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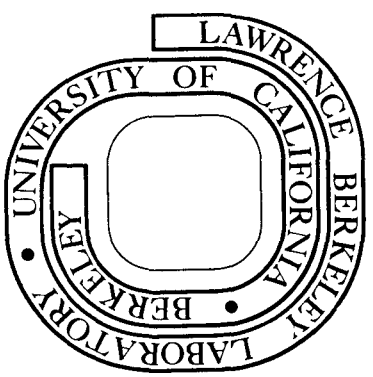

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HOW PLASTIC IS THE NERVOUS SYSTEM?

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I. Introduction

Dramatic evidence of plasticity of the nervous system has been flooding in from many sides in the 1960's and 70's in striking contrast to the evidence of fixity of neural structures and connections that prevailed in the 1940's and 50's. Opinions on this topic have ebbed and flowed in the past and may do so again, but the present tide must be recognized. As examples, let us note some representative recent publications that are devoted in whole or in part to this subject: Plasticity and recovery of function in the nervous system (Stein, Rosen & Butters, Eds., 1974), Neural mechanisms of learning and memory (Rosenzweig & Bennett, Eds., 1976), Elements of the behavioral code (DeFeudis & DeFeudis, 1977), Brain and learning (Teyler, Ed., 1978) Recovery from brain damage (Finger, Ed., 1978), and Neuronal plasticity (Cotman, Ed., 1978). The foreword to a recent symposium on protein synthesis in the brain starts with this sentence, "It is only recently that the high degree of plasticity in the brain could be recognized" (Roberts, Lajtha & Gispin, eds., 1977). Even if most of the research in this area is not yet at the point of being applied, many of the findings and concepts give hope to applications to such problems as those of enhancing intellectual ability and preventing some forms of mental retardation, preventing or alleviating senile decline of mental functioning, and aiding recovery of function after brain injury. Before going ahead to examine evidence and speculations about neural plasticity, let us first take up the plan and scope of this chapter.

A. Plan and scope of this chapter

At the request of the editors, this chapter is intended to be partly speculative in character. We have interpreted this charge to mean that we should both review research in this area and also attempt to make some extrapolations from it. Some extrapolations will take the form of suggestions

for further research and others will predict possible applications of current and future research. We will try to label the speculations clearly to aid readers in separating fact from fancy, although such distinction is not always easy even in the case of research literature, as will be seen in some areas of controversy and dispute upon which we will touch. Some speculative material will be sprinkled through the chapter; other such material will be found in the final section. A catalog of plastic changes in the nervous system will be presented on pages 26-36.

We should note that most of the material in this chapter comes from research with animal subjects rather than from observations on human beings. Most investgators of neural mechanisms take the use of animal models largely for granted. Much justification, both practical and theoretical, can be supplied for extrapolating from animals to human beings where brain-behavior relations are concerned, but it is well to remember that not all such extrapolations are found to work out. Rather than discuss these problems here, we will simply cite two current references (~~Warren & Kolb, 1978~~ 76, 112; ~~Rosenzweig [Rehab. Symp., in press]~~).

Some of the main topics and questions to be considered in the chapter are these:

To what extent are neural connections predetermined by heredity and to what extent can they be altered by postnatal determinants? We will consider effects of several factors, including damage to other parts of the system, sensory deprivation or distorted sensory input, and training and experience.

Can new connections be formed in the adult mammalian nervous system? Such connections have been reported when tissue from other organs is implanted into parts of the brain. Also, it has been shown in some brain regions that when one input tract to the region is removed, the endings from other inputs then sprout and occupy the vacated synaptic sites. Changes in neural connections have also been demonstrated when animals are given enriched experience

or formal training.

Does recovery of function after brain damage involve formation of new compensatory connections or only learning ways of using residual capacities to make up for the loss? (And if learning is involved, does this imply formation of new connections and/or modification of pre-existing ones?)

Before starting our review of recent evidence and current speculations let us look back briefly to gain some historical perspective.

B. Changing Viewpoints

Views concerning the plasticity of the nervous system have changed widely during this century. Up through the 1920's and 30's the prevailing assumption among pyschologists and physicians was that the behavioral repertoire of the organism is largely a product of accumulated training or conditioning. This was partly based on the research of Pavlov and on the teaching of Watson that almost any form of behavior could be taught by appropriate techniques. It also appeared consistent with the inability of Franz, Lashley, and Goldstein to find any specific locus for memories in the brain in studies involving experimental lesions in animals or brain-injured human beings. Even localized cerebral representation of sensory-perceptual functions was questioned. Lashley suggested that if the surgery were feasible, the striate cortex could be circumscribed and undercut, lifted out, rotated 180° and then reconnected--probably without seriously disrupting visual perception. Experimental reports stated that after motor nerve connections to the muscles in a limb were reversed, normal coordinated behavior reappeared, presumably mediated by adjustments of central connections.

A strong challenge to the proponents of functional plasticity was presented by Roger Sperry in the 1940's. When he conducted experiments involving surgical transplantation of nerves to muscles, he found that the predicted readjustments did not occur. Sperry also conducted extensive experiments on regrowth of the visual or retino-tectal system of amphibians and fishes and found great specifi-

city and rigidity of connections. For example, if the eye of such a subject was removed and reimplanted after a rotation of 180°, the connections of retina to tectum were re-established precisely and the animal showed inverted vision; furthermore this inversion was found to persist indefinitely without any correction by re-education. Behavior reverted promptly to normal, however, upon surgical re-rotation of the eyeball back to its original orientation. On the basis of such results, Sperry concluded that fiber pathways and connections in the nervous system are precisely ordered and established without regard to function; he suggested that the guidance of the precise connections should largely be ascribed to the operation of highly selective cytochemical affinity.

In the 1960's and 70's, much evidence has become available that new connections can be formed in the adult nervous system. Some of this came from the work of our group at Berkeley showing that differential experience leads to anatomical and chemical alterations in the brain, including changes in numbers of dendritic spines (~~Bennett, Diamond, Krech, & Rosenzweig, 1964; Bennett, 1976; Globus et al, Rosenzweig & Bennett, 1976, 1977, 1978~~ 7, 8, 41, 80, 81, 82, 43). Greenough (~~1976~~) found that differential experience causes changes in dendritic branching. Schneider (~~Schneider & Jhaveri, 1974~~ 90) showed sprouting of some connections of nerve cells when other connections of these cells are removed. Extensive sprouting was also found to take over empty sites when one neural tract to a structure is removed (Lynch & Wells, 1978). When tissue from any of a number of organs is implanted into the brain, it attracts innervation (~~Moore, 1976~~ 67). Hubel and Wiesel and their collaborators have shown in a rich program of experimentation that visual deprivation or distorted visual inputs early in the life of cats or monkeys leads to changes in visual receptive fields and also to measurable changes in the anatomy of the cortical receptive areas. Training or differential experience has been demonstrated in a number of laboratories to aid recovery of function after brain lesions in experimental animals (~~Schwartz, 1964; Greenough, Fass, De Voogel; &~~ 44, 91, 118

Will, Rosenzweig, Bennett, Hebert & Morimoto, 1977). Several of these indications of neural plasticity will be taken up in some detail later in this chapter.

The rapid survey of indications of neural plasticity in the last paragraph indicates both the wealth of research in this area and the growing recognition of possibilities of plasticity even in the adult mammalian nervous system. Rather than considering this as a swing of the pendulum back to an earlier position, we would prefer the analogy of a spiral ascending pathway on which we have now reached a higher outlook whence we can see more clearly both the opportunities for plastic change and the limitations imposed by characteristics of the neural system.

II. Plasticity in Central Connections

A. Study of retino-tectal projections

Although some of the most convincing demonstrations of predetermined specificity in connections of the nervous system were afforded by research in the visual system (Sperry, 1943; 1951; 1963; Attardi & Sperry, 1963), 5, 95, 97, 98 further research on retino-tectal connections has given indications of some plasticity in this system, and research with mammalian subjects has shown much evidence of both anatomical and electrophysiological plasticity.

