Functional Implications of Changes in the Senescent Brain: A Review

CHARLES H. M. BECK

SUMMARY: *The morphological, chemical, and physiological changes in the brain accompanying old age are reviewed. The deterioration of the striatal and hypothalamic dopaminergic systems were implicated in the onset of age related Parkinsonian-like slowing of performance and altered affect. Cholinergic hippocampal and neocortical systems were chemically and physiologically abnormal in the aged. The implications for slowed cognitive processing and persistance of the memory trace are presented.*

RÉSUMÉ: *L'auteur passe en revue les changements morphologiques, physiologiques, et chimiques qui accompagnent la vieilesse. La détérioration des systèmes dopaminergiques stries et hypothalamiques est associée chez les vieillards aux phénomènes de ralentissement de performance du type Parkinsonien, et aux emotions modifiée. Les systèmes cholinergiques de l'hippocampe et du néocortex manifestent aussi chez les vieillards des anormalités physiologiques et chimiques. L'auteur discute les implications de ces changements pour la domaine des processus cognitifs et pour la persistence des traces de mémoire.*

Dementia refers to a progressive loss of the mental faculties. The most common cause of a progressive impairment of the mental faculties in the older adult population is the degenerative brain disease known as senile dementia. If the disease begins before the age of 65 years it is referred to as presenile dementia or Alzheimer's disease. Presenile and senile dementia are diseases of nervous tissue as opposed to atherosclerotic dementia which is a degenerative disease of the circulatory system. Together these two categories account for the majority of all cases of degenerative brain disease in the aged. The incidence of senile dementia is twice as high in women as in men. The proportions are reversed for atherosclerotic dementia (Roth, reported by Kent, 1977).

The mental symptoms of senile dementia, from the clinician's viewpoint, include flattening of affect, confusion in spatial and temporal orientation, impairment of memory especially for recent events, and a general slowing of movements and though processes. The onset is gradual, beginning with a dislike for change, a reduction in ambition and activity, an increased difficulty in comprehension and an increase in time and effort necessary for performance of familiar duties. Presenile dementia is viewed as an acceleration of this process of mental deterioration (Kolb, 1968).

The first section of this paper describes the physically visable, i.e., morphological changes, that can be seen in aging brain. Although the discussion will be restricted to the literature on normally aging individuals and people with presenile and senile dementia, it is noteworthy that a higher than normal incidence of the same physical signs have been observed in Down's syndrome retardates (Ohara, 1972) and Parkinson patients (Hirano, 1970). Down's syndrome retardates develop the symptoms by age 35 years. In addition to reviewing the physical signs of dementia, the first section of the paper will discuss the functional implications of these signs.

The second portion of the paper describes the chemical and physiological correlates of the aging process and outlines their functional implications. In the third and final section there is a detailed analysis of the behavioral scientist's perspective of aging.

MORPHOLOGICAL SIGNS OF AGING IN THE BRAIN

Physical evidence for a diagnosis of presenile dementia includes the presence in the brain of (1) senile plaques containing amyloid, an immunoglobulin byproduct; (2) tangles of neurofibrils, normally longitudinally arranged in the nerve fiber and thought to participate in the

Reprint requests to: Charles Beck, Department of Psychology, Biological Sciences Building, University of Alberta, Edmonton, Alberta, T6G 2E9, Canada.

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From the Neuropsychology Unit, Department of Psychology, University of Alberta, Edmonton, Alberta.

transport of vital substances along neurons; (3) areas of degeneration, consisting of silver staining granules surrounded by spaces or vacuoles; (4) collections of lipofuscin or age pigment inside neurons, representing an accumulation of oxidized nerve cell membranes; and (5) loss of nerve cells.

