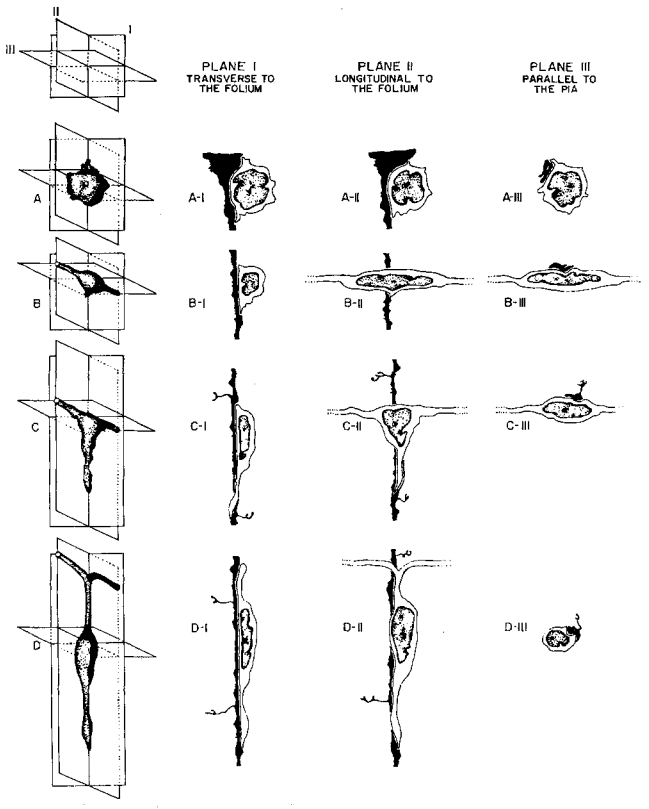

Fig. 7. Semidiagrammatic outlines of the postmitotic migrating granule cells as seen in three cardinal planes of section at different depths of the external granular and molecular layers. In the left column is a three-dimensional reconstruction of cell shapes followed by the columns with cellular profiles as seen in the plane transverse to the folium (*I*); longitudinal to the folium (*II*); parallel to the pial surface (*III*). The profiles of Bergmann fibers are rendered in black. Level A, a cell of the superficial zone of the external granular layer; level B, a cell in the deep zone of the external granular layer; level C, one in the outer zone of the molecular layer; level D, a cell in the middle zone of the molecular layer (from [12])