Using amphibian embryos, experimenters found that when they made a compound eye by joining either two nasal half-retinas or two temporal halves, the fibers from the compound eye seemed to project not just to the corresponding half of the tectum but to the whole tectum, each half spreading its representation across the entire tectum in a mirror image pattern (Gaze et al., 1965; Stranznicky et al., 1971). 37, 101 It was also reported that in goldfish when the posterior half of the tectum is removed, the whole retina will in time come to project in an apparently orderly but compressed pattern on the remaining half-tectum (Gaze and Sharma, 1970; Yoon, 1971, 1972). 38, 120, 121 Meyer and Sperry (1974) 66 have reviewed much of this work and have raised questions about accuracy and interpretation of results apparently indicating plasticity of projection. Further research along

this line, however, appears to yield quite convincing evidence of plasticity. Thus Udin (~~1977, 1978~~ 106, 107) studied retino-tectal mapping in frogs after regeneration of fibers when the operations were performed in adults; the tests after regeneration included both recording of action potentials and behavioral tests of accuracy of orientation to visual targets. The caudal half of the tectum was removed and in some experiments the optic nerves were left intact whereas in other experiments one nerve was also transected. When the caudal half of the tectum was removed on one side of the brain but the optic nerves were left intact, the terminals displaced from ablated tissue formed a permanently disorganized projection superimposed on the unaltered representation of those parts of the retina that normally projected to the rostral half of the tectum. The new connections appeared in the electrophysiological records about seven weeks after operation; they could be discriminated from old connections because the action potentials of new connections were only about half as large as the old and the new occurred singly or in isolation while old connections were in multi-unit clusters. The behavioral tests of turning toward a visual target showed lack of accuracy in the part of the visual field that projected to the ablated half of the tectum. When the caudal half of one tectum was removed and the optic nerve was also transected, then the whole visual field obtained a compressed representation on the remaining rostral half of the tectum. Electrophysiological mapping showed that all parts of the visual field were represented. The behavioral tests also showed representation of the whole field but with less accuracy in the affected side than in the control side.

Schneider and collaborators have carried out an extensive program of research on determinants of visual connections in the hamster and have found examples of sparing of function in spite of removal of tissue, loss of function, and maladaptive alterations of function after damage inflicted early in life

(~~Schneider & Jhaveri, 1974~~ 90). If the superficial layers of the superior colliculus are destroyed unilaterally at birth, axons from the eye contralateral to the lesion not only grow out to the area of early damage but, in most cases, they also form an abnormal decussation, crossing the midline of the tectum to form terminations in the undamaged colliculus. This projection to the "wrong" side of the midbrain increases greatly if the undamaged colliculus is deprived of its normal innervation by early removal of its contralateral eye. Hamsters with such anomalous connections show a behavioral deficit--they turn to the wrong direction in response to stimulation in a large area of the upper and temporal visual field. Some of the factors that control the formation of abnormal connections have been specified, based on a program of neuroanatomical experiments: (1) Growing or regenerating axons tend to invade vacated terminal spaces and to compete with other axons for occupancy. (2) Axons tend to conserve at least a minimum quantity of terminal arborization. For example, fibers of the accessory optic tract form connections part way along their route at the dorsal terminal nucleus and also form terminal connections at the optic tectum. If the tectum is destroyed, these fibers then show hypertrophy of their connections at the dorsal terminal nucleus. (3) The retino-tectal projections tend to preserve their topographic order even if they are forced to terminate in an abnormally small area such as the residual caudal part of the superior colliculus after ablation of the superficial layers of the rostral tectum at birth.

Recently So and Schneider (93) have been studying how much of the abnormal ipsilateral sprouting occurs when the superior colliculus is removed at birth and one eye is removed at various later ages. Up to about Day 12, the abnormal connections spread all the way across the superior colliculus, but if removal is delayed until Day 14, only a small amount

of spread is observed. Several hypotheses that might account for the limitation of spread by Day 14 have been tested. When the visual cortex is ablated, thus removing some of the projects to the superior colliculus, this encourages growth of the retinal projections to the colliculus. It is now possible to obtain ipsilateral connections up to Day 16, and further prolongation of the growth period will undoubtedly be possible. Such studies of factors that limit and factors that promote formation of connections in the brain may eventually be of therapeutic significance. Some cases of recovery of function after destruction of neural tracts appear to involve establishment of new pathways or strengthening of existing ones. It may be possible in the future to promote selectively the formation of new connections linking chosen brain regions.

B. Effects of Visual Deprivation or Distorted Visual Input on Cortical Connections and Responses

A vast amount of research beginning in the 1960's has shown changes in cortical visual receptive fields and in cortical connections when one eye of a cat or monkey is deprived of visual input during early development or when such animals are exposed to restricted and distorted visual inputs such as being exposed only to horizontal lines or only to vertical lines or small spots of light. No attempt will be made to review this extensive research in any detail here; the interested reader is referred to the reviews by Grobstein and Chow (~~1976~~ 46), Chow (~~1973~~ 14), and Lund (~~1978~~ 62, Chapter 15).

Monocular deprivation of vision was shown by Wiesel and Hubel (1965) to reduce severely the number of cortical visual cells responding later to the previously occluded eye. Whereas in normal kittens most cortical units respond to either eye, in kittens in which one eye had been occluded for several weeks during early development, the cells responded almost entirely to the eye with visual experience. Later research showed a clear

anatomical correlate of this effect. In layer 4 of the primary visual cortex, connections from the lateral geniculate body are monocular, the two eyes being represented by alternate bands of connections. At other layers of the cortex, the projections from the two eyes converge so that most units represent both eyes. When one eye has been deprived of light during early development, its bands of representation in layer 4 are much reduced in width, and the bands representing the eye with normal experience are correspondingly broader (~~Hubel, Wiesel & La Vay, 1976~~ 50). Research with the radioactive deoxyglucose method has confirmed that ocular dominance columns are present in monkey striate cortex on the day of birth, that monocular deprivation begun early in life leads to narrowing of the columns representing the deprived eye, and that such plasticity has ended by the preadolescent period (~~Des Rosiers et al., 1978~~ 19). It now appears, however, that the observed reduction in connections from the deprived eye is not sufficient to account for the almost total failure of this eye to drive cortical cells. There remain connections, but they are inhibited by those from the stimulated eye, as we will discuss below (p. 30).

A large number of reports have claimed that if a young kitten is exposed only to vertical or to horizontal stripes or to some other sort of restricted visual stimulation, then receptive fields tend to respond to the stimulation experienced and in general not to other types of stimulation (~~Hirsch and Spinelli, 1970; Blakemore and Cooper, 1970; Pettigrew and Freeman, 1973~~ 10, 49, 70). Recently it has been claimed that these results are not completely replicable (~~Stryker and Sherk, 1975~~ 102) and further work is needed in this area. It has also been claimed that structural changes can be found in response to restricted experience. Preliminary reports by Spencer and Coleman (~~1974~~ 94) and Flood and Coleman (~~1978~~ 32) have indicated that in kittens exposed only to vertical stripes, the dendritic fields of cells in the primary visual cortex were elongated along the anteroposterior

axis of the cortex; in kittens exposed to horizontal stripes, the dendritic fields were elongated along the dorsoventral axis. In the kittens with normal visual experience, the dendritic fields tended to be round, while dark-reared kittens showed smaller dendritic fields than did normal control animals.

A number of investigators have reported effects of differential early visual experience on later visual behavior. Blakemore and Cooper (10 ~~1970~~) reported dramatic effects--kittens that had been exposed only to horizontal stimuli could scarcely see vertical stimuli; they would blunder into the legs of tables and chairs in the laboratory. Hirsch (48 ~~1972~~) found less striking results. He obtained small but significant differences in thresholds for horizontal and vertical lines. Eyes exposed only to horizontal or only to vertical stimuli were inferior even in the orientation of exposure, to eyes with normal visual exposure. Such effects were reported to be long-lasting, remaining months or even years after the animals had been given normal visual experience. Chow and Stewart (15 ~~1972~~) showed that the effects of restricted early stimulation, while severe, could be overcome to a large extent by long and patient training.

People with astigmatism have suffered from reduced visual input along certain visual meridians in which their vision is blurred. Since astigmatism tends to be present from very early on, such people have been involuntary subjects in a natural experiment on differential stimulation of visual meridians. Freeman and Thibos (33 ~~1973~~) found that astigmatic subjects showed a small deficit in visual acuity along the orientation of their astigmatism and that this deficit could not be completely overcome by optimal visual correction. Their only subjects not showing such a deficit were two individuals who had been given visual correction before three years of age. Thus human beings may incur a persisting visual deficit caused by distorted sensory input, and it may be impossible to correct

this completely unless remedial efforts are undertaken early in the life of the person. Just as hard-of-hearing youngsters are being given hearing aids in their first few years to promote normal development of speech, so it may be important to give children visual corrections earlier than is now common in order to prevent permanent establishment of abnormal central visual connections.

