Changes in Nervous System With Age

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THE NERVOUS SYSTEM is unique and its basic cellular structure is very highly specialized and diversified. The individual nerve cells in one small circumscribed area or nucleus may be markedly different in structure, action, and reaction from those neurons that form an adjacent group. These neurons, even with their many unsolved problems, are far better known anatomically and physiologically than the greater bulk of the nervous system, their supportive structures. These structures, including the glia and the ground substance, are within the bounds of the existing frontiers of neuroanatomy and neurophysiology. So much of the normal picture of the nervous system is so scantily known that departures from the normal are at best determined with difficulty.

A host of neuroanatomical alterations in the nervous system accompanying the process of aging have been described. Many of these so-called manifestations of aging occur in the very young as well as in the old. Some of these, when they occur in the young are undoubtedly abnormal, whereas the frequency with which they occur in the old might cause them to be labeled as normal alterations accompanying aging. Aging should be looked upon primarily as a physiological stage and not a pathological condition. The normal alterations that bring about or occur with the gradual and continual advance from one plateau of life to another are apt to be quite subtle. They therefore are difficult to determine or locate accurately, and difficult to separate from abnormal changes brought about by modifications in internal or external environmental conditions as influenced by disease or trauma. The separation of these changes from artifacts or post-mortem changes, often uncontrollable in human material, cannot be overemphasized.

In human peripheral nerves it has been shown that there is an increase in connective tissue and a reduction in the patency of the blood vessels (*1*, *2*). This begins in the fourth decade of life as an endothelial proliferation and hyalinization of the vessels with an increase in the endoperineurium invading and apparently replacing areas of the nerve bundles by connective tissue elements. With this gradual reduction in blood supply and increase in connective tissue, there seems to be a gradual alteration and reduction of the nerve fibers, especially the larger ones. These findings parallel the measurements of the conduction velocity in human nerves (*3*) which indicate that, beginning in the fifth decade of life, there is a slight but continual decrease in conduction velocity. Again the responsibility may be placed on a decreased vascular supply due to a local ischemia and changes in permeability of the vessels accompanying metabolic depression.

The conduction velocity of peripheral nerves in the rat (*4*) markedly increases during development, with a leveling off at maturity. In contrast to findings of the human studies, little change in conduction velocity was noted in rats after maturity was reached.

Counts of fibers in the dorsal and ventral roots of the eighth and ninth thoracic levels, as

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well as cell counts of those dorsal root ganglia, taken from human cadaveric material (*5*, *6*), indicate a marked decrease in both number of myelinated fibers and cells after the fifth decade of life. However, in view of the rather wide range of variation within the relatively small groups of similar ages in these studies and the degree of overlap between groups, additional studies of this type are needed to substantiate the existing evidence.

Certainly, if in the normal course of aging, the metabolic activities of peripheral nerves are so disturbed as to produce a marked numerical decrease in the components, the effect on the normal course of the processes of degeneration and regeneration might be quite marked. One study of the effect of age on wallerian degeneration in the rat was carried out on fairly young animals (*7*). In this study it was demonstrated that in young animals there was a more rapid cellular proliferation and a less rapid loss of myelin than in older animals (160 days of age). Another report (*8*) demonstrates that in older animals more general and extensive signs of retrograde degeneration were present than in young animals, with a striking increase in the number of macrophages present in the sectioned dorsal roots of the older animals, but with a slower rate of removal of debris. This might be due to a lower metabolic rate, although it is not entirely in keeping with the findings of a comparable nerve fiber regrowth rate as evidenced by similar numbers of regenerating axons distal to the anastomosis. In the older animals, there was a diminution in the number of fibers successfully crossing the scar and in the rate of growth beyond. The proliferation of capillaries in the anastomosed roots of the senile rats was quite impressive.