It is widely held that the pervasiveness of these signs is positively correlated with the degree of dementia both for patients stricken before age 65 and for those afflicted later in life (Blessed et al., 1968). However, it is not generally recognized that virtually all people by 80 years of age present similar, though less invidious, examples of the same physical pathology (Dayan, 1970; Gellerstedt, 1931; Matsuyama et al., 1966). There is a positive correlation between age related cell loss, severity of tangle formation, and degree of granulovacuolar degeneration in both normals and dements. However, the yearly rate of cell loss is five times as great in the Alzheimer patients as in normal persons (Ball, 1977; Ball and Lo, 1977).

Brody (1955) hypothesized that the degree of dementia is directly related to the incidence of cell loss. Meier-Ruge (1975) suggested that this hypothesis is untenable because subsequent studies of senescent rodent brains have revealed less than 1% cell losses (Brizzee et al., 1968; Klein and Michel, 1977). However, these studies examined only the rodent neocortex. Studies of the old rodent's medial dorsal nucleus of the thalamus (Stein and Firl, 1976) and hippocampus (Vijayan, 1977) showed serious degeneration. In humans the physical signs enumerated above appear in many parts of the brain including the neocortex. However, the pathology has a predilection for the hippocampus and in Alzheimer's disease for the posterior hippocampus in particular (Ball, 1977; Brizee et al., 1974; Gellerstedt, 1931). The magnitude of the hippocampal cell loss by 70 years of age is fairly substantial. There is approximately 12% cell loss in normals and 60% in presenile dements (Ball, 1977). Damage to the medial dorsal thalamus and hippocampus has been related to memory impairments in humans (Milner, 1970; Victor et al, 1971). The memory deficits of the demented and aged have been attributed to hippocampal damage (Ball, 1977; Malamud, 1972). Other authors (Brizzee et al., 1974; Scheibel et al., 1975, 1976) prefer to emphasize the importance of the diffuseness of the signs of physical damage throughout the brain, in accounting for general slowing of information processing accompanying aging.

Prior to the disintegration of the nerve cell body there is an age related deterioration of axonal (output) and dendritic (input) terminal processes (Bondareff and Geinisman, 1976; Machado-Salas et al., 1977; Scheibel et al., 1975, 1976).

In summary, morphological changes in the brain with age provide a picture of gradual degeneration and cell loss, especially in structures involved in memory. The normal aging process is accelerated in Alzheimer's disease and Down's syndrome. Theories of aging emphasize either the relation between hippocampal degeneration and memory deficits or that between diffuse degeneration and slowed processing. The functional implications of neurofilbrillary tangles and cell membrane instability will be detailed in the next section of the paper.

CHEMICAL AND PHYSIOLOGICAL SIGNS OF AGING IN THE BRAIN

The most prominent theory of aging is the error catastrophe theory of Orgel (1963; Comfort, 1974). In all tissue, the RNA transcription of the genetic code for protein has an increased error rate with age, resulting in the age related decline in levels of critical enzymes. Thus there is an age associated decline in uptake, turnover, and utilization of amino acids and a decline in RNA biosynthesis of enzymes (Tonna and Singh, 1976). In general, biochemical anabolic functions deteriorate through the loss of enzymes controlling carbohydrate, intermediate protein, and lipid metabolism (Roberts et al., 1976). With age, a decrease occurs in glucose oxidation (Patch, 1977) and in formation and utilization of ATP, an energy source (Ermini et al., 1971; Sun and Samorajski, 1975). This results in a reduction in oxygen turnover (Chen et al., 1972). One would predict from this a reduced cerebral blood flow with age and with increasing dementia and this is indeed the case (Lassen et al., 1960; Ingvar and Lassen, 1970; Simard, 1971). Slowing of cerebral blood flow occurs over the temporal region in the brains of memory impaired senile patients, and in the parieto-occipito-temporal region in patients with aphasia symptoms (Hagberg and Ingvar, 1976; Obrist et al., 1970). Since old people have a greater arteriovenous O_2 content difference, indicating the brain is extracting more O_2 per unit of blood (Dastur et al., 1963), and since the cerebral capillary network of the senescent brain is more extensive than that of the younger person (Huziker et al., 1978), the diminished cerebral blood flow is more likely a product of metabolic than morphological variables.