There has been considerable speculation as to whether the developmental plasticity of the visual system has some functional value. Perhaps this simply reflects the fact that the visual system, like other parts of the nervous system, is not completely specified genetically and that evolution has occurred under circumstances that normally entail a contribution of information from the environment. Others have suggested that at least some aspects of the plasticity of the visual system may be present because genetic information may be intrinsically inadequate to create optimal connections (e.g. 46 ~~Grobstein and Chow, 1976~~). This may be especially true in the case of acuity for binocular disparity. The adult viewer is highly sensitive to small binocular disparities, and these provide clues to depth and distance in the visual field. But in neonatal kittens, the precision of binocular representation is poor (69 ~~Pettigrew, 1974~~). In the young kitten a 3° field in one eye summates with a point stimulus in the other eye. Over a six-week period, this reduces to 0.5° in kittens that receive normal visual experience, but such a reduction does not occur unless the two eyes receive experience at the same time. Shlaer (92 ~~1971~~) raised kittens with a prism over one eye, causing a vertical displacement of a few degrees. After some weeks of this experience, the cortical representations of the visual fields of both eyes were measured without the prisms present. In prism-reared kittens, cortical cells tended to receive input from non-corresponding points in the visual fields of the two eyes, such as to compensate for the displacement that had been caused by the prism over one eye. Apparently the visual systems had been able to compensate

for small discrepancies during experience, although earlier experiments had shown that no compensation was possible for a large discrepancy such as occurs in strabismus. Precise correspondence of registration of the two eyes depends on a number of factors including the exact optics of the eyes and their positions in the eye sockets as determined by the extra-ocular muscles. The two eyes have somewhat independent histories of development, so only after the system begins to function can it be determined exactly what positions on the two retinas see the same region in visual space. Thus, within a development of visual connections that is broadly specified genetically, the effects of specific experience may be required for the fine tuning of the correspondence of connections.

C. Plasticity in the Hippocampus

Recent research on the hippocampus shows that when one set of its input fibers is eliminated, fibers from other sources rapidly sprout new endings to occupy the vacated synaptic sites. This search for plasticity in the hippocampus was begun with young animals, presumably on the wide-spread premise that plasticity may be confined to early development. But it was then extended to adult animals, and evidence was found of continuing "competition" for connections even in adult brains. Let us review this research briefly.

The hippocampus is a three-layered structure of paleocortex. The relative simplicity and regularity of its structure makes it especially suitable for analysis of structure and function. In the dentate gyrus of the hippocampus, the middle layer is made up of granule cell bodies whose dendrites project up into the molecular layer where they receive projections from a variety of sources. In the inner one-quarter to one-third of the molecular layer, the part closest to the granular cell bodies, the dendrites receive afferents mainly from the

contralateral hippocampus through the lateral ramus of the hippocampal commissure. The same region also receives projection from association fibers of the ipsilateral hippocampus but not as many as from the contralateral. In the outer one-half to two-thirds of the molecular layer, dendrites of the granule cells receive projections from the ipsilateral entorhinal cortex and a much less dense projection from the contralateral entorhinal cortex. Entorhinal cortex is a transitional form of cortex in the anterior part of the temporal lobe. If one of the normal afferent pathways is eliminated, then two types of reorganization may occur: (1) the spreading or sprouting of afferent fibers into areas of the dendritic field adjacent to the areas that they would normally occupy; and (2) the development of a thicker or denser afferent projection into parts of the dendritic field that these fibers would normally innervate only sparsely.

The experimental procedures used by Lynch, Stanfield, and Cotman (~~1973~~ 63) consisted of several stages. In the experimental group, entorhinal cortex was removed unilaterally in eleven-day-old rats. Time was then allowed for complete degeneration of projections from the entorhinal cortex and for the products of degeneration to be removed by phagocytosis. Then, when the rats were 91 days old, the commissural pathway to the hippocampus was transected. Five days later the rats were sacrificed to study the distribution of the newly degenerated projection from the commissure to the dentate gyrus. The pattern of degeneration was compared in the two hemispheres and also with control animals in whom entorhinal cortex had not been removed. On the side deafferented by the entorhinal lesion, the commissural fibers now spread through more than 9/10 of the molecular layer. This broad distribution contrasted sharply with the pattern in the other hemisphere of the early-lesioned rats and with both hemispheres of the controls. In the latter, the picture was normal with the commissural projection restricted to a narrow zone just above the granule cell

body. The results suggested that the normal narrow distribution is probably maintained by competition among inputs.

Lynch, et al. (63 ~~1973~~) then compared effects when entorhinal cortex was removed at 11 days of age or in adults at least 100 days old. Following a recovery period of at least 150 days, the experimenters then removed dorsal hippocampus contralateral to the original entorhinal lesion. A few days thereafter the animals were sacrificed in order to determine the spread of connections from the dorsal hippocampus through the commissure to the contralateral hippocampus. The median percentage of the width of the molecular layer of the dentate gyrus occupied by the band of commissural degenerations was 52% in rats that sustained the entorhinal lesion at 11 days of age, 44% in the adult-lesioned rats, and 27% in the controls. Thus the width of the projection increased by 90% after removal of the entorhinal projection in rat pupps and by 60% after removal in the adult.

Current work has extended this investigation to 24-month-old rats (~~Scheff, Benardo and Cotman, 1977~~ 89). Preliminary indications are that axonal sprouting to occupy vacated sites is slower to start in the older rats than in young rats, but that, given enough time, the effect in the older animals may be as great as that in the younger animals, or very nearly so.

Changes in the density of synapses in the hippocampus in response to enriched vs. impoverished experience in post-weaning rats have been reported by Altschuler (~~1976~~ 44).

III. Effects of Differential Experience and Training on Brain Measures

Now let us consider how experience and training can affect the brain. The preceeding sections have shown that plastic changes occur in response to severe or harmful treatments--depriving young animals of normal sensory stimulation or transecting tracts in the brain. Such severe treatments are not necessary to induce cerebral effects. A large number of experiments, first in our laboratories at Berkeley and later in several other laboratories

as well, have demonstrated that differential experience and training lead to measurable changes in the biochemistry and the anatomy of the brain. Furthermore, many of these effects occur not only in young animals but also in adults. Only a brief survey of these findings will be presented here, since several rather extensive recent reviews are available (Greenough, 1976; Rosenzweig & Bennett, 1976, 1977, 1978). 43, 80, 81, 82

Most of the experiments on this subject have involved placing laboratory rodents for periods lasting from a few weeks up to a few months in differential environments--environments either enriched or impoverished in comparison to the usual animal colony cages. The enriched environments have usually included both more social stimulation and a greater variety of inanimate objects than the colony cage; that is, 10-12 animals are placed in a large cage with a variety of stimulus objects or "toys." In some experiments, the social stimulation and the inanimate stimulation have been varied separately (Rosenzweig & Bennett, 1976); 80 social stimulation cannot account for the full enrichment effect (Rosenzweig et al., 1978). 85 For impoverished experience, the subject is placed alone in a colony cage, instead of having one or two cagemates as in the standard colony situation.

A. Effects on Brain Weights

Typical results in terms of brain weights are these, when littermate rats are compared after exposure to the enriched condition (EC) versus the impoverished condition (IC): Rats with EC experience show greater weight of total brain by about 2-3%; this is statistically significant in most experiments. The overall brain difference is due mainly to changes in cerebral cortex which shows effects of about 5% while the rest of the brain differs by only about 1-2%. A very stable measure that tends to yield highly significant differences between groups is the cortical/subcortical weight ratio. Because both cortical weight and subcortical weight are

correlated with body weight, the ratio tends to eliminate the influence of body weight and to provide, in effect, a covariance on body weight. Within the cerebral cortex, the occipital area shows the largest difference between EC and IC, the occipital effect often amounting to 8% or more.

The results just described are found in experiments in which starting ages range from 25 days to over 200 days. (See Table 17.1 of Bennett, ~~1976~~ 7, for specific results with a variety of starting ages and experimental durations.) Thus these effects of differential experience can apparently be evoked at any part of the lifespan. In this respect they differ from the changes in the visual system caused by deprivation or distorted stimulation, since these visual alterations can be produced only during a sensitive period early in development. As we will see in Section IV B., effects of differential experience are also found in brain-lesioned rats, and these effects may be important in recovery of function.