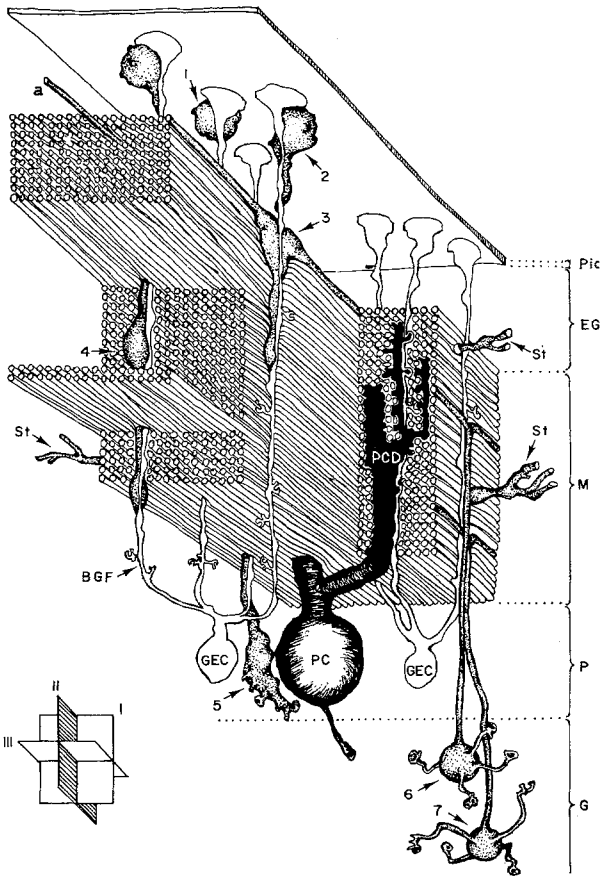

Fig. 8. "Four dimensional" (time and space) reconstruction of the developing cerebellar cortex. Geometric figure in the left lower corner indicates the orientation of the planes: *I*, transverse to the folium; *II*, longitudinal to the folium; *III*, parallel to the pial surface. The thickness of the layers are drawn in approximately their true proportions, but the diameters of the cellular elements, particularly the parallel fibers are exaggerated in order to make reconstruction more explicit. Description of the temporal and spatial transformations of the postmitotic granule cell (designed with numerals 1 to 7) and other details are given in the text. Abbrevations: *a* parallel fiber; *BGF* Bergmann glial fiber; *EG* external granular layer; *GEC* Golgi epithelial cell; *G*, granular layer; *P* Purkinje layer; *PDC* Purkinje cell dendrite; *St* stellate cell (from [12])

process (LP) and a trailing process (TP). In the cerebellum Rakic finds that the granule cells migrate down the filaments of the Bergmann glia (cf. the 3-dimensional reconstruction of Fig. 7), being directed in this way perpendicularly to the surface and down to the granular layer. Fig. 8 shows a composite picture of the granule-cell migration along the filaments of Bergmann glia (BGF) in the developing cerebellar cortex, a series of 7 granule cells (numbered 1–7) being shown in different stages of migration. Several growing fibres may even be guided by a single glial filament (Fig. 6 D). No theory has yet been developed to account for this close adhesion of sliding growth, but one can envisage that it is due to contacts between surfaces resembling those that guide the establishment of synaptic connections. There must be some chemical recognition depending presumably upon surface-membrane configurations.

The Primary Process

However, a second problem has not so far been raised and that concerns the initial process, which is the triggering of an axon to produce a branch. It is one thing for the glia to guide the branch home to the vacant synaptic site. Quite another problem is raised when one asks how the branch starts in the first place. Fig. 9 displays diagrammatically a suggestion as to how a degenerated synapse exerts this triggering role on an adjacent normal presynaptic fibre. Raisman and Field [8] have shown by beautiful illustrations (Figs. 4 and 5) the way in which the astroglia ingests the degenerating synaptic terminal and eventually breaks it up and apparently digests it. It is suggested in this theory that because of this ingestion of the degenerating synapse the astroglial cell develops a changed internal constitution which affects the surface contacts it makes with presynaptic fibres so that it acts as a stimulant for their growth. Thus we have two separate functions for glia. One is the trigger function whereby the glia through the ingested synaptic knobs stimulates the presynaptic fibre to branch, and the second is the guiding role of glia whereby the branch grows so as eventually to reach and occupy the vacated synaptic site.

In Fig. 9 there is shown an astroglial cell ingesting

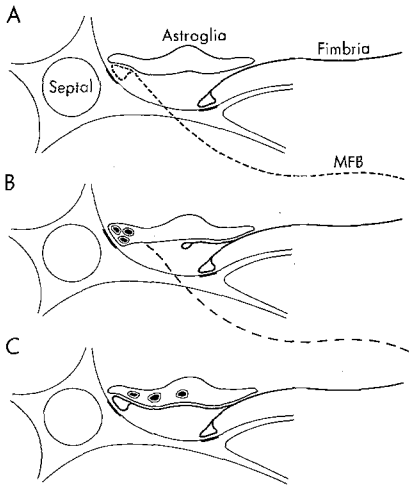

Fig. 9A–C. Diagram resembling that of Fig. 4C showing degeneration of the MFB (A) and in B, C the ingestion of the degenerated fragments of the synaptic knob (cf. Figs. 5A, C and 6b–e). As a consequence it is proposed that the astroglial cell triggers sprouting of the fimbrial axon (B) and guides it to the vacated synaptic site (C)

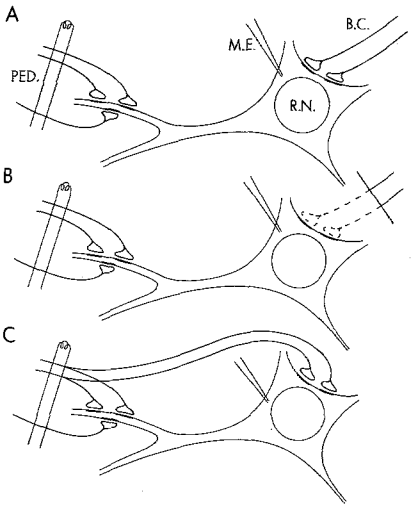

Fig. 10. Diagram to show a red nucleus neurone (*RN*) with synapses of the brachium conjunctivum fibres on its soma and of the peduncle fibres *BC* on its dendrites. *ME* is the recording microelectrode. In (B) destruction of the interpositus nucleus results in degeneration of the *BC* synapses on the soma. In (C) sprouts of the peduncle fibres are shown growing in to occupy the vacated synaptic sites on the soma

