CHAPTER *4*

An Arc Across the Lifespan: From the Beginning

Virtually all biological systems normally undergo functional changes with aging, and the brain is no exception. We can think of age-related changes in brain function as being on the trajectory of an arc that begins decades earlier during fetal development. At any age, distinguishing normal variations in brain function from pathological conditions is sometimes challenging and can be especially difficult in later years. Individual differences in the timing, nature, and extent of functional decline are common. Social perceptions can also influence how we interpret obvious abnormalities in brain function. Neurologist Peter J. Whitehouse notes, "Our concepts of Alzheimer's disease moved from a social model before the turn of the 19th century to a focus on biology in the early 1900s, to a return to psychosocial aspects in mid-century, and then again to the current biological focus at the end of the 20th century."[1]

Age-related changes in brain function must also be considered within the context of more general biological and social health. Aging inevitably includes changes in the physiologic functions of most systems of the body. Ultimately, of course, aging leads to loss of resilience and increased vulnerability to disease, finally resulting in functional losses that are incompatible with life, and death follows.

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Physiologic Changes Associated with Normal Aging

Fetuses, infants, and children acquire functional capacities at various times during development. For example, different metabolic systems come on line throughout fetal development and infancy. Lung function is not fully developed until young adulthood. Reproductive functional development begins in the fetus and infant, undergoes a period of latency, and is reawakened in puberty.

Toward the other end of the arc, as people age genetic and other kinds of chromosomal damage increase while cellular repair

壽 Chinese symbol for longevity

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responses decrease. Renal blood flow and kidney function decline. Motility of portions of the intestinal tract decreases, as does gastric acid secretion. Combined with decreased intake of nutrients in the elderly, these changes may result in malnutrition.[2]

Some liver enzymes responsible for metabolizing pharmaceuticals and other foreign chemicals or environmental contaminants are reduced in the elderly.[3] Consequently, the toxicity of chemical agents can be enhanced or, on occasion, reduced if metabolic activation by enzymes is necessary to form a more toxic substance. Levels of many hormones decline with age, sometimes dramatically as during menopause. The function of the blood-brain barrier also declines with age, allowing blood-borne toxicants to acquire previously restricted access to brain tissue.[4] Thus, as the brain ages it may also become more vulnerable to environmental factors that contribute to further degeneration.

It is also important to consider the influences of genetics and a lifetime of social and environmental influences in order to understand the timing and severity of functional declines and vulnerabilities in later life.

The Natural History of Brain Development and Aging

Brain Development

Brain development begins soon after conception and continues into young adulthood. In the fetus, cells in the brain proliferate, migrate to their appropriate positions, and differentiate into various specialized cell types. Complex networks of neurons are connected through synapses, many of which are normally pruned in early childhood. Many nerve fibers are coated with a sheath of fat-containing myelin that facilitates nerve transmission. Myelination in

the fetal brain begins during the later stages of pregnancy and continues throughout childhood and the teen age years.

During the first few years of life, children develop motor skills (rolling over, standing, walking) and begin to understand and express language. Later they begin to regulate attention and emotional expression; improve motor coordination, visual processing, and visual-spatial skills; and develop more complex information processing.

With the onset of puberty the brain undergoes further transformation under the influence of sex hormones. New axons and dendrites elaborate from neurons. New neural connections develop while others are pruned back. Further myelination results in a net increase in the ratio of white-to-gray matter.[5] These changes ultimately contribute to further development of abstract thinking, organizational and planning skills, and the ability to store and retrieve information and make decisions in early adulthood.

Factors that converge to affect this trajectory of skill acquisition include genetic inheritance; maternal nutrition during pregnancy and nutrition throughout infancy, childhood, and early adulthood; the quality of the social environment; education; and the presence or absence of exposures to toxic agents, infections, illnesses, or injuries that can interfere with normal brain development.