B. Interpretation of Brain Weight Effects in Terms of Cellular Changes.

The occurrence of changes in weights of brain, and especially of cerebral cortex, as a function of exposure to different environments is interesting but more refined analyses are required if we are to progress toward the level of understanding cellular functions. Fortunately a number of further observations have been made, although more types are still required. It has been found by Greenough and collaborators that neurons show greater branching of dendrites in EC rats than in their IC littermates (~~Greenough, 1976~~ 43). This also is a regional effect, occurring with greater magnitude in the occipital cortex than in the other cortical regions measured. Globus et al. (~~1973~~ 41) found that the number of dendritic spines per unit of length of dendrite was significantly greater in EC than in IC rats. This effect was localized even within neurons, the difference in spine density on basal dendrites amounting to 9.7% ($P<.01$), on oblique dendrites, 3.6% ($P<.05$), and no effect occurring on apical dendrites. Along with

this increase in the dendritic tree, it was found that the cross-section of the neuronal cell bodies was significantly larger in EC than in littermate IC rats (~~Diamond, 1967~~ 21). Presumably the cell body must be more active metabolically to support a larger dendritic aborization, and such an increase in biosynthetic function was supported by the finding of greater amounts of RNA in cortex of EC rats, as compared with IC littermates (~~Bennett, 1976~~ 7). Hydén and Rönnbäck (~~1977~~ 54) have recently reported that the incorporation of valine into brain protein of frontal, entorhinal, cerebellar and visual cortex and the hypothalmus was much greater in rats raised in an enriched environment than in rats raised in a dark and restricted environment for 90 days beginning at 15 days of age. Enriched experience may also cause an increase in the number of glial cells to minister to the more active neurons; an increase in glial/neural counts has been reported in EC vs. IC rats (~~Diamond et al., 1966~~; Szeligo and ~~Leblond, 1977~~ 23, 103).

Putting this evidence together, we attribute the increase in cortical bulk with enriched experience mainly to the growth of neural ramifications. Presumably the interconnectedness of cortical neurons increases; this may reflect both greater redundancy (and thus greater effectiveness of some circuits) and also the establishment of novel circuits.

We should note that evidence of structural plasticity with differential experience is not limited to rats. It has also been found in laboratory mice and in gerbils (~~Rosenzweig & Bennett, 1969~~ 78) and in feral deermice. Unfortunately, little research of this sort has yet been done with subjects other than rodents. It would be highly desirable to extend this research to other orders of mammals, and especially to carnivores and primates. Not only would such work test the generality of the results obtained so far and indicate more clearly to what extent the conclusions might be

extrapolated to human beings, but research with larger and more precisely mapped brains would permit the use of more powerful and refined techniques than are available for rodent subjects. A collaborative project to study effects of differential experience on brains of monkeys has been initiated by two pyschologists, William T. Greenough of the University of Illinois and Gene P. Sackett of the University of Washington (~~Greenough and Juraska, in press~~ 45).

C. Regional Brain Changes Measured by Tomography?

Perhaps new radiological techniques, and particularly computerized axial tomography, can be applied to study changes in the conformation of specific brain regions during training. In computerized axial tomography, the head is exposed to X-rays at doses equivalent to those now used in routine diagnostic procedures, and the absorption information is fed into a computer which transforms the data into cross-section pictures of the brain and skull. As Galaburda et al. (~~1978~~ 35) have reviewed, structural asymmetries have been found between the two hemispheres in the human brain.. The best defined asymmetry in the gross configuration of the human cerebral cortex is that the planum temporale on the upper surface of the temporal lobe is significantly larger in the left hemisphere than in the right hemisphere of most subjects (~~Geschwind and Levitsky, 1968~~ 39). Galaburda et al. present a computerized axial tomogram of a human brain showing asymmetry of the planum temporale (~~1978~~ 35, fig. 3, page 855). It has been concluded that this asymmetry does not represent effects of experience since asymmetry in the same direction is present in the newborn infant and can be observed as early as week 31 of gestation. It is not clear, however, that the magnitude of the difference between hemispheres cannot be affected by experience. In the case of the brain of the rat, the cortex differs in thickness among various regions but the magnitude of these differences is affected by experience (~~Diamond, 1976~~ 22).

Hemispheric asymmetry is not limited to human beings; the great apes also show hemispheric asymmetry in the Sylvian fissure which marks the superior boundary of the temporal lobe. We would like to suggest that this powerful technique be applied to the chimpanzee and other apes that are now receiving unprecedented amounts of training in communication in several laboratories (e.g. the laboratory of the Gardners at the University of Nevada and the laboratory of Fouts at the University of Oklahoma). Chimpanzees in these laboratories are receiving training in the use of American sign language, and training often extends through several hours a day over a period of several years. The subjects of these experiments could receive tomographic examinations at the outset of their training and at regular intervals during training. It might be possible in this way to study the course of changes at several points during the program of training, especially if comparison could also be made with the cerebral development of non-trained controls.

A few months after we wrote the paragraphs above (and also Section VI.B.) suggesting possible uses of tomography to study brain plasticity, a paper was published that made our proposals seem less far-fetched than they originally might have appeared. Carlen et al. (~~1978~~ 12) found that computed tomography scans revealed cerebral atrophy in the brains of eight chronic alcoholics; the four who then abstained and showed functional improvement also showed partial reversal of the atrophy. The investigators suggested that the partial recovery may have been due to regrowth of axons and dendrites of neurons that were damaged but not killed by ethanol abuse. This study not only indicates the feasibility of such investigations but it also provides new evidence of plasticity of human brain in gross anatomical measures.

D. Hypotheses to Account for Cerebral Effects of Differential Experience

We originally began to use the differential environments as a way of

providing animals with differential opportunities to learn. This step was taken after we had found that giving rats formal training appeared to alter cortical acetylcholinesterase (AChE) activity (~~Rosenzweig et al., 1961~~ 87). We hoped to test this effect of training more clearly and to enhance the magnitude of the results by providing round-the-clock opportunities for self-paced learning over a period of several weeks. When we obtained differences in cortical AChE following exposure to enriched or impoverished laboratory environments, we were inclined to attribute them to differential learning. Nevertheless, in our first publications we tested alternative hypotheses and showed that neither the greater handling of the EC rats nor their greater amount of locomotor activity could account for the observed effects (Krech, ~~Rosenzweig & Bennett, 1960; Rosenzweig et al., 1961~~ 5 9 87).

During the last 18 years, many alternative hypotheses have been proposed, and quite a few have been tested. There is no need to discuss most of them at length here, because they have already been reviewed elsewhere (Greenough, ~~1976; Rosenzweig and Bennett, 1977, 1978~~ 43, 91, 92). Let us simply note some of the frequently mentioned alternatives that research has allowed us to reject. Thereafter we will note some recent evidence that provides further support for the hypothesis that the cerebral changes are consequences of learning and memory storage.

1. Tests of several hypotheses

a. Stress is frequently offered as an explanation for the cerebral effects--either "isolation stress" in IC or the stress of information overload in EC. Neither IC rats nor EC rats show enlargement of the adrenal glands in comparison with littermate SC rats, so it is unlikely that these rather mild treatments involve appreciable amounts of stress. Furthermore, imposition of overt stress daily for 30 days on IC or EC rats did affect weights but

did not alter EC vs. IC cerebral effects in measures of brain weights or AChE activity (Riege and Morimoto, 1970[73]). Therefore the cerebral effects of differential experience cannot be attributed to stress.

b. Hormonal mediation is probably not required for production of the cerebral effects. Not only do EC and IC rats not differ in adrenal weight/body weight or in thyroid weight/body weight, but hypophysectomy does not prevent the development of typical cerebral differences between rats in EC or IC (Rosenzweig, Bennett and Diamond, 1972[83]).

c. Speeded maturation in an enriched environment has been suggested as a possible cause of cerebral differences between rats in EC or IC environments. This might seem able to account for some of the characteristics of EC rats such as greater weight of cerebral cortex and greater branching of dendrites. But on other measures, EC rats resemble young animals more than do IC rats. Here are two examples: (1) The cortical/subcortical weight ratio declines with age, but it is higher in EC than in IC rats. (2) The RNA/DNA ratio declines after about 30 days in the rat, whereas EC causes an increase in this measure. Furthermore, we have shown that most of the EC-IC differences can be induced even when the differential treatment is initiated in adult animals, so speeded maturation is clearly not the cause of these effects.

d. Deprivation or distortion of sensory input has been demonstrated to alter aspects of perceptual functions, receptive fields of cortical neurons, and even cortical anatomy. We believe, however, that this does not provide a general model for neural events in learning or for effects of differential experience. Three criteria enable us to distinguish the effects of sensory deprivation or distortion from those of differential experience of the EC-IC sort: The effects of differential experience occur even in adults, they require direct interaction with stimuli, and severe deprivation or distortion

of stimulation is not required in the EC group. In contrast, the sensory effects occur only during a limited period of development, they have been reported to be produced by simple passive exposure to stimuli, and severe departures from normal stimulation are required to alter sensory development.