Ganglial Degeneration

Cells of the dorsal root ganglia and the gasserian ganglion in the human, as well as in cats and rats (*9*, *10*), undergo a fatty degeneration which consists of a clumping of the Nissl substance, a subsequent destruction of the neurofibrillar reticulum, and a coalescence of the vacuoles. The cell becomes quite foamy and swollen and finally is destroyed, leaving behind only cellular debris. Although cell counts made on this material indicated no marked difference between young and old individuals, the numbers were relatively small, and statistical measures could not be applied to test the data. Atypical cells, such as the frayed cells of Cajal, fenestrated cells, cells with end bulbs, and so on, seemed to occur commonly in these ganglia at all ages.

Degenerate changes in occasional cells with a moderate degree of neuronophagia have been reported in human autonomic ganglia, with an increase of the interstitial tissue of the ganglia (*11*), as well as variations in the chromidial substance, shrinkage, hyalin degeneration, hydropic alterations, pigmentation, nuclear displacement, vacuolization, and partial or complete destruction of the cell (*12*). While in dogs, many of these variations seem to be related to aging, there was some question about the correlation in man. Even pigmentation was questionable since in man apparently many factors contribute to deposition of pigment.

A subsequent study of this pigment (*13*) found it to be a lipofuscin type closely related to ceroids and not to melanin. It seems to be one of three materials present in the nerve cells that are periodic-acid Schiff positive. The other two are glycogen, which is found in dogs of all ages, and a mucoprotein. Lipofuscin was not found in dogs less than 10 years of age, while in man it was present in varying amounts at all ages from 7 to 92 years. The mucoprotein is limited to nerve cells of the peripheral nervous system and is present to a greater degree in the autonomic cells. It is present in all nerve cells in a granular form in both senile and young dogs but is not concentrated enough in the young animals to be demonstrated by the periodic-acid Schiff method (*14*). Lipofuscin has a much wider distribution and seems to be more concentrated in the efferent nerve cells.

The pigment of the autonomic ganglion cell has been considered (*15*) to be, or to contain, a hormone or a similar substance which represents part of the neurosecretion of the nervous system. The origin of the pigment from the Golgi apparatus has been suggested.

The variability of the Nissl pattern and of the number of cells in the chain ganglia of similar size has been shown in the rat (*16*) and in the guinea pig (*17*). The series of animals used

in these studies did not, unfortunately, include senile forms, but the series from fetal to mature stages form bases for further investigation.

No data on the effect of age on the regenerative capacity of the fibers of the autonomic nervous system exists. It would be most interesting to follow this process in senile forms.

Central Nervous System Changes

Changes similar to those described in the ganglion cells are reported in the various areas of the central nervous system. In the spinal cord (*18*), the general histological structure begins to alter after 30 years of age, and by 60 years the changes are quite marked. Vascular alterations, gliosis, and demyelination, especially in the fasciculus gracilis, pigmentation of cells, and formation of corpora amylacea were among the findings. Pyknosis and chromatolysis in the cells of the ventral horn did not occur frequently and certainly were in no instance pronounced enough to be significant.

Pigmentation was such a constant finding in individuals in the fifth decade of life and older that it was felt that if pigment atrophy is considered an abnormality one could scarcely find a normal spinal cord after the age of 40 and, by the seventh and eighth decades, hardly a normal ganglion cell could be found. In some cells the change was so severe that the cell appeared as a pyknotic pigment spot. Corpora amylacea were not reported in spinal cords of persons less than 30 years of age; after the fourth decade it was a frequent occurrence, especially around the entrance of the dorsal roots.

Changes in the Brain

Several studies indicate that the gross weight of the brain decreases with age. One of these (*19*), a study on 2,060 brains of white males whose ages ranged from 12 to 96 years, reported that there was a gradual increase in the weight of the brain up to 30–34 years of age, and then a gradual, uniform decrease takes place. The maximum decrease occurring between the 3d and 10th decades of life was approximately 11 percent. Accurate determination of the weight of the brain is quite difficult. It has been pointed out (*20*) that simple severance of the brain, the treatment of the meninges, and the removal of the cerebrospinal fluid are rather variable factors (*20*). These sources of error can be minimized if one individual removes and handles the brains; otherwise, those variables must be considered in analyzing samples.