In presenile and senile dementia, but not in atherosclerotic dementia, the occurrence of neurofibrillary tangles is proportional to the accumulation of aluminum in the brain cells (Crapper et al., 1976). The concentration of aluminum in Alzheimer patients is four times that in normal patients (Crapper, 1974; Crapper et al., 1973). Implantation of aluminum into the brains of animals results in neurofibrillary tangles indentical to those in senile humans' brains (Terry and Pena, 1965). Aluminum disrupts protein synthesis in nerve cells (Miller and Levine, 1974). The origin of the metabolic error causing the aluminum accumulation is unknown.

Another anabolic process which deteriorates with aging is that of the synthesis, release, and uptake of neurotransmitters. Old brains experience 25% slower rate and 50% reduced volume of axonal transport of substances essential for transmitter production (Geinisman et al., 1977a, 1977b), a shortage of the enzymes necessary for transmitter synthesis (McGreer et al., 1977; Spillane et al., 1977; Vijayan, 1977), an impairment of waste reducing uptake of unused neurotransmitter (Jonec and Finch, 1975; Sun, 1976), fewer transmitter receptor binding sites (White et al.,

1977), reduced number of neurotransmitter storage vesicles (Sun, 1976), and lowered sensitivity of the chemical response of the receiving neuron to delivered neurotransmitter (Govoni et al., 1977, Spano et al., 1975).

Conversely, products which degrade or catabolize neurotransmitters increase with aging. Acid phosphatases, perioxidases, monamine oxidase, and catechol-o-methyl transferase all increase in the old brain (Broch, 1973; Brunk and Ericcson, 1972; Robinson et al., 1977). The latter two molecules degrade the catecholamine transmitters, dopamine and norepinephrine.

If the neurotransmitter changes referred to above affected systems controlling behaviors which deteriorated with age, then it is apparent that the behavioral deficits of the aged would be ascribable to metabolic dysfunction rather than frank cell loss as the primal causal agent. The evidence for this view is growing. The aging brain undergoes a significant decline in the functional effectiveness of the dopamine system in the striatum (Finch, 1973; Govoni et al., 1977; McGeer et al., 1977; Robinson et al., 1977). There is also a decrease in the number of cells in the substantia nigra with age (McGeer et al., 1977). Behaviorally, this would mean that the normal aging process would move people toward the Parkinsonian ratio of excess acetycholine to dopamine in the critical system linking the substantia nigra and the striatum (McGreer et al., 1977). Thus one would expect slowness of movement, rapid fatiguing, tardy movement initiation, loss of associated movements, and diminished kinetic grace, characteristic of Parkinson patients, to become more obvious with advancing age. Evidence that the same dopaminergic deficit may be responsible for a flattening of affect and a loss of incentive motivation is available (Phillips and Fibiger, 1973).

The ergot alkaloids, e.g., dihydroergotoxine, which stabilize the terminal membranes of dopaminergic neurons (Goldstein et al., 1978; Spano and Trabucchi, 1978) protect the organism against the metabolic effects of reduced blood flow (Boismare et al., 1978; Gygax et al., 1978) and alleviate the complaints of the aged (Bazo, 1973; Hoffbrand et al., 1976). No one has described the effects of the ergot alkaloids on the physical signs of cerebral senescence.

Dopamine is released by certain nerve terminals in the retina in response to light (Kramer, 1971). In aged mammals the cells receiving the dopamine become hypersensitive to released dopamine (Spano et al., 1975) in an attempt to compensate for functional dopaminergic dennervation (Govoni et al., 1977). It is possible that such paradoxical hypersensitivity may contribute to the longer dark adaptation time (Reading, 1968) and the increased aggravation from light glare (Wolf, 1960) experienced by old people. Usually the effects are attributed to increased opacity of the lens and cornea.