2. Effects of self-paced maze training on cerebral measures

In order to test directly whether specific training leads to anatomical and biochemical changes in the brain, we have recently conducted a series of experiments in which individual rats ran self-paced trials in mazes (Bennett et al., manuscript). The maze consisted of a plastic box inserted as a floor or story inside the larger cages that are used for the enriched condition; the box is as broad and as deep as the large cage and is 10 cm high. Food was available on the ground floor of the cage and water was available above the top of the plastic box. In order to get from food to water, the rat had to climb up into the plastic box (by a door open in one corner), traverse the box and exit above by a door in another corner. Each rat in this condition was moved from one cage to another each day, and it found a new pattern of maze barriers in the plastic box every day over a 30-day period. We called this condition "Individual in Complex Maze," (I-CM). Each I-CM rat had a littermate assigned to a standard EC group and another in the IC environment.

Results showed that the I-CM rats differed significantly from their IC littermates in brain weights and in brain RNA (N = 70 per condition). These I-CM vs IC effects were about half as large as the EC-IC differences obtained in the same experiments. The last several experiments (N = 26 per condition) included a stringent control condition to test whether the cerebral effects observed with I-CM might be due to the exercise of climbing into and out of the plastic box, the exposure to a series of large cages, etc. The control condition was exactly like I-CM except that the plastic box contained no barriers; this condition was therefore called "Individual in Empty

Box" (I-EB). In contrast to the effectiveness of the I-CM treatment, I-EB was almost completely ineffective in altering brain values. Thus these experiments demonstrate more clearly than heretofore that training causes significant modifications in brain measures.

IV. Recovery of Function

How may various kinds of neural plasticity contribute to recovery of function after damage to the nervous system? This question is too large for review in this chapter, so only a few points about the subject will be made here. For a good deal of information and varied discussion of this subject, see the following books: Plasticity and recovery of function in the nervous system, edited by Stein, Rosen and Butters (~~1974~~ 100), and Recovery from brain damage, edited by Finger (~~1978~~ 30).

Sperry (~~1945, 1971~~ 96, 99) has denied that adaptive changes occur in the nervous system following injury. He has stressed that in many cases the impairment caused by brain damage persists. Where behavioral improvement occurs, he has attributed this to the animal subject or the human patient using "tricks." That is, the individual learns to substitute some other movement or function to replace the still impaired one. It is somewhat surprising to see a contrast being made between behavioral and physiological mechanisms of recovery, as if all behavior did not have a physiological basis. If learning is used to overcome a behavioral deficit, does not learning have a physiological basis, and is not evidence accumulating that learning involves plastic changes in synaptic connections?

A. Recovery through Reconnection

In many cases recovery does occur through restoration of the original function and not through a "trick" or substitution of other behavior. For example, many cases of aphasia show excellent recovery although extensive

destruction of neurons has occurred. Polio patients have recovered manual dexterity even though postmortem examinations revealed destruction of many ventral horn cells. Animal subjects have demonstrated recovery of normally coordinated locomotion after various types of experimental lesions, including damage to motor cortex, spinal cord sensory or motor tracts, and cutting of several dorsal spinal roots.

The neural mechanisms of most of these examples of recovery of function are not yet known, but there is considerable evidence that recovery after experimental transection of some dorsal spinal roots is related to axonal sprouting from remaining roots. An early observation along this line was that of Liu and Chambers (~~1958~~ 61). They cut dorsal roots (e.g. T11-L6) unilaterally. After recovery of hind limb coordination, they examined the spinal cord anatomically to determine the spread of terminals from axons entering through an adjacent root (e.g. L7), both on the experimental side and on the normal control side. Much more extensive branching and spread of terminals was found on the affected side. Recent work relating such collateral sprouting to recovery of coordination has been done by Goldberger (42). Another mechanism that may aid such recovery is the release from inhibition of quiescent neurons or parts of neurons; evidence of such release will be presented and discussed below, pp. 29-31.

The mechanisms stated in the last paragraph may be of considerable importance in making possible recovery of function when most but not all of the fibers of a tract have been destroyed. Here are two examples of recovery that may be based on these mechanisms: Bach-y-Rita (~~1975~~ 6) has reported the excellent recovery over a period of about three years of a man who suffered a stoke at the age of 65, resulting in severe right-sided hemiplegia and aphasia. A post mortem examination seven years after the stroke revealed

that extensive damage had occurred in the lower left pons and medulla, destroying most of the corticospinal tract. "A few fibers remained intact and these may have formed the basis of the functional reorganization." The other example is from an unpublished case of Rasmussen, cited by Bach-y-Rita (~~1975~~ 6, pp. 211-212). This is the case of a man who became paraplegic following an automobile accident but who gradually regained complete function and was able to enlist in the U.S. Navy. He served three enlistment periods with no physical limitations and then died in a second automobile accident. Autopsy revealed that an apparently complete separation of the spinal cord at the level of T7 had resulted from the first accident; the gap was approximately 1 cm long. However microscopic study revealed approximately 150 axon cylinders embedded in the fibrous tissue separating the two portions of the spinal cord. Thus, it is likely that recovery was obtained by the functional reorganization of the input to the cell bodies of the 150 remaining fibers, as well as the possible redirection of the axon terminals.

B. Experience and Training Aid Recovery of Function

A growing volume of research with animal subjects indicates that varied experience and/or specific training can reduce the impairment of function caused by brain injury. In different experimental designs, the experience may be provided before the brain damage is inflicted, or it may be given between two stages of surgery in a serial-lesion study, or it may follow the lesion. Research in this area has been reviewed by Greenough, Fass and DeVoogd (~~1976~~ 44) and by Finger (~~1978~~ 31).

Since providing enriched experience following the lesion may offer a model for behavioral therapy and since such experience has been shown to produce some changes in brain measures, we will review this research briefly here. Schwartz (~~1964~~ 91) removed tissue from occipital cortex of neonatal rats and then raised them in either groups of 2-6 in a standard colony (SC) environment or in enriched-experience cages (EC) where they lived in groups of 4-8 and

had a variety of stimulus objects. At about 130 days of age, the rats were pretrained and then tested on the standard series of 12 mazes of the Hebb-Williams test. Both brain status (lesioned versus intact) and environment (SC versus EC) affected the scores significantly. Lesioned-EC rats performed as well as intact-SC rats; best of all were intact-EC, and worst were lesioned-SC. Thus, post-lesion enriched experience helped overcome effects of the brain lesion. Experiments in our laboratory have since replicated and extended this finding. We found beneficial effects of enriched experience not only after neonatal lesions (Will et al., 1976), but also when the damage was inflicted after weaning (Will et al., 1977) and even after 100 days of age (Will and Rosenzweig, 1976). Furthermore, the subjects included both male and female groups, and rats of two strains different from those of Schwartz were employed. Shorter periods of enrichment than those in Schwartz's experiment were found to yield positive effects; in one experiment, 2 hr/day of EC over a 60-day period was found to be as effective as 24 hr/day. Among the brain-injured as among the intact rats, EC led to an increase in cortical weight and in cortical RNA/DNA. Thus it is clear that even an impaired brain responds to experience, as shown by both behavioral and cerebral measures.

V. A Catalog of Plastic Changes in the Nervous System

In the earlier sections of this chapter, we have mentioned many ways in which neurons can change in response to demands and modifications of their environments. Here we will compile a partial catalog or roster of plastic capabilities in order to present them in one place, adding some findings not mentioned earlier. While we will focus on changes that are known to occur during adulthood in mammals, we will start with changes that are characteristic of early development, and we will also mention some kinds of plasticity that are best known in invertebrates. Changes in developing animals or in

invertebrates will be mentioned not simply for completeness but also because some processes that were once thought to be restricted to those forms have later been found to occur in adult mammals as well, and more similarities and generalities of plastic modifications among diverse animal forms will undoubtedly be discovered in the future. While most points in this catalog are well substantiated in research, a few are speculative.