The brain size has been said to fluctuate inversely with economic level (*21*). Since most of the brains obtained in routine autopsy in hospitals come from persons of the lower social strata, they may not be too representative of a cross section of the total population.

The reported decrease in brain weight does not seem to be due entirely to a difference in water content. There are studies that report a definite decrease in water content in the brain throughout the entire life span (*22*, *23*). This decrease varies somewhat with different species since there seems to be a remarkable correlation between physical and mental development at the time of birth and subsequent water loss. One report on senile human brains differs from the others in that it states that there is an increase in the water content in senile brains (*24*). There seems, however, to be universal agreement on the higher water content of the cortex and the lower water content of the medulla, which has suggested that the phyletically newer parts of the brain are wetter.

Phyletically different brain areas also seem to show differences in the cholinesterase activity (*25*). In rabbits, the medulla reached its maximum activity at 15 days and then fell 50 percent by 2½ months of age. The activity remained fairly stable after that time. In the frontal cortex and caudate nucleus, the maximum activity was reached at 18 months and then held steady. However, no general conclusions as to the correlation of the cholinesterase activity have as yet been made with senility.

Young and adult rats differ in that the adult brain contains more fat and phosphorus. In extreme age there are small decreases in fat, acid soluble phosphorus, and potassium, with an increase in sodium (*23*).

The cerebral physiology of the human has been studied by the nitrous oxide method to show that there is a close correlation between advancing age and decreasing blood flow with a concomitant decrease in oxygen consumption (*26*, *27*). This decrease in oxygen availability

and consumption may be closely related to neuronal activity. There seems to be almost universal agreement that, with increase in age, there is a marked decrease in the number of neuronal elements in the brain. However, most of the observations and cell counts upon which this conclusion is based have been made on relatively small series of human brains, even on a single specimen and with known mental deterioration frequently clouding the issue. Counts on large series of experimental animals are likewise scarce.

A recent report shows a decrease in the number of cortical neurons with increasing age, especially in the superior temporal gyrus and the lower quarter of the precentral gyrus (*28*). Unfortunately, this study is based on a very small sampling of a remarkably variable population. Variability is immediately apparent when one examines the raw data presented by the various investigators.

Only by the use of large samples, which in studies of this kind are most difficult to procure and study, can this source of error be overcome. It is indeed reasonable to believe that, in a cell which has lost its ability to reproduce and which functions more or less constantly over the years, physiological and anatomical deterioration can readily occur either as a perfectly normal process or as a consequence of some external or internal environmental disturbance. Therefore, not only is the mass of evidence—even though still circumstantial and not entirely conclusive—in favor of the decrease in cell numbers with age, but it seems logical to expect it. I merely point out here that there is still a great need for quantitative studies on the brains of humans and experimental animals, quantitative studies that consider variables and try to control them. Proof for one species cannot necessarily be had from studies on another, since it appears more and more that there is a marked difference in the aging of the nervous system in different species.

Purkinje Cells

The population of the Purkinje cells is reported to suffer severely with advancing age. In a description of the Purkinje cells of a 92-year-old man, it was stated the cells "appear considerably shrunken, both nucleus and protoplasm, though not more so than normal daily fatigue" (*29*). This individual was in a coma and endured 6 days of inanition prior to death. The Purkinje cells were reported to be 25 percent fewer than in the cerebellum of a 47-year-old man. In another study of the cerebellums from 63 humans of both sexes, aged 12–92 years, 43 cerebellums were eliminated from consideration because they "showed the greatest losses," and "cell losses are frequently due to disease" (*30*).