A considerable amount of plasticity (the ability to physically and functionally change and adapt) is inherent in the brain, ensuring some capacity to cope with or buffer challenges to normal development. But that plasticity is also limited and studies show that damage resulting from exposure to neurodevelopmental toxicants, such as lead, sometimes in combination with micronutrient deficiencies and compromised social circumstances, can only partially be alleviated.[6] [7] Consequently, early life events or circumstances can have enduring impacts on adult cognitive abilities and behavior.[8]

The capacity of the brain to change and adapt is not confined to periods of early development. Learning and memory throughout life are based primarily on the strengthening of synaptic function or structural changes that occur in response to experience.[9] Neuroscientists have shown that the adult brain is even capable of generating new neurons from primitive stem cells in some areas, overturning long-held dogma that this was impossible.[10] Compensatory mechanisms can counteract age-related declines in brain function.[11] These observations are important when considering strategies for delaying the onset or slowing cognitive decline in later years. We will return to this later.

Healthy Brain Aging

As healthy people age, declines in cognitive function and other evidence of neurological degeneration become increasingly likely. This occurs in virtually everyone although some people experience altered brain function at an earlier age or at a faster rate than others. The reasons for this variability are not always well understood, but in addition to genetic susceptibility factors such as hypertension, poor nutrition, excessive alcohol ingestion, lack of exercise, and stress can increase the rate and extent of cognitive decline.[12] Hormonal changes during normal aging are also likely to play a role.
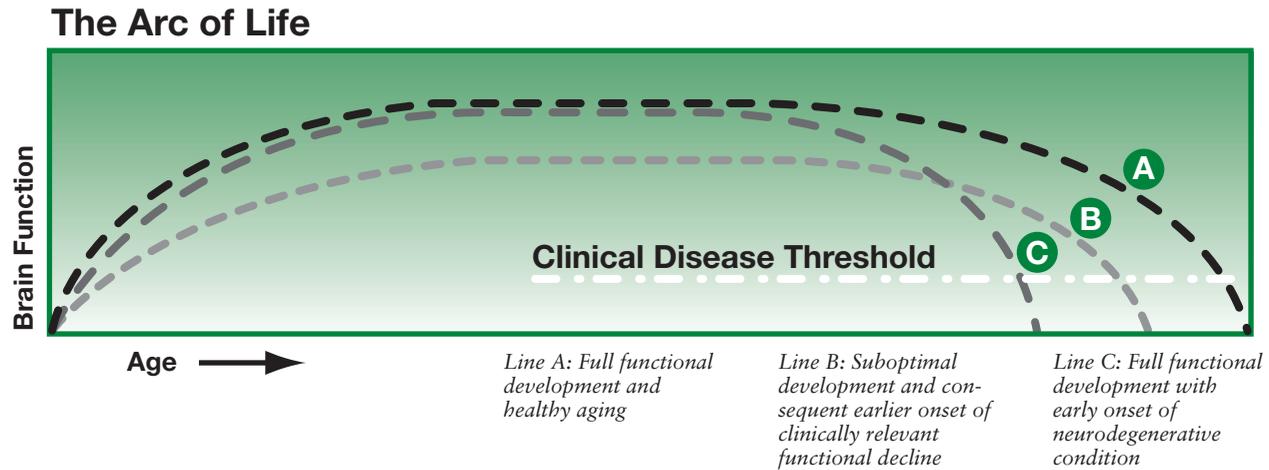
Distinguishing the cognitive decline of normal aging from that due to various pathological processes, including Alzheimer's disease, is an ongoing challenge. Memory impairment in tasks that rely on attention and controlled processing of information is common with normal aging.[13] [14] In particular, memory necessary for the acquisition and processing of new information, as well as memory necessary for holding information during processing, tend to decline with age.[15] Some kinds of learning, particularly those that require speed and motor coordination, become increasingly difficult with age.[16] These impairments are associated with volume loss and depletion of certain neurotransmitters in the frontal region of the brain. The number of synapses and synaptic function in some areas of the brain also diminish with advancing age.[17] [18] Receptors for the neurotransmitter glutamate decrease in synaptic junctions, contributing to decline in synapse function.[19] Levels of neurotransmitters, including dopamine and acetylcholine, also decline in several areas of the brain.[20]

It would be a mistake, however, to conclude that normal brain aging inevitably results in inalterable, steadily declining function. Recent studies in animals and humans show that retained plasticity enables aging brains to acquire or reacquire motor and cognitive skills. The mechanisms and brain circuitry involved, however, may be quite different from those used for skill acquisition during brain development.[21] [22]

The Arc of Life

Brain Function

Clinical Disease Threshold

A

B

C

Age ➝

Line A: Full functional development and healthy aging

Line B: Suboptimal development and consequent earlier onset of clinically relevant functional decline

Line C: Full functional development with early onset of neurodegenerative condition

In summary, we can think of an arc of brain development and function that begins soon after conception and progresses along a trajectory into adulthood and older age. The shape of that trajectory—its features, length, and rate of change—can be profoundly influenced by many interacting genetic and environmental factors encountered throughout the lifespan.