A. Changes Characteristic of Early Development

Early in the development of the nervous system, the cells divide, and young daughter cells often appear to remain uncommitted for a period as between becoming neuroglia or neurons; neuroblasts may be able to differentiate into any of several specific types of neuron. It is sometimes said that neurons do not divide after birth in the mammal, but in the rat most of the cerebellar neurons are produced after birth and so are some forebrain neurons. After new neurons are formed, many of them migrate considerable distances to their final sites, often passing through layers of already established cells. Only after having reached their final locations, do the neurons begin to assume their characteristic and varied shapes, sending out an axon, pushing out branches and branchlets of the dendritic tree, and in some cases growing dendritic spines. Even in neurons that take up their stations prenatally, the processes of assuming the adult form often requires months of postnatal growth. During this period, the growth and formation of connections of neurons in many locations can be influenced by stimulation and activation and by competition with neighboring units, as we saw in the case of development of sensory systems. For a review of migration and differentiation of cortical neurons, see Rakic (~~1975~~ 71); concerning migration and differentiation in the cerebellum, see Altman (~~1977~~ 2).

B. Changes Occurring in the Adult Nervous System

Now, moving on the the adult organism, let us consider what kinds of plastic changes may occur in its nervous system that could subserve learning, memory, and progressive changes in behavior after disease or injury to the nervous system (i.e. both recovery of function and progressive deterioration). We will take these up in an order going from least to most: (a) Functional changes that involve no or only minor anatomical alterations in existing units. (b) Anatomical changes in parts of existing neurons--axon terminals, dendritic branching, and dendritic spines. (c) The possibility of migration and specification of immature neurons and even production of new neurons in the adult brain. (d) Finally, observed changes in glial cells as a function of experience should not be ignored, even though none of the hypothesized roles of glia in learning and memory has yet been established.

1. Plasticity requiring little or no anatomical change

a. Changes at existing synapses

Functional changes at existing synapses without any anatomical modification of synapse number or location would be sufficient to subserve many instances of learning; indeed, functional changes must suffice in the case of short-term memory where the memory can be retrieved within seconds after learning occurs and there is no time to accomplish anatomical changes. This is more or less like altering a circuit by turning switches on or off or by changing the setting of a variable resistor without altering the existing hardware. Changes in the functional properties of existing synapses during habituation to repeated stimuli have been studied in a number of preparations. In some cases the habituation persists well beyond short-term memory, lasting for hours or even days and suggesting that some long-term memories may be held in terms of chemical changes at existing synapses. For a review of research on functional changes in synapses of the much-studied invertebrate, Aplysia, see Kandel (~~1977~~ 5??).

For research on functional changes at synapses of the hippocampus of the rat during habituation, see Lynch and Wells (~~1978~~ 64) and Teyler and Alger (~~1978~~ 105).

A rather simple anatomical change at existing synapses has been suggested as a correlate of post-tetanic potentiation and possibly of other functional changes. This is the observation of swelling of dendritic spines in the fascia dentata of the hippocampus after tetanic stimulation of the afferent perforant fibers (~~Van Haareveld and Fifkova, 1975~~ 108).

b. Changes between active and quiescent states of neurons or parts of neurons

Somewhat akin to the notion of altering neural circuits by modulating the properties of existing synapses is the possibility that entire neurons or parts of neurons may be made to be either quiescent or active, depending upon circumstances (~~Wall, 1976~~ 111). Cass et al. (~~1973~~ 13) showed that two or three nerves run to the muscles in a salamander limb, each nerve occupying its own territory. These territories are not absolutely predetermined, since cutting one nerve leads to expansion of the territories of the other nerves. Furthermore, the timing of this expansion was highly revealing. Two or three days after the nerve was cut, some muscle innervation appeared as a marginal extension of the territories of adjacent nerve roots. A week or two later, the adjacent innervation spread considerably further into the denervated zone. Thirty days after the section of the nerve, it grew back into its original area, and the adjacent nerves were no longer able to command these muscle fibers. Then the nerve was cut for a second time and the muscle fibers were again paralyzed, not responding to stimulation of any nerve. Three days later, however, the whole of this denervated area responded to the adjacent nerves. The investigators suggested that the rapid spread of innervation that occurred 3 days after cutting a nerve, either the small

spread the first time or the extensive spread the subsequent time, resulted from the emergence into function of pre-existing but quiescent nerve terminals.

Evidence of quiescent terminals in the spinal cord of the cat was obtained by Wall (1976). He mapped the receptive fields of cells in dorsal column nuclei and selected some single cells that responded only to stimulation of the foot. Then the cord was blocked by cold in the lumbar 4 segment. Most of the cells being monitored simply lost their receptive field to peripheral stimuli but continued to show some ongoing activity. A few of the cells, however, now showed a receptive field to stimulation on the abdomen which had not been effective before. On removal of the cold block, these cells responded again to the foot but not to the abdomen. Thus some cells have alternative inputs--the afferents that operate under normal conditions and an alternative group that can become effective as soon as the normal input is silenced or removed.

Research in the visual system has also provided results that have been interpreted in terms of inhibition of connections from a visually deprived eye by those of the normally stimulated eye. In a young cat or monkey, occluding one eye for a period of a few weeks reduced substantially the percentage of striate cortical cells that responded to stimulation of that eye. Thus in kittens with lids of one eye sutured closed for their first 4-5 months, testing showed that only 0-10% of the cortical cells could be driven by stimulation of the deprived eye (Kratz et al., 1976). Although there is probably some anatomical loss of connections from the deprived eye, it is probably not as great as this functional evidence might suggest. Kratz et al. (1976) found that if the normally stimulated eye is removed while the anesthetized kitten is in the testing situation, the deprived eye is then able to drive 30-40% of the striate cortical units. This increase is present during the first 12 hr after enucleation; it was not possible to state exactly how promptly

the recovery occurs, because it required 20-30 min for the anesthesia to wear off, and finding units is a rather slow affair. There was no difference between the percentages found in the first 12 hr or thereafter, nor was the percentage increased if the recording was done only 3 or 12 months after enucleation.

Independent evidence that some connections from the deprived eye are functionally inhibited rather than being eliminated was obtained by a quite different technique in a study conducted by Duffy et al. (26 1976). Kittens in this experiment were monocularly deprived of vision by eyelid suture in their fourth week, and 8 months later single unit recordings were made in primary visual cortex. Of 33 cells evaluated in 5 kittens, all responded to stimulation of the normal eye but only one could be driven by stimulation of the amblyopic eye. Since several lines of evidence suggest that inhibition in the visual system of the cat is mediated by gamma-aminobutyric acid (GABA), the experimenters then tried to restore central responses to the deprived eye by administering a drug that blocks GABA-receptors. Within 30 seconds, 17 of the cells became responsive to the amblyopic eye and remained so for several minutes; a few more showed a delayed onset of responsiveness. During the brief duration of responsiveness, it appeared that the receptive fields for the amblyopic eye were closely similar to those found for the normal eye. These findings provide strong evidence that many connections from the deprived eye remain present and capable of normal function but are inhibited by connections from the stimulated eye.

2. Changes in axon terminals, dendrites, and synapses

Existing neurons in the adult mammal may form new synaptic connections under a number of circumstances, several of which have been mentioned in earlier sections. Many aspects of neurons have been demonstrated to undergo changes in the adult; these include axon terminals, dendritic branches and dendritic spines, and synaptic receptor areas. Let us note some examples

of each of these kinds of changes.

If one input to a region has its flux of messages sharply reduced or if the input tract is transected, then terminals of other inputs to that region may sprout and form new functional endings. We saw examples in the case of closure of one eye during the critical period in development and in the case of removal of one input tract to the hippocampus. It may not be necessary for one set of endings to degenerate in order for sprouting of a competing set to be induced. Cajal (~~1911~~ 11) noted that nerves often grow relatively long distances to reach their target organs but do not start to sprout collateral branches until they arrive at the target location. Furthermore, the sprouting results in rather uniform innervation, without either large open spaces or areas of heavy concentration. To account for this, Cajal hypothesized that the target tissue secretes substances that promote sprouting and that the collaterals release factors that neutralize these influences. Support for these hypotheses comes from the following recent finding: Applying colchicine to one hindlimb nerve of a salamander induced sprouting into its field by the adjacent nerves, even though the colchicine did not impair conduction of impulses but only interrupted axoplasmic transport (~~Aguilar et al., 1973; J. Diamond et al, 1976~~ 1, 20). Presumably the colchicine prevented transport and release of factors that neutralize promotion of sprouting, and the terminals of neighboring nerves therefore responded to the signals to sprout.