Calcium ion concentrations increase in muscle (Gutmann and Hanzlikova, 1972) and nervous tissue with aging (Sun and Seaman, 1977). This may be related to abnormally low levels of parathyroid hormone in the senescent (Fujita et al., 1976). Calcium plays an important role in neurotransmitter release. The redressing of the Ca^{++} imbalance has been suggested as the mechanism underlying the efficacy of chronic chlorpromazine therapy in reducing neuronal lipofuscin accumulation (Samorajski and Rolsten, 1976). Chlorpromazine has multiple effects on release and uptake of dopamine and norepinephrine.

Chemical blocking of pathways requiring the neurotransmitter acetylcholine impairs performance on memory tests. The deficits were similar to those observed in normal old persons (Drachman and Leavitt, 1974). Many neurons terminating in the hippocampus release acetylcholine. There is a significant age related decline in the hippocampal concentration of the enzyme necessary for acetylcholine synthesis (Perry et al., 1977; Vijayan, 1977). This decline is even more marked in Alzheimer patients, but not in chronic schizophrenics, chronic unipolar depressives, or multi-infarct dements. It is significant in degree not only in the hippocampus but also in the frontal, parietal, temporal, and occipital cortices of Alzheimer patients (Perry et al., 1977). Normal old people do not experience significant declines in acetylcholine enzyme levels outside the hippocampus (Perry et al., 1977). The dysfunction in Alzheimer patients is presynaptic, i.e., in acetylcholine synthesis, rather than an impairment in postsynaptic receptor site sensitivity (Perry et al., 1977; Spillane et al., 1977; White et al., 1977). Such abnormality is consistent with electron microscopic evidence of gross degenerative changes in presynaptic structures and the normal appearance of receptor membranes (Wisniewski and Terry, 1976). The greater the depletion of the cholinergic enzyme, the greater the degree of neurofibrillary tangles evident (White et al., 1977). Geinisman et al. (1977a, 1977b) suspect that the tangles may be partly responsible for the reduced availability of the enzyme at presynaptic membranes.

In response to stress, the medulla of the adrenal gland liberates a number of neurotransmitter substances into the blood stream. The urinary and blood plasma levels of epinephrine, norephinephrine, and dopamine beta-hydroxylase increase with age (Freedman et al., 1972; Giorgino et al., 1969; Kvetnansky et al., 1978) as does the size of adrenal medulla (Kvetnansky et al., 1978; Sotgiu et al., 1960). Hyperfunction of the adrenal medulla in the aged coupled with their exaggerated sensitivity to its hormones (Frolkis et al., 1972) may be related to increased incidence of hypertension, atherosclerosis, and cardiac infarction in old people (Kvetnansky et al., 1978).

The hippocampus is capable of inhibiting the secretion of adrenocorticotrophic hormone from the anterior pituitary. This hormone controls secretions of other hormones, e.g., corticosterioids, from the cortex of the adrenal gland. Neurons of the hippocampus have receptor sites for one of the corticosteriods, namely corticosterone. Corticosterone modulates the genetic processes governing anzyme synthesis in the hippocampus (Lee et al., 1977). These enzymes are necessary for neurotransmitter production and, as noted above, are

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depleted in old age (Perry et al., 1977). There is a positive correlation between the degree of hippocampal neuron degeneration in the individual and the resting levels of corticosterone in the blood plasma (Landfield and Lynch, 1977). Resting plasma corticosterone level decreases in old age. Continued degeneration of the hippocampus with senescence may result from increased sensitivity to the circulating hormones (Frolkis et al., 1972). It would be interesting to measure corticosterone levels and sensitivity in Alzheimer patients.

In summary, the senescent brain experiences dysfunctional biases toward the Parkinsonian state of striatal dopamine depletion and consequent slowing of movement as well as toward mnemonic impairment precipitated by hypofunction of the hippocampal and cortical cholingergic systems. A common age related deterioration of the genetically controlled transcription of protein may underly both trends.

RELATED BEHAVIORAL SIGNS OF AGING

Whether intelligence as defined by the traditional intelligence test does decline with age (Birren and Morrison, 1961; Williams, 1970) or does not (Barton et al., 1975; Ford and Roth, 1977; Schaie et al., 1973) appears to depend on methodological issues which are not central to theme of this review. Two main categories of subtests in these and more recent batteries (Branconnier and Cole, 1978; Shader et al., 1974) appear to be age sensitive. These are speeded subtests and the memory subtests.