Early Life Events and the Developmental Basis of Adult Neurodegenerative Disease

Brain Reserve

Neuroscientists generally acknowledge the likelihood that, in many people, neurodegenerative conditions—whether the normal cognitive impairment of aging, relentlessly progressive Alzheimer's disease, or Parkinson's disease—may be initiated decades before symptoms become apparent.[23] However, the timing of the onset and progression of symptoms may be influenced by brain "reserve"—delayed in people with more reserve and accelerated in those with less. This means the onset of symptoms due to a neurodegenerative condition could conceivably be delayed either by slowing down the pathological process or by increasing brain reserve.

The idea of brain reserve took hold in the 1980s after an autopsy study of nursing home residents with and without dementia.[24] It showed that the brains of some elderly people without signs of dementia before death had abundant plaques and tangles, hallmarks of Alzheimer's disease, but without the typical loss of neurons and brain volume. This suggested either that they had somehow

Epigenetics

Epigenetics refers to modifications to genes, other than changes in the DNA sequence, that influence gene expression. These modifications can include adding molecules, such as methyl groups, to the DNA backbone of a gene or altering histones, which are proteins associated with the gene. RNA interference with gene expression is a third mechanism. The end result of epigenetic changes is alteration of the pattern of protein synthesis under the control of the involved gene. Recent evidence suggests that some epigenetic changes are heritable from one generation to the next, showing how environmental factors that alter gene expression in an individual can also influence gene expression in his or her descendant generations.

escaped the neuronal loss seen in most cases of Alzheimer's disease or that they began with a larger initial reserve of neurons.

Additional studies have confirmed that some individuals have dementia without extensive pathological findings, while others have extensive pathology without much cognitive impairment. In a recent effort to understand these discrepancies, 81 patients with the diagnosis of Alzheimer's disease and no other recognizable reasons for their cognitive decline were carefully evaluated in order to quantify the extent of their dementia.[25] Following their deaths, the researchers examined their brains for pathological changes. They concluded that there was a fairly close correlation between the numbers of plaques and tangles in brain tissue and the degree of dementia in people who had early-onset Alzheimer's disease, but the correlation became less prominent in older people. These findings are consistent with the hypothesis that the manifestations of Alzheimer's disease in older people are more likely to be influenced by multiple interacting factors such as vascular disease and reduced blood flow, social isolation, undernutrition, and so on. Whether or not early-onset and late-onset Alzheimer's are fundamentally different in other ways is not known. But a variety of factors, including nutrition, experience, education, and social support, have been proposed as contributing to brain reserve and building resilience to disease or age-related declines in function.

The Barker Hypothesis and Early Origins of Adult Disease

The related concepts of early origins of adult disease and building resilience to reduce disease risk have strong support in other areas

of clinical medicine. In the 1980s, David Barker and colleagues from the UK published an influential study of a large cohort of individuals in which they noted that low-birthweight babies were at increased risk of heart disease as adults, even when other known risk factors were taken into account.[26] Barker theorized that somehow growth restriction in utero set the stage for subsequent adult heart disease. These findings spurred considerable interest in the concept of the fetal (or developmental) origins of adult disease. Most attention has been given to the impacts of fetal, infant, and childhood nutrition on subsequent risks of cancer, diabetes, obesity, and cardiovascular dis-ease. It remains unclear whether birthweight or subsequent "catch-up" growth is the important risk determinant for heart disease. Nonethe-less, a growing body of evidence now points to the important influence of early life events on subsequent disease risk.

More recently, a limited but growing body of evidence is beginning to point to developmental origins of neurodegenerative conditions, including Alzheimer's disease and Parkinson's disease.[27] [28] [29] The brain reserve hypothesis proposes that early life exposures to environmental chem-icals, inadequate nutrition, or other environmental stressors, alone or in combination, can reduce the number of neurons, alter levels of neurotransmitters, or reduce synaptic density in critical areas of the brain. Clinical symptoms of neurological disease then emerge much later in life when these abnormal changes combine with normal declines in cell numbers and function.[30] [31]

The developmental origins of adult disease can also be medi-ated through epigenetic mechanisms in which gene expression is altered by environmental variables without any mutational change in the DNA sequence (see sidebar previous page.).