A number of different kinds of axonal growth may occur, including the following: (a) An existing terminal may form a second nearby synaptic contact with the same dendritic spines. (b) An existing axon may form additional end boutons that make contact with other dendritic spines--so-called terminal proliferation. (c) An axon may form new branches that travel for some distance

before making contact with new target cells--collateral sprouting. Lynch and Wells (64 ~~1978~~) concluded that the capacity of axons for such growth, unlike that of dendrites, becomes reduced with the onset of maturity. If this is true, then what would supply the input for the dendritic branches and dendritic spines that have been demonstrated to form in mature nervous systems? On the contrary, Lasek and Black (60 ~~1977~~) have concluded that axon terminals may always be ready to grow. They analyzed the axonal flow and turnover of axonal cytoskeletal proteins in guinea pig phrenic nerve and concluded as follows: "Our analyses of axonal transport suggest that the axon is continually supplied with the full complement of proteins necessary either for growth or for the formation of synaptic endings. The decision--to grow or not to grow--appears to depend upon cues in the axon's immediate environment and their effect on proteins which are always present in the axon" (p. 161).

Dendrites and dendritic spines have been demonstrated to respond to the stimulation of enriched experience and/or training. Thus, when rats receive post-weaning exposure to enriched versus impoverished environments, neurons in the occipital cortex show increased numbers of higher-order branches of dendrites (43 ~~Greenough, 1976~~) and increased numbers of spines per unit of length of dendrite, especially on basal dendrites (41 ~~Globus et al., 1973~~) In fish, isolation rearing was found to decrease the number of dendritic spines and to alter the proportion of the spine head to the shaft in the optic tectum (16 ~~Coss and Globus, 1978~~). There is reason to believe that enriched experience produces these neural effects at least in part because of the increased opportunity for learning that it affords (9; 43, pp. 267-8; 82 ~~Greenough, 1976, pp. 267-8; Rosenzweig and Bennett, 1978; Bennett et al., in press~~). Furthermore, some of these changes have been observed as a result of formal training. Thus Greenough (43 ~~1976~~, p. 270) has found that maze training produces similar increases in dendritic branching

to those found with enriched experience. Rutledge (1976) has reported on cats that were conditioned to associate shock to the foreleg (UCS) with electrical stimulation of the serprasylvian gyrus (CS). Stimulation of the cortex alone led to some changes in the form of terminal branches of apical dendrites and in their spine counts, and conditioning led to further changes. Rutledge has described several kinds of changes in apical dendrites and spines in these experiments (see his Fig. 22.6, 1976): (a) increased length of terminal portions of apical dendrites and also new spines appearing on new surfaces of vertical dendrites; (b) new small spines on new, thin, terminal twigs; (c) secondary spines that form near established spines; (d) new spines clearly separated from older ones, and (e) increased area of synaptic contact on established spines.

Increases in the length of postsynaptic thickenings (presumably the receptor area) have been shown in synapses in the occipital cortex in enriched-environment rats versus impoverished-experience littermates (West and Greenough, 1972; Diamond et al., 1975). Enriched experience also led to increased density of synaptic contacts in the hippocampus (Altschuler, 1976).

3. Possibility of differentiation and even of formation of new neurons in the adult.

In some species of fish, neurons proliferate even in the adult, but this is generally thought not to be possible in adult mammals. Yet there have been some recent suggestions that even in the adult mammalian nervous system, there may be a low level of production of new neurons and/or reservoirs of storage of undifferentiated neurons. Thus, Altman and Das (1964) hypothesized production of new neurons to account for increased length of the cerebral hemispheres of the rat as a consequence of enriched post-weaning experience. They suggested that these neurons were formed in the ependymal layer lining

the lateral ventricles. Wall (1976) has speculated that some small cells in many regions of the central nervous system (e.g. in the substantia gelatinosa) "may form a pool of undifferentiated nerve cells, arrested in their progress from the germinal epithelium in the embryo and free to continue their voyage if conditions permit in the adult" (p. 361). Whether such production of new neurons or differentiation of neurons actually occurs, and if so which conditions induce these events, remains for further research to determine.

4. Plasticity of glial cells

Although it is not clear that neurons can proliferate, differentiate, and migrate in the adult mammalian brain, there is no doubt that glial cells do so readily. Abnormal glial proliferation can result in brain tumors--gliomas. The finding that brain cholinesterase (ChE) activity increased even more than did acetylcholinesterase (AChE) with enriched experience (Bennett et al, 1964) led us to make counts of glia and of neurons in cortical tissue, since cholinesterase is found in glia but not in neurons. The cell counts showed a significant increase in the number of glia per unit of cortical volume in enriched-experience vs. impoverished-experience littermates (Diamond et al, 1966), and this has since been confirmed by other investigators (Szeligo and Leblond, 1977).

May these changes in glia be related in any direct way to mechanisms of learning and memory? Although there has long been speculation along these lines (e.g. Galambos, 1961; Hyden, 1973), no relation has yet been demonstrated. We have tended to suppose that the glial changes are consequent upon neural changes, since significant differences in ChE activity appeared only after about 8 weeks of differential experience, whereas differences in AChE activity were clearly present in 30 days or less (Rosenzweig, Bennett & Diamond, 1972). Perhaps larger neurons with more dendritic ramifications require more glial

cells to minister to them. On the other hand, Lynch and Wells (1978) showed that glial proliferation (on days 1-4 post-lesion) preceded neural sprouting (beginning on day 5 or 6) when one input to the hippocampus was removed. They suggested that the glial reaction may actually stimulate the axonal sprouting since it has been found in tissue cultures that glial cells can release material that stimulates the growth of neurons (Patterson, 1976; Varon and Saier, 1975). Since types of glia are diverse and the functions of glia are many and varied, it is quite possible that glial responses precede and promote neural responses in the case of brain damage but that neural reactions are the primary ones in the case of normal learning. The evidence is still so scanty, however, that more well-planned research will be needed before any valid conclusions can be reached about possible roles of glia in brain plasticity.

VI. Research on Neural Plasticity: Possibilities for Further Advances and for Applications

Our survey has shown many ways in which the nervous system changes, anatomically and biochemically, even in the adult mammal. And many circumstances evoke these changes, ranging from extreme treatments such as surgical intervention or sensory deprivation to mild and natural demands such as those involved in learning and memory. Since the plasticity of the nervous system presumably evolved to meet the requirements of behavioral adaptation and adjustment, it is not surprising that behavioral techniques can inflect and modify many aspects of the nervous system.

Of course our knowledge of the forms and extent of neural plasticity is still fragmentary. Although investigators at the end of the last century could already glimpse some aspects of anatomical plasticity of neurons, it is only since about the 1950's that techniques have been emerging that have allowed real progress to be made in this field. There is still much descriptive work to be done. And beyond this lies the testing of hypothesized

mechanisms and assessing the functional significance of different kinds of plasticity.

But we already have a platform from which to launch speculations, both to guide further research and to envisage possibilities of application of research findings to problems of individual and social behavior. If we could determine the factors that facilitate and that limit plastic changes in the nervous system, what are some of the conditions and problems to which we could hope to apply this knowledge? It seems to us that an imposing set of topics could be attacked in this way, including these examples: (a) Enhancing intellectual ability (b) on the other side of the coin, preventing or alleviating some kinds of mental retardation and some kinds of learning disabilities; (c) alleviating or retarding senile decline in intellectual abilities, and (d) promoting recovery of function after damage to the nervous system. We have already touched on some of these topics, but let us take up in more detail the first two on this list.

A. Enhancing intellectual ability

Both behavioral and physiological methods are being studied to promote full growth and development of the brain and of behavioral capacities. It is of course, a matter of debate to what extent behavioral capacity is related to cerebral development, so we might note some recent research and discussion of this question before going further. It has long been presumed by lay people that head size is related to intelligence, but empirical tests of this hypothesis have been few and far between. A recent review by Van Valen (~~1974~~ 169) reported correlations ranging from 0.08 to 0.22. Van Valen argued that when allowance is made for the fact that brain size is not directly measured by head circumference and for other problems of measurement, the true correlation between brain size and intelligence may be as high as 0.3. Jerison (~~1979~~ 56) criticized Van Valen's argument, but he presented new data

indicating correlations of about 0.1 between head size and intelligence in children, when the influence of stature was partialled out. (The raw correlations, without allowing for stature, were about 0.3). Thus a positive but low correlation between brain size and intelligence is probable, based on the available data on human subjects.

Several kinds of animal studies have been conducted in an attempt to test the hypothesized relation between brain size and intelligence. In some cases, mice have been selectively bred to produce high-brain weight (HBW) and low-brain weight (LBW) strains from the same foundation stock (Roderick, Wimer & Wimer, 1976; Fuller, 1979). The selection programs were successful--brain weight is a trait that shows considerable genetic determination. Some behavioral consequences of the selections were also found--the HBW strains tended to be more active than unselected or LBW strains, and the HBW mice were also superior on some but not all tests of learning. Within genetically heterogenous stocks of mice, brain weight has also been found to correlate positively with several measures of learning ability (Jensen, 1978). Part of the difficulty of this kind of research is that no single behavioral test yields an adequate measure of learning ability or intelligence. (In the case of brain chemistry also, different measures correlate with different behavioral tests, and it is difficult to make overall generalizations (Will, 1977)). Our own work has shown that enriched environment both increases cortical growth and leads to improved learning behavior. These cerebral and behavioral effects are parallel in a number of respects (Rosenzweig & Bennett, 1977), but correlation of course does not demonstrate causality.