the degenerating synaptic knob and providing in that way a trigger stimulus to induce a sprout from the nerve fibre and guide it to the vacant site. This concept of astroglial stimulation of nerve sprouting after ingesting degenerating synaptic knobs raises several interesting conjectures. We can imagine that the enzymes of the astroglial cell break down the protein structures of the synaptic knob converting them into macromolecules which could be the specific molecules that trigger growth. Furthermore, it seems that the effect is relatively nonspecific because in the septal nuclei there are synaptic knobs differing in their synaptic vesicles, some having many dense core vesicles and others being free of dense cores.

It has long been known that adrenergic fibres are stimulated powerfully by the nerve-growth factor (NGF) discovered by Levi-Montalcini [14]. The NGF is highly selective in its action and apparently has no appreciable effect on nerve fibres other than the adrenergic. Hitherto NGFs for other kinds of nerve fibres have not been identified. It is now suggested that these NGFs may be generated by astroglia digesting synaptic knobs. One can think of the technique of having a large tissue culture of astroglia and feeding the cultured glia with synaptosomes (broken down fragments of the nervous system composed largely of synaptic knobs) in the hope that they would carry out the same process *in vitro* as is here postulated *in vivo*. In that case NGFs for other nerve terminals could hopefully be extracted from the astroglia at the appropriate time after their synaptosome ingestion. If such substances could be isolated, there would be most interesting possibilities of their use in aiding regenerative processes in the central nervous system.

It has been suggested that this synaptic regeneration as disclosed in the septal nucleus has no functional meaning because, as illustrated in Fig. 3, synapses from one type of input regenerate to occupy synaptic sites of quite different inputs, the so-called heterotypic regeneration. However, it must be envisaged that the experimental demonstration by Raisman and his colleagues could be obtained only if there were massive degeneration. If only a small fraction of the inputs from the fimbria or from the MFB were cut, then it would be impossible to discover any regeneration that presumably would be occurring. In other words, we have to recognize that, compared with possible naturally occurring random degenerations, the surgically induced degenerations are massive and exclusive.

Physiological Effectiveness

I now come to some very recent work in which it has been most elegantly shown by Tsukahara and associates that not only is there synaptic regeneration as found by Raisman, but also that this synaptic regeneration is physiologically effective. Fig. 10 shows the synaptic connections upon a red nucleus neurone. These have been thoroughly investigated, both histologically [15] and also with intracellular recording [16]. Fig. 11B shows that the stimulation of the interpositus nucleus (IP) gives a very sharp and short EPSP, as would be expected for the locations of the synapses on the soma of the neurone, as is illustrated in Fig. 10A. On the contrary, stimulation of the cerebral peduncle (Ped.) gives a much more slowly rising and declining EPSP (Fig. 11A, D), as would be expected if its monosynaptic sites were far out on the dendrites, as is illustrated in Fig. 10A. The difference in the time course of the respective EPSPs is fully accountable to the electronic distortions resulting from the