Modified gene expression alters the production of proteins under control of that gene. In brain tissue, where neurons have an extremely long lifespan, life-long effects from gene expression altered

Widespread changes in modern, industrial society… created the conditions for an explosion of neurodegenerative diseases in the aging population.

during development are entirely plausible. Animal studies show that early life exposure to lead, for example, can strongly influence the expression of a gene responsible for producing a protein involved in Alzheimer's disease much later in life[32] (see chapter 7). The same level of lead exposure in the adult animal does not have the same effect on gene expression.

Other conditions that may develop early or at any time throughout the lifespan and that increase the risk of developing Alzheimer's disease or other kinds of dementia include hyperinsulinemia, insulin resistance, diabetes, obesity, and others that feature up-regulation of inflammatory markers.[33] [34] The science underlying this cluster of relationships is discussed in chapter 6 and should raise a warning flag among public health officials and decision-makers at every level—from school boards to city planners to Congress. As we have noted, health-trend tracking in the U.S. and many other countries consistently shows increases in the prevalence of diabetes, obesity, and a variety of other chronic diseases characterized at least in part by inflammation. Widespread changes in modern, industrial society largely responsible for the changing pattern of disease have also created the conditions for an explosion of neurodegenerative diseases in the aging population. We have only begun to get a glimpse of what is to come if we do not act on what we already know. As we discuss in more detail in chapter 9, these patterns of disease clearly suggest opportunities for their primary prevention.

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FOOD *for* THOUGHT

Still Healthy at 100 – What's the Secret?

IT MAY BE NO SECRET at all, but good genes combined with the old-fashioned values of eating well and in moderation, hard work, community spirit, and faith foster the health of the longest-lived among us.

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The centenarians of the Japanese prefecture of Okinawa are among the healthiest elders in the world. The Okinawa Centenarian Study, the world's longest-running population-based study of centenarians and now in its 29th year, has revealed a broad range of lifestyle characteristics that are likely contributing to amazing health well into later years. (They really are that old; ages were validated recently.[1]) The study has concentrated on genetics, diet, exercise habits, and psychospiritual beliefs and practices.

The Okinawans typically are optimistic, adaptable, and easy-going. They value spirituality and social engagement. They consume a diet rich in vegetables, fiber, flavonoids, and good fats, including omega-3s. These centenarians have been lean throughout their long lives, eating a low-calorie, low-glycemic-load diet. They limit food intake in a cultural practice known as *hara hachi bu,* literally "stomach 80 percent full," and keep physically active via a variety of daily activities. Compared to North Americans, they have lower rates of dementia, certain cancers such as breast and prostate, osteoporosis, and cardiovascular disease.[2]

Many of these lifestyle characteristics have been found in other, less studied populations. The Blue Zones project has been taking scientists around the world for the past five years to investigate where people live the healthiest long lives. Among Blue Zone inhabitants are a group of elders on the Nicoyan peninsula of Costa Rica who chop wood, ride bicycles, and

grind corn by hand, and mountain people in Sardinia, Italy, whose secrets include "wine with staggering levels of antioxidants and a tradition of celebrating old age."

The Blue Zone researchers have identified common denominators for healthy aging that are consistent with many of the findings from the Okinawa study. They include:

- regular physical movement incorporated into everyday activities,

- good community and family relationships,

- eating well (and less) and drinking wine each day, and

- a sense of purpose in life as well as a centered and calm outlook.

The practices of the Costa Rican elders reflect these—they eat fewer calories, enjoy physical work in daily chores, maintain social networks, and have a strong sense of purpose.[3] [4]

The New England Centenarian Study at Boston Medical Center also points to certain activities and characteristics. Its "Predictors of Reaching 100" list notes that few centenarians are obese and that substantial smoking history is rare. A preliminary study suggests that centenarians are better able to handle stress than the majority of people.

Good genes do help. The New England study found that at least half of centenarians have parents, siblings, or grandparents who have also achieved very old age.[5]

Endnotes

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