The memory deficit of the aged is *not* specific for any particular mnemonic subfunction such as memory storage capacity (Eber, 1976; cf. Salthouse, 1978); level of memory processing (Eysenck, 1974; Zelinski et al., 1978; cf. Mergler et al., 1977); ignoring irrelevant stimuli (Rabbitt, 1965; cf. Klauser and Kleim, 1978); registration as opposed to retrieval (Adamowicz, 1976), or on long versus short delays of recall (Schneider et al., 1975). Rather, the deficit seems to be a general slowing of information processing (Adamowicz, 1976). This suggests that the speeded and memory categories of subtests are measuring the same thing. For example, memory tests would produce "speed" deficits if the pace of stimulus presentation and response production is too rapid for the old person. When taken to identical original learning criteria, young and old are no different on subsequent recall (Hulicka, 1965). When allowed to pace themselves, the elderly took longer to learn the task than did young persons but did just as well as the young on recall tests (Adamowicz, 1976). Total learning time available rather than rate of presentation is the critical variable (Winn and Elias, 1977).

If the slowed processing were a general characteristic, one would expect an increased deficit with the amount of information processed on verbal tasks (Anders and Fozard, 1973; Klauser and Klein, 1978) and on nonverbal tasks (Benton, 1977; Fozard et al., 1976); slowed retrieval search of both primary and secondary memory (Anders and Fozard, 1973), and slowed rotation and comparison of spatial depth figures (Gaylord and Marsh, 1975). The studies cited have demonstrated these effects with the normal aged.

Partitioning of the total response time into reaction time and movement time revealed that both were slow in the aged and that the reaction time was responsible for the greatest part of the deficit (Spirduso, 1975). Retarded movement time was attributable to slower peripheral nerve conduction velocity (Retzlaff and Fontaine, 1965), loss of muscle fiber mass (Gutmann and Hanzlikova, 1976), decreased frequency of miniature end-plate potentials and slowed contraction coupling time (Gutmann and Hanzlikova, 1972).

Several mechanisms may contribute to the slowed reaction time. Raised sensory thresholds (Clark and Mehl, 1971; Dyck et al., 1972, 1974; Harkins and Chapman, 1976; Kokmen et al., 1978; Whanger and Wang, 1974) and slowed conduction time of brain neurons would at best contribute 10% to the total retardation of the reaction time (Retzlaff and Fontaine, 1965). A more significant factor would be the hypofunction of the dopaminergic system discussed above. McGeer's (1977) hypothesis was that the dopaminergic bias in the aged is toward that of the Parkinsonian neuropathology. Parkinson patients exhibit not only slowed movement times but also slowed pre-electromyographic reaction times (Brumlick and Boshes, 1966). Parkinson patients persist in an error response for a longer duration on tracking tasks than do normal individuals (Angel et al., 1970; Bowen et al., 1972). The degree to which simple stimuli persist in memory, as measured by the critical flicker fusion test, increases with increasing severity of Parkinson movement dysfunction (Riklan et al., 1970). Personality inflexibility as measured by the F-Scale increases in the same manner (Ploski et al., 1966). Comparable examples of stimulus trace persistance and response mode persistance for the aged will be described below.

Another mechanism that may contribute to slowed processing is dysfunction of the hippocampal cholinergic system. Damage to the hippocampus causes the organism to fail to adjust to changing reinforcement contingencies and to fail to habituate to novel stimuli (Kimble, 1968). The organism tends to persist in performing current or habitual modes of responding. It is possible that the slowness of the aged is partly the result of a tendency to prolong the response to internally or externally generated stimuli (Axelrod, 1963; Botwinick, 1973). If the subsidence of the neural response to the initial stimulus is slow, the perception of the second stimulus would be retarded and slowed processing of information would result. If this were the case one would look for evidence in the aged of the persistance of brief images at the registration level and for the perseveration of sets at the cognitive level.

