BOOK REVIEW

Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease

by Rudolph E. Tanzi and Ann B. Parson
Perseus Publishing, 2000. 281 pages.

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The general public tends to view scientists as cold-hearted fact seekers whose single-track minds aim for fame and fortune at any cost. Hollywood portrayals of the "mad scientist" contribute to this stereotype, as do media accounts of events such as the recent unsubstantiated claims of human cloning. The impenetrability (from the general public's perspective) of technical reports in scientific journals erects a barrier to understanding and trust that is hard to penetrate. In their 2000 book *Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease*, Rudy Tanzi and Ann Parson successfully break down many barriers by making the culture, practice, and output of human genetics research accessible to the general reader.

Tanzi is Professor of Neurology at Harvard Medical School and Director of the Genetics and Aging Unit at Massachusetts General Hospital. He heads one of the many laboratories whose members have made seminal contributions to our understanding of the molecular mechanisms of Alzheimer's disease. Ann Parson is a science journalist who has taught at Boston University. Their book is in part a memoir of Tanzi's scientific career and in part a history of scientific progress in the genetics of Alzheimer's disease, with Tanzi's accomplishments placed within the context of the findings of other researchers.

I assigned this book in my upper level seminar in Human Genetics. The class focused on a different genetic disorder each week, relying on original research papers to learn about gene cloning strategies, molecular mechanisms underlying disease, animal models, and treatments. Alzheimer's disease was our topic for the ninth week of the course; students read two chapters a week of *Decoding Darkness* (with written summaries turned in, in addition to their regular assignments) during the preceding weeks. The students thoroughly enjoyed the book. It provided fodder for discussion on many issues relating to life as a scientist, and it provided especially good background for the research papers we read on Alzheimer's disease. I found the book's effectiveness to be tripartite: readers feel particularly connected to the narrative from the very beginning; the science is clearly and skillfully presented; and readers not familiar with the world of research are particularly struck and enlightened by the portrayal of the politics of big science.

College-age readers of *Decoding Darkness* feel a connection to Tanzi from the beginning of the first chapter, in which he describes being "twenty-one years old and fresh out of college," a scruffy keyboardist in a rock band, fascinated by music and Eastern philosophies, and not entirely sure what direction his life would take. Tanzi happened upon a job as laboratory technician, just as many young science majors may begin their post-college years. He mentions his boyhood perception of scientists as "white- and green-coated demigods," thus making readers feel allegiance as outsiders and eliciting confidence that their journey into human genetics will be guided by someone just like themselves. Seeing Tanzi's career trajectory from a starting point resembling their own both energizes and encourages students about their prospects at becoming scientists.

A second parallel narrative in the book makes readers feel further connected. The Introduction describes the personality of one Alzheimer's patient, Julia Tatro Noonan. Subsequently, before each chapter, short vignettes depict scenes from her life, from birth to childbearing to the onset and ultimate fatal result of the disease. Many readers will have witnessed the effects of Alzheimer's disease on a family member and will thus be reminded of the relevance of research to their own lives. Readers who have no affected relatives or friends will nevertheless learn how profoundly the disease can affect a family and may project themselves as members of the Noonan family to experience the human toll.

Explaining complicated science to a general audience is challenging, but Tanzi and Parson strike just the right balance between simplification and detail. Undergraduates with some basic genetics will have no trouble with the concepts introduced. Students with more extensive knowledge of gene mapping and cloning will feel especially gratified at their complete grasp of the material; Tanzi and Parson include enough detail to satisfy such advanced readers. While readers with no genetics background may encounter moments of confusion, the narrative is structured so that general ideas are intuitive even when details are missed, and consequently the book is utterly readable for anyone.

An early chapter covers the history of Alzheimer's disease from Alois Alzheimer's 1906 written description of a patient with dementia to George Glenner's 1983 isolation of brain amyloid, one of the two substances that form abnormal aggregates in the brains of Alzheimer's patients. Tanzi and Parson's skillful use of colorful language is typified in their description of the histology of affected brain tissue: "…amyloid's microscopic plaques are forming and lodging between brain cells like strewn boulders…Amyloid also is collecting in the brain's blood vessels, clinging to their walls like barnacles." A second form of aggregate, the neurofibrillary tangle, forms inside neurons of affected

people. The majority of *Decoding Darkness* centers on scientists' dissection of amyloid's role in Alzheimer's pathogenesis. Earlier contentions that neurofibrillary tangles may initiate Alzheimer's have not been borne out.