Similar decreases in Purkinje cells in the dog, the macaque (*31*), and the rat (*32*) are reported. Reducing the rat to the equivalent age of man, it was concluded that destruction of the cells or the processes leading to destruction take place 30 times as fast in the rat as in man.

A loss as high as 40 percent in the Purkinje cells of guinea pigs has been reported (*33*). However, this figure is based on the number of cells in the newborn as 100 percent, and it is important to note that the highest percentage loss—66.7 percent—occurred in one animal of 193 days of age (*34*). In one area of the cerebellum, 7 animals out of the 10 younger than the oldest (1,800 days) of this series showed more loss of Purkinje cells than did the oldest animal.

In my own series of guinea pigs, whose ages range from 139 to 2,765 days, I have been unable to measure quantitatively any loss of the Purkinje cells. On the contrary, the population seems to be quite stable, and certainly there are no discernible areas in which cells have degenerated and have been removed.

Pigmentation

Almost every conceivable cytological alteration has been described and associated with age changes (*33*). These alterations are not restricted to any one part of the brain but seem to occur everywhere. Of these, "the most constant element indicating aging in nerve cells is lipofuscin, the lipochrome pigment. It rarely appears in younger subjects, but does appear beyond a certain age. . . . while we can get lipofuscin in some pathologic conditions, the truth is that we can get a great deal of

this material in elderly persons. . . . this is the most important element shown in the cell and that other elements, such as variation in the neurofibrils, Golgi apparatus and, in some cases, the Nissl bodies will have a secondary place" (*35*).

The accumulation of pigment occurs at different time intervals in different regions. Certain nuclei are prone to early pigmentation; others fail to show pigment even in advanced age. It has been suggested that constantly activated cells are less prone to pigmentation, while those that undergo periods of rest or inactivity are more likely to become pigmented during the aging process (*36–38*). In this connection, it is interesting to note that the accumulation of pigment in the nerve cells, as well as some of the other changes with age, are more marked in the human species than in other mammals (*33*).

The Glia

The role of the glia in aging is undoubtedly a very important one, although, except for the phenomenon of satellitosis, with the concomitant process of neuronophagia, little is known about these structures. Studies of satellitosis and neuronophagia of the cortical cells of the human (*39*) and of the horse (*40*) report definite, increasing occurrence with advancing age. In the rat and mouse, satellitosis was not nearly so marked (*41a*). This process also occurs in the brains of young animals and humans, where it may be even more frequent than in the very old individuals (*41a*). No marked qualitative change in glial cell types participating in this process has been reported (*41b*).

Ante-Mortem and Post-Mortem Changes

In the human and in the experimental animal, it is at times extremely difficult to separate the changes which can occur in the cells of the brain before and after death. Post mortem artifacts are real stumbling blocks in neurohistological studies and should not be underestimated. I personally do not contend that nerve cells do not show signs of degeneration, die, and are removed by phagocytosis or lysis. However, I do feel that we must proceed as cautiously as possible in our interpretations of what is normal and what is abnormal in the aging brain.

C. Vogt and O. Vogt (*36*) point out that the time course and morphologic features of aging are different in each of the hundreds of different cell types, and that "the aging process or 'involution' of a cell is different from any regressive process of 'degeneration' it may undergo, but degenerative processes may, of course, occur in combination with an involution. . . . The aging process always leads to the death of the cell. If it occurs at an average (normal) time, it causes partial death of the brain through normal death of the cell type in question. If a person lives sufficiently long, partial death of the vital cells of the medulla causes his or her death, as a normal phenomenon. This form of death is a rare occurrence, because death through disease usually terminates the individual life at an earlier stage." These authors suggest that the aging process may produce counter-reactions, such as hypertigrosis produced by the increased activity of the nucleolus, or hyperchromatosis and pyknosis of the nucleus which has hitherto been wrongly interpreted as a degeneration. This reaction as a defensive or compensatory change on the part of the individual nerve cells may include division of the nucleoli and the nuclei of the cells as well (*33*).

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