Exaggerated persistance of the iconic trace has recently been demonstrated to result in superior performance in the recognition of fragmented words in the aged compared to the young (Kline and Orme-Rogers, 1978). Complementary halves of a single word were flashed on

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a screen one after the other. If the persistance of the trace of the initial word half in the mind of the viewer was superimposed on the flash of the second half of the word, recognition of the word would result. Old people were especially superior for the longer intervals between word fragments. In addition, old persons show enhanced persistance of complementary after-images (Kline and Nestor, 1977), and, as one might expect, poor temporal resolution of shocks to the skin (Axelrod et al., 1968), slowed temporal processing of auditory stimuli (Corso, 1975), lowered visual critical flicker fusion thresholds (Misiak, 1951; McFarland et al., 1958), lowered auditory click fusion thresholds (Weiss, 1959), protracted susceptibility to backward masking (Kline and Szafran, 1975), and longer lasting visual evoked responses to photic stimulation (Mundy-Castle, 1953). It is easy to see how such persistance, if also applicable to items retrieved from primary of secondary memory, would slow down retrieval search time (Anders and Fozard, 1973).

When one speaks of secondary and permanent memory one usually speaks of perseveration of sets rather than persistance of traces. Old people perseverate in viewing ambiguous figures in only one mode (Botwinick et al., 1959), persist in viewing the Necker cube in only one view (Heath and Orbach, 1963), and fail to reverse the figure ground relationship in order to read ambiguous words (Kline et al., 1977). Tasks requiring a shifting of problem solving set are expecially taxing for the aged (Botwinick et al., 1957, 1958, 1959; Goodrick, 1972; Heglin, 1956). Old people have anecdotally described the persistance with which unwanted tunes and thoughts run through their minds.

What can be done to postpone the development of senility? As previously noted the ergot alkaloids and phenothiazines may offer some hope. At the present time the largest contribution to longevity variance in the healthy rat is the factor controlled by diet (Ooka et al., 1978; Ross and Lustbader, 1976; Segall et al., 1978). There is some evidence that training may modulate cognitive deficits in the elderly (Birkhill and Schaie, 1975; Hoyer et al., 1973; Plemons et al., 1978). Physical exercise seems definitely to influence physiological performance (Retzlaff and Fontaine, 1965; de Vries, 1971) and reaction time (Spirduso, 1975; Spirduso and Clifford, 1978). The last study is especially provocative since exercising men in their sixties performed with reaction times comparable to men in their twenties. One would like to know what would be the iconic trace persistance times and retrieval search times of those active oldsters.

In conclusion, evidence has been presented for an age dependent slowing of information processing. Such an impairment may relate to persistance of sensory traces and perseveration of cognitive sets. Persistance would be an advantage only in tasks in which retention of a single item or mode of response was required. Serial search or serial learning tasks would produce deficits in performance, unless there was adequate time for shifts between items.

Evidence has been presented that dysfunction in dopaminergic and cholinergic brain systems may underly these persistance effects. Avenues for future research suggest themselves. Persistance measures have not been applied to the other types of human abiotrophies (Bowen et al., 1976) or their animal models (Crapper, 1974; Ungerstedt, 1971). One disturbing possibility is that schizophrenia which supposedly has a dopaminergic bias opposite in direction to that of Parkinsonism is also said to be characterized by slow information processing (Davidson and Neale, 1974; Saccuzzo et al., 1974; Yates, 1966; Yates and Korboot, 1970) and trace persistance (Gruzelier et al., 1972). It would be helpful to know whether the persistence measures in the aged are changed by exercise or drug therapy. The hypothesis that persistance and perseveration beget cognitive slowing needs to be examined. Are the three tightly correlated or can they be dissociated? Possibly it will be found that persistance and perseveration always result in slowing of information processing, but that slowing may occur as a result of other causes, for example excessive caution (Birkhill and Schaie, 1975).

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