Insert 38a

Zamenhof (1979) has attempted to produce large-brained individuals by various biological treatments. For example, allowing only one rat fetus to develop (whereas there are usually ten or more) causes all of the maternal resources to be devoted to the single fetus. Such a singleton is larger

Elsewhere we have speculated on possible reasons for evolution of resporsiveness of the nervous system, even in gross morphology, to environmental demands (77 ~~Rosenzweig [Hahn, Ed.], in press~~).

than normal, and it has more brain cells than the normal rat. Preliminary behavioral evidence indicates that such "super rats" are also better in behavioral tasks than are control animals of the same stock. Zamenhof has also observed that some rats with unusually large brains occur without any experimental intervention. He argues that the factors that limit brain size are largely unknown and that it should be possible to inhibit some of them to produce large-brained (and potentially more intelligent) individuals. Zamenhof hopes that research along these lines will eventually be applicable to human beings, but in the meantime behavioral methods are available, as we will discuss shortly.

Attempts have also been made to look for relations between brain size and intelligence across species of mammals. Some investigators have argued that such an effort is misguided, since different species have evolved for different specific behavior rather than for overall ability (see Glickman, 1977, for a discussion from this point of view). But others (e.g. Riddell, 1979) have claimed that tests of general cross-species intelligence are possible and that they correlate positively with various indices of the "excess neurons" that a species possesses above those needed for vegetative functions.

The fact that brain size can be affected by various biological factors does not mean that behavioral factors can be neglected. Dudek (1979) recently investigated whether the genetic constitution of high-brain weight strains of mice guaranteed maximum growth of brain regardless of environment and experience. He found that the brains of the HBW strains responded just as much to enriched or impoverished environments as did the brains of LBW strains. Furthermore, the selection for brain weight may actually have been made partly on a behavioral basis, according to recent work of

Hahn (1979). Hahn investigated the effects of cross-fostering mouse pups (i.e. assigning HBW pups to LBW mothers and LBW pups to HBW mothers) versus in-fostering (i.e. assigning pups to foster mothers of their own strain). Cross-fostering reduced substantially the differences in brain size, whereas in-fostered pups showed the characteristic brain weights of their strains. Thus there is a parental effect on brain weight in these strains. Whether it is due to behavioral differences (e.g. the HBW mothers have been observed to be more active with their pups than LBW mothers) or to other causes (e.g. the HBW mothers might have a better milk supply) is not yet known and will require further research to determine, but other work has already shown effects of differential preweaning experience on brain measures (Malkasian and Diamond, 1971; Rosenzweig et al., in preparation). Furthermore, much research with human infants has shown effects of environmental stimulation and complexity on behavioral and intellectual development (e.g. Yarrow et al., 1975; reviews by Hunt, 1976, 1979).

The fact that both environmental and genetic factors contribute to mental growth is also implicated in the work of Piaget and his colleagues on stages in intellectual development. A sequence of specific stages has been found, such that one stage (e.g. the stage of formal operations) cannot occur until the preceding one has been achieved (e.g. stage of concrete operations). Moreover, typical ages have been observed for the several stages, although results of all workers do not jibe completely concerning the exact ages or the fixity of the ages. A brighter child masters a stage more rapidly, but passes through the same sequence as a duller child. A rather controversial attempt has been made by Epstein (1974a & b; 1979) to link the Piagetian behavioral stages to alleged spurts in brain growth. According to Epstein, there are spurts in growth of brain and intellect

(called "phrenoblysis") at ages 2-4, 6-8, 10-12, and 14-16, with periods of slow growth in between. While the brighter child can accomplish each mental stage more quickly, according to this viewpoint he or she must wait for the next phase of cerebral growth before beginning the next stage of mental development. But even if the brain has matured to the point where it can sustain more complex mentation, this is unlikely to occur unless the environment is sufficiently rich and challenging to promote such development.

B. Preventing or Alleviating Mental Retardation and Learning Disabilities

Hunt (1976) has stated that there is mental retardation of social origin, occurring when the environment of a child does not provide sufficient stimulation to foster normal development. He has reviewed many studies whose results support this interpretation. Some of Hunt's own research has been done at an orphanage in Iran where children were considerably retarded in development of motor behavior and of speech. He was able to show that providing more interaction with caretakers led to significantly faster development. Different types of interaction affected different aspects of behavior. As Yarrow et al. (1975) reported from their work with infants, an environment is not generally enriching or impoverishing but rather there are specific kinds of experience that lead to development of one or another aspect of behavior. In Hunts's latest orphanage group, special attention to development of speech led to even faster progress than among U.S. children living at home. Thus, depending upon the number of children per adult and the instructions and training given to the caretakers (who were rural women with little formal education), the same orphanage, drawing upon the same population, could produce either retarded or advanced children.

It is possible that some specific intellectual deficits and learning disabilities may be related to inadequate growth and development of certain

regions of the brain. It is becoming possible to study relations between brain anatomy and behavior in living subjects by use of radiological techniques such as computerized axial tomography described above in Section III C (p. 18). Galaburda et al. (1978)[35] suggest that some deficiencies in language abilities may be related to the fact that the brain contains speech areas that are small in both hemispheres. They mention the case of a man diagnosed as having developmental dyslexia and whose father and brother also had similar difficulties. Preliminary study of the brain of this subject has indicated that the planum temporale on both sides is smaller than in normal brains. It has also been hypothesized that retarded development of speech and reading occurs when neither hemisphere has a clear dominance for these functions. Let us suppose that through further work of this sort certain characteristics of the gross anatomy of the brain can be correlated closely with difficulties in communication abilities. Suppose further that with the advance of radiological techniques, the necessary X-ray exposure can be reduced to completely non-harmful levels. It is possible then to imagine that in the future young children will be routinely examined for cerebral anatomical indications of developmental difficulties in language skills and other abilities. Remediation could then be started at early ages when it can be most effective rather than waiting for several years until frank disability is evident.

VII. Summary and Conclusions

Recent research has demonstrated that the nervous system is plastic not only in ways hypothesized decades ago but also in ways grasped only recently, and further discoveries of this sort are inevitable. Yet this is not the general and almost unlimited plasticity that many assumed during the first four decades of this century. Both the overall layout of the nervous system and many specific connections are determined by genetic

instructions. Thus, we now know far more about both plasticity and the limits of plasticity than was true a decade ago.

Many plastic changes in ramifications and connections of neurons have been demonstrated in response to severe or harmful treatments such as depriving young animals of normal sensory stimulation or transecting tracts in the brain. But such harsh treatments are not necessary to induce significant cerebral effects; mild experiences in differential environments and also formal training lead to measurable changes in the biochemistry and anatomy of the brain. Furthermore, many of these effects occur not only in young animals but also in adults. Several alternative hypotheses to account for the cerebral effects of differential experience have been ruled out by direct tests; thus the cerebral effects cannot be attributed to stress, to hormonal mediation, nor to speeded maturation, nor do they follow the model of effects of sensory deprivation or distortion. Recent experiments with improved controls show more clearly than heretofore that training causes significant modification in brain measures.

A catalog of plastic changes in the adult nervous system showed that many possibilities have now been demonstrated. These include the following: (a) Functional changes at existing synapses. (b) Changes between active and quiescent states of neurons or parts of neurons. (c) Anatomical changes in axon terminals, dendrites, dendritic spines, and synapses. (d) Proliferation of glial cells. Although it has been dogma that the production and differentiation of new neurons can occur only early in life, some authors have suggested that even these events can occur to a limited extent in the adult mammalian brain.

Although our knowledge of the forms, extent, and limitations of plasticity is still far from complete, we can envisage possible applications to many conditions and problems of individual and social importance. Among these

are the following: (a) Enhancing intellectual ability. (b) Preventing or alleviating some kinds of mental retardation and some kinds of learning disabilities. (c) Alleviating or delaying senile decline in intellectual abilities. (d) Promoting recovery of function after damage to the nervous system. Much can be accomplished along these lines by behavioral techniques, in some cases alone, and in other cases in conjunction with physiological techniques.

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