Tanzi and Parson capture the excitement and urgency as research on Alzheimer's genetics began in the 1980s. In previous decades, brains from elderly senile patients had indicated the extreme prevalence of late-onset Alzheimer's in the general population; this observation was a "stunning revelation" because Alzheimer's in its rarer, early-onset form was originally seen as having very little impact. Advances were being made in other neurodegenerative disorders like Parkinson's, and with the advent of molecular genetics, the stage was set for the genetic exploration of inherited forms of Alzheimer's.

James Gusella's group at Massachusetts General Hospital (where Tanzi started as a technician in 1980) was mapping the Huntington's gene. Fortuitous findings during that effort led Tanzi to map chromosome 21. Mapping chromosomal landmarks and the genes that lie between requires linkage analysis, in which one determines whether particular versions of two landmarks/genes are inherited together over the generations more often than they would by chance. (When a gene is mapped, the stage is set for its actual identification, after which the molecular basis of a disease can be further elucidated.) Linkage analysis is a difficult concept for general readers, yet Tanzi's description of explaining the idea to fellow bus passengers sets readers at ease even if the details remain murky.

Upon hearing that Down syndrome patients consistently develop signs of Alzheimer's disease, Tanzi and colleagues in Gusella's group began linkage analysis to test whether early-onset inherited Alzheimer's might be associated with a gene on chromosome 21. While results were negative, hopes were raised again in 1986 when Tanzi (then a graduate student) and several others independently demonstrated that the gene encoding Glenner's amyloid protein was on chromosome 21. Actually, the gene in question turned out to encode a larger amyloid precursor protein (APP) from which the plaque-forming amyloid snippet is cleaved.

Subsequent chapters of *Decoding Darkness* elaborate on the research of many laboratories to identify additional Alzheimer genes. Mutations in the gene encoding APP were found to be associated with only a small subset of early-onset cases. Tanzi and many others showed that most inherited Alzheimer's cases stem from mutations in genes encoding "presenilin" proteins that play a primary role in cleaving APP into the harmful amyloid snippet. Susceptibility to late-onset Alzheimer's was shown by Allen Roses and colleagues at Duke to be associated with a certain version the gene encoding the cholesterol transporter APOE.

Tanzi and Parson's account of the dynamics among the competing research groups during the Alzheimer gene hunts is particularly striking. Uneasy collaborations gone sour, secrecy, whispered rumors of other people's advances, and even fraud color the reader's preconceived notions of the purity of scientific pursuit. My students invariably mentioned surprise at the politics and intrigue inherent to the research process. One wrote, "I was very surprised at how cutthroat research can be. Relationships between some labs have a degree of camaraderie and support, while others seem to be archenemies who would love nothing better than to beat the enemy to the answer." Many students remarked on the tensions at conferences; one stated, "It appeared that the researchers spent their time hoping no one else would present findings that they were currently researching." Another student asserted, "...we'd all like to see…scientists working together to tackle a disease. In reality we see a lot more egos getting in the way.." Tanzi himself notes that his field was cited by a newsmagazine as "one of the most cutthroat areas of research." Tanzi ponders, "Were our egos all sadly the larger because of the large terrible disease we were pitted against? Was it the potentially sizeable professional and financial reward of getting to the other side of Alzheimer's? Both, perhaps, and more. For fate seemed to have arbitrarily thrown together more than a handful of particularly intense personalities."

Readers of *Decoding Darkness* do see mundane and often comic aspects of life as a molecular biologist, from superstitions to joke award ceremonies. Tanzi observed that luck in the lab seemed to parallel the ups and downs of the 1986 Red Sox; Bill Buckner's error in the World Series that October subsequently caused significant worry concerning the validity of the recently-identified gene encoding APP. Tanzi describes the sense of humor apparent among his colleagues at the 1998 Society for Neuroscience meeting when "Alois Awards" (named after Alois Alzheimer) were presented for such distinctions as "Best Highlighted yet Confusing Research Topic."

Overall, Tanzi and Parson's narrative conveys a consistent sense of excitement, discovery, and flair, maintaining relatively evenhanded coverage of the work done by all the primary researchers in the field. Illustrations by Robert D. Moir are generally helpful though so simplistic on a few occasions that they do not add to what is conveyed by the text. The book is well indexed, and the excellent notes section includes annotated references that allow students to find easily any original research paper cited in the text. As a teaching tool, *Decoding Darkness* is effective at drawing students in to the history, teaching them the basic science of gene hunts, and educating them about the politics encountered by many in our field. The book ends with coverage of treatment strategies that have been tested on animal models. Tanzi notes, ironically, that the only Alzheimer's patient he has saved thus far is a choking elderly man at a restaurant in Boston. While no cures for Alzheimer's disease are currently available, Tanzi and Parson conclude on a hopeful note, optimistic that continued research will ultimately lead to effective treatments. Students finish the book excited about genetics and eager to learn more.