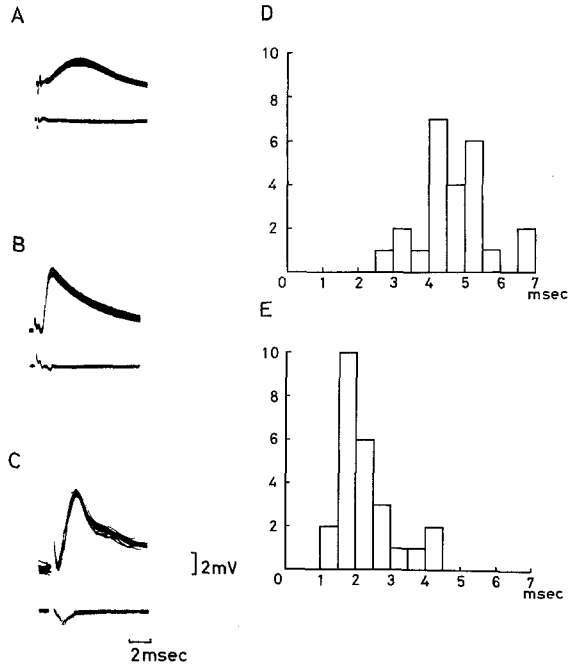

Fig. 11. (A–C) Upper traces are intracellular responses in red nucleus (*RN*) neurones, while the lower traces show the corresponding field potentials recorded at a just extracellular position. (A) and (B) illustrate a Ped.-EPSP and an IP-EPSP, respectively, (same cell) from a normal cat. (C) shows a Ped.-EPSP after IP destruction. Time and voltage calibrations for all intra- and extra-cellular responses are shown at (C). The histograms in (D) (normal cats) and (E) (after IP lesion) illustrate the frequency distribution (number of cells on the ordinate) of the "time-to-peak" of Ped.-EPSPs (from [16])

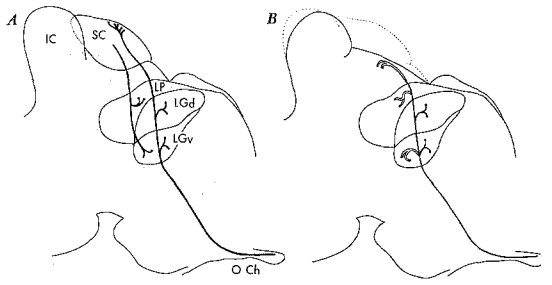

Fig. 12. (A) lateral-view reconstruction of rostral brainstem of normal adult hamster. Heavy line depicts schematically the course of a group of optic-tract axons and some of their terminations; the tecto-thalamic pathway is shown in a similar manner. (B) similar view of brainstem of adult hamster which had undergone destruction of the superficial layers of the superior colliculus in the neonate. Anomalous optic-tract connections are depicted by double lines. Abbreviations: *IC* inferior colliculus; *LGd* dorsal part of the lateral geniculate body; *LGv* ventral part of the lateral geniculate body; *LP* lateroposterior nucleus of thalamus; *OCh* optic chiasm; *SC* superior colliculus (from [18])

transmission from the distal generating sites to the intracellular recording that is effected by the microelectrode in the soma of the neurone [16, 17].

This preparation leads to the most exquisite experimental testing of synaptic regeneration. When the interpositus nucleus is destroyed (Fig. 10B), it is found that, after two to three weeks, stimulation of the peduncle results in an EPSP having features both of synapses on the soma and of synapses on the dendrites, the intracellular EPSPs of Fig. 11A being changed to those of C. All tests carried out have shown that the terminals of the peduncular pathway ending on the dendrites have sprouted to give synaptic sites occupying the vacant sites on the soma (Fig. 10C), hence transforming the EPSP from that of Fig. 11A to that of Fig. 11C. We can conjecture that glia likewise have been responsible for triggering this growth and for guiding the growing fibres to the vacant synaptic sites. Here again we have a heterotypic regeneration just as with the septal nuclei.

Schneider [18] has described elegant investigations on the visual pathway of very young hamsters. In the visual pathway the fibres decussate completely in the optic chiasma so that the left eye projects entirely to the right geniculate body and superior colliculus and *vice versa* for the right eye. The distribution of the axonal branches in these nuclei is shown in Fig. 12A, as viewed from the right side. From the optic chiasma (OCh) the fibres of the optic pathway traverse both components of the lateral geniculate body (LGv and LGd) and terminate in the superior colliculus (SC). When the right superior colliculus is removed from day 0 to day 5, the terminals of that part of the visual pathway projecting to the superior colliculus are severed and there is a reconstitution of connections as indicated in Fig. 12B. The new growths have been studied histologically and are shown by double lines.

Two explanations are offered by Schneider to account for the observed distribution of the new sprouts. (1) As shown in Fig. 12A, the superior colliculus sends fibres to the LP and LGv nuclei. These will degenerate with removal of the superior colliculus and this degeneration will induce sprouting in the optic fibres that are traversing these nuclei. It will be noted that there is no new formation of sprouts into the LGd nucleus, where there are no degenerating synapses from the superior colliculus. This explanation is in line with the explanations for the regenerations in the septal nucleus and the red nucleus as described above. (2) Schneider suggests that there is also another factor concerned in the sprouting of the severed terminals in the optic-tract projection to the superior colliculus, namely that these fibres sprout from their severed ends and try to find neurones upon which they can make synapses. This growth gives rise to a quite remarkable new tract that crosses the midline and ends upon neurones in the intact superior colliculus on the other side. Schneider suggests that this excessive sprouting of the severed fibres is related to the pruning effect obtained with plants. Certainly the formation of this tract cannot be attributed to the fibres growing along glia or other guidelines to vacated synaptic sites. It would seem to be a growth guided perhaps by glia but in itself an exploration into new neuronal territory.

