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Guest Editorial

Living Better Longer Through Technology

Not long ago, I saw a science fiction film with the premise that genetic, medical, and computer technology had excelled to the point that within a matter of seconds, any ordinary citizen could submit a minute skin or hair sample for DNA analysis, which would yield his or her future lifetime medical history within rather certain probabilities. In this future society, I could learn that my newborn grandson would have an 83% probability of a severe myocardial infarction by age 62 and that if he survived it, he had a 91% chance that his Alzheimer's disease (AD) would progress to the moderate level by age 78.

Is this future science fiction or merely a fictional rendition of future science? Today's geneticists are hurriedly working to map the 80,000 or so human genes. Modern linkage analysis allows us to rapidly hone in on hot spots of any complex disease of choice and search for candidate genes. Genes on four different chromosomes have been discovered for AD. An Italian group has already found a gene for an early-onset form of Parkinson's disease in rare families.

This progress has important implications for our aging society. Psychogeriatricians are well aware of the Age Revolution. Thanks in large part to advances in medical technology, the developed countries of the world are "graying," a trend that will continue into the 21st century. For example, in the United States, people age 65 years or older now constitute nearly 13% of the population, a proportion that will grow to 20% by the year 2025 with the maturation of the baby boomers, the 76 million Americans born between 1946 and 1964. We are living longer, but are we living better?

Age-related diseases diminish quality of life for far too many. Heart disease, stroke, AD, Parkinson's disease, and diabetes are just some of the common illnesses that keep older people from living active, healthy, and long lives. For many of these diseases, the beginnings are quite subtle. Those "senior pauses" that plague all older persons are initially difficult to differentiate from the more malignant impairments in delayed recall that herald early AD. As the disease progresses, patients and family members suffer considerably as the patient's quality of life and functional capacity plummet until some often welcomed intercurrent illness, like pneumonia, "the old man's friend," finally hastens the patient's demise. Most of us would choose to go quickly rather than to suffer for many years. I've heard geriatricians jokingly quip that they would prefer to live disease-free until age 90 and then die suddenly from the bullet of a jealous lover.

These complex, age-related diseases have strong genetic components, and there is mounting evidence that the film fantasy of predicting future disease may not be so far off. Recent observations also imply that some diseases that begin late in life may actually show subtle manifestations years earlier. Perhaps the best example is AD. When our group (Small et al., 1995b) combined measures of brain function using positron emission tomography (PET) and genetic risk (apolipoprotein E-4 [APOE-4]), we found that people in their mid-50s with mild memory complaints had significantly lower function in brain regions known to be affected by the disease if they also had the genetic risk for the disease. Moreover, such parietal metabolic patterns appeared to predict future cognitive decline in people with age-related memory complaints (Small et al., 1995a). Reiman's group (1996) confirmed these genetic risk and PET studies and extended them to additional brain regions affected by the disease, including posterior cingulate, temporal, and prefrontal regions.

Evidence of preclinical disease comes from several approaches, however, not just from measures of brain function. When structural images of the hippocampus and other medial temporal regions are carefully defined and quantified, early atrophy is yet another predictor of future cognitive decline (de Leon et al., 1993).

Evidence of preclinical neuritic plaques and neurofibrillary tangles, the neuropathological hallmarks of AD, makes the argument for very early and subtle preclinical changes even more compelling. Morris and associates (1996) studied cerebral amyloid deposition in 21 healthy elderly subjects who had been followed longitudinally. Seventy-eight percent of the subjects with high neocortical plaque density had mild cognitive impairment (a condition that has a high probability of converting to AD within several years), whereas the 12 subjects with few or no plaques had no cognitive impairment. The work of Braak and Braak (1991) suggests that neurofibrillary tangle density begins to increase in some persons, presumably those who will eventually develop AD, early in adult life, perhaps even by the third decade.

Findings from the Nun Study support this idea. Snowdon and colleagues (1996) assessed the early autobiographies (mean age = 22 years) and the later (age 75 to 95) cognitive performances of 93 nuns. They found that low idea density and grammatical complexity in early life were associated with low cognitive test scores in later life. All 14 sisters who died with definite AD had low idea density in early life. Thus an age-related, gradually progressive disease with strong genetic components may subtly begin decades before the patient manifests obvious symptoms. Is our future bleak, then? Do our genes tell the whole story? Do many of us already suffer from age-related diseases and have no recourse?

Our genes may well be expressing subtle phenotypic changes early in life, but they don't tell the whole story and the future is by no means bleak. Discovering genetic causes and susceptibilities is likely to lead to clarification of underlying disease mechanisms and discovery of interventions that will alter pathogenesis. Early intervention may then delay disease onset and perhaps even prevent some age-related diseases. Studies of AD in twins corroborate the genetic contribution to the disease (Small et al., 1993). The concordance rate for monozygotic twins approximates 50%,

whereas dizygotic twins are more likely to be discordant for the disease. However, these studies also confirm an environmental component, otherwise the concordance rate would approach 100%. Epidemiological studies point to several possible risk factors such as head trauma, as well as possible protective factors, including nonsteroidal anti-inflammatory drugs and estrogen. Future antidementia interventions may offer more than just symptomatic effects. If a treatment or combination of treatments is found to truly modify disease course, then the prospect of early intervention offers the hope of delaying disease onset. Interventions that diminish our environmental exposures and risks and enhance environmental protections may well complement approaches that interfere with genetically determined disease mechanisms.

I look forward to the day when medical, genetic, and computer technology will provide my grandson with his "DNA health probability forecast" because I am confident that the printout will also include his "health probability prevention program." With the prediction of 91% probability of AD by age 72 will come a recommendation of 2,000 IU of daily vitamin E and a new selective estrogen receptor modulator to be started at age 25. His mother will enthusiastically embrace the recommendation that he give up his plan to become a professional boxer. If only our future technology could somehow eradicate handguns so he could avoid the gunshot wound from the jealous lover when he reaches age 90.

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