It must be pointed out that these results have obtained in very young hamsters 0–5 days. Experiments have not yet been done in old hamsters. In summary, this work of Schneider [18] in part falls into line with the two previous investigations, but adds another feature

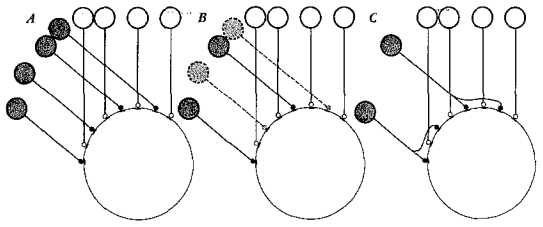

Fig. 13. (A) Drawing to show the synaptic knobs that are made on a neurone by two sets of afferent pathways. In (B) there is degeneration of half of the fibres of one set. In (C) there is occupation of the vacated synaptic sites by the remaining fibres of that set (homotypic regeneration) rather than by the fibres of the other set (heterotypic regeneration)

of growth into neuronal territory devoid of degeneration.

There have been many other investigations showing regeneration at the higher levels of the mammalian central nervous system. Particularly notable are the experiments of Cotman and his colleagues on the hippocampus in which degeneration by removal of the entorhinal cortex on one side leads to the new growth of connections from the intact entorhinal cortex [19, 20]. This work is important because it was possible to show that these new synaptic growths exhibited effective synaptic action. The work of Guillery [21], Lund and Lund [22] and Wall and Egger [23] should also be mentioned.

Cell Death during Aging

Let us now consider the ongoing process of cell death during aging that was referred to at the beginning of the lecture. There we have in a random manner one cell or another degenerating so that on any one neurone there would be only a few degenerated synaptic sites. Under these conditions one can imagine that the homotypic regeneration would be dominant. Not only would the appropriate fibres be in close juxtaposition to the degenerative sites, but also there would be the advantage of the correct steric structures for appropriate synaptic formation, such as occurs in the initial process of neurogenesis. Thus we have to reinterpret the experiments of Raisman, Tsukahara, and Schneider for example, as being of great importance in the responses to the random neuronal deaths occurring throughout life. Because of this new growth of synapses presumably triggered by the glia, the neurones go on having their normal complement of synapses despite the death of a number of nerve cells that normally provide synaptic inputs. This recovery is biased strongly, as has been suggested, for homotypic synaptic connections and as indicated in Fig. 13. Thus the disability suffered by the nervous system as a result of neuronal death can be considered as being merely from loss of the normal convergence number, by which one means the number of neurones of any one species converging synaptically upon a neurone. This loss (from 4 to 2 in Fig. 13) would result in some coarsening of the grain of the control of neuronal responses, but no reduction in their effectiveness.

These investigations in many sites in the mammalian central nervous system certainly show that under appropriate conditions there is an effective new growth compensating for the death of neurones and their axons. It is therefore with optimism that one now looks at the often enigmatic and ambiguous clinical findings described during stages of recovery from lesions of the human brain. The most remarkable account of this has recently been given by Brodal [24], a distinguished neuroanatomist who suffered a vascular accident in his right cerebral cortex and made quite a remarkable recovery in a year or two, as has been fully described in a paper he has published. However, apart from these major accidents, we are always, as I have stressed, continually suffering from random neuronal death and we have no way of replacing our neuronal population. However, this new story of synaptic regeneration shows that the nervous system can go on functioning reasonably well with the disability of a less fine grain despite losses which may even halve the neuronal population. The postsynaptic sites can be recognized by virtue of their dense staining, and it is generally recognized that very few of these vacant sites can be seen in electron micrographs of the central nervous system at all ages. This indicates a general principle that vacant synaptic sites tend to be occupied, and in fact one can say that the central nervous system abhors a vacant synaptic site!

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Received June 30, 1975

