quantum paradoxes, not so much because of the detailed character of the trajectories that it defines as because of the mere existence of these trajectories.

The level of presentation in this book is not elementary; a solid background in quantum theory would be extremely helpful. On the other hand, the wealth of details and literature citations make this a valuable reference work with which anyone with a serious interest in the foundations of quantum mechanics should become familiar. Despite his strong advocacy of a particular theory, Holland comes across as refreshingly open-minded. He concludes that "we are in a period of transition between two great world views—the universal machine of the classicists and a new holistic universe whose details we are only beginning to glimpse. The end is not in sight for theoretical physics."

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Vignettes: Medical Trends

In ten of the twelve instances in which chloral hydrate, the bromides, sulfonal, and trional are used for therapeutic purposes [in Agatha Christie's novels], they appear in works published between 1920 and 1940. By contrast, the appearance of barbiturates and Christie-simulated barbiturates are more evenly distributed throughout her writing career: novels published between 1920 and 1940, three; 1941 and 1960, two (and *Curtain*, written in the early 1940s but delayed for publication until 1975); and 1961 and 1976, two.

—*Michael C. Gerald*, in *The Poisonous Pen of Agatha Christie* (University of Texas Press)

The canonical chromosomal sex of humans—the XX female and XY male—is not as rigid as we sometimes think. It is important to keep in mind that in the United States sexually ambiguous babies are "fixed" at birth. (Endocrinologists make these babies mostly into girls; urologists make mostly boys.)

—*Londa Schiebinger*, in *Nature's Body: Gender in the Making of Modern Science* (Beacon)

The New Genetics

Human Gene Mutation. DAVID N. COOPER and MICHAEL KRAWCZAK. Bios Scientific, Oxford, U.K., 1993 (U.S. distributor, Books International, McLean, VA). xiv, 402 pp., illus. $99 or £49.50.

A book on human mutation is clearly overdue given the major discoveries that have occurred in the field within the last 15 years, the era in which recombinant DNA technology has been applied to human genetics. In the traditional Mendelian view chromosomal genes are transmitted in a stable manner from generation to generation. As recently as 15 years ago there was thought to be a one-to-one correspondence of the gene and its protein product, and the range of mutations causing disease was limited to point mutations, deletions, duplications, and other rearrangements affecting the coding regions of genes or *cis* sequences in close proximity to them. Recombinant DNA technology revealed that our understanding of human genetics was incomplete at best and in some cases just plain wrong.

For example, in 1977 the discovery of intervening sequences (introns) in genes between protein coding blocks that must be accurately removed by splicing at the mRNA level in order to connect the coding blocks showed the idea of linear correspondence of gene and protein product to be incorrect. A more recent surprise was the realization of the great distance over which *cis* sequences can act. Alterations in so-called locus control regions eliminate the expression of entire families of genes, including members that are placed 50 to 75 kilobases downstream. Likewise, sequences repeated at great distances from each other can mispair, leading to crossing-over events that produce deletions, duplications, or inversions of millions of base pairs.

New modes of inheritance and unusual types of human mutation were added to the classical view and greatly altered the perspective of human geneticists. Mendelian inheritance remained, but the old laws were broken by new forms of non-Mendelian inheritance, including the maternal inheritance of mitochondrial DNA, the inheritance of two copies of a chromosomal homolog from one parent and no copies from the other (uniparental disomy), the two-stage inheritance of expanding trinucleotide repeats, the inheritance of disease from an unaffected parent owing to germinal mosaicism in that parent, and the role of somatic mutation in carcinogenesis.

Mutations in mitochondrial DNA can either be passed through the maternal germ line or originate in somatic cells and cause a variety of diseases (for example, chronic external ophthalmoplegia). Rarely, uniparental isodisomy can lead to inheritance of an autosomal recessive disease when only one parent is heterozygous for a defective gene. That parent may provide two copies of the chromosome bearing the defective gene while the other parent makes no contribution. This unusual form of inheritance has now been observed in a number of conditions, including cystic fibrosis. When an individual has germinal mosaicism he or she has two populations of gametes, one normal and the other affected with a mutant gene. Five to 10 percent of "new" cases of autosomal dominant diseases (for example, osteogenesis imperfecta) are due to germinal mosaicism, and the parents face a significant risk of disease recurrence in subsequent offspring.

Examples of surprise mutations include the aforementioned expansion of unstable repeats, genomic imprinting, and retrotransposition of mobile elements. Unstable trinucleotide repeats that can change in size from one generation to the next or even from one mitosis to the next have been found to cause six diseases (including the fragile X syndrome), and the list has just begun. These mutations can inactivate genes through expansion of the repeats. Occasionally the repeat number may contract, reverting the disease gene to a normal gene. A sizable portion of the genome is subject to imprinting, in which one copy of a gene is inactivated while the other remains functional. Which copy is inactivated depends on its parental origin. We are just beginning to learn of diseases whose etiology is related to mutations that disrupt normal imprinting (for example, Beckwith-Wiedemann syndrome and Wilms tumor). Mobile repeated elements, notably L1 and Alu, have been observed to retrotranspose through an RNA intermediate from their normal genomic location into a new site, occasionally producing disease (for example, hemophilia A).

Another surprise for human geneticists is the ease with which known mutations can

be detected rapidly with new techniques such as the polymerase chain reaction and the Southern (DNA) blot. In fact, it will soon be possible to rapidly characterize unknown mutations in large genes using the very rare transcripts isolated from white blood cells (so-called illegitimate transcripts) and ingenious new detection techniques.

Human Gene Mutation contains discussions of many of these unexpected new concepts and techniques, including unstable repeats, genomic imprinting, mitochondrial mutations, two-hit mutations in tumor suppressor genes, retrotransposition, and new mutation detection techniques. However, the reader is given only a glimmer of their novelty and the substantial impact they are currently having on the thinking of human geneticists. The editors have attempted to cover the broad subject of human mutation in an easily accessible, concise monograph. The book is comprehensive and well written, with excellent and plentiful illustrations and extensive and well-chosen references. I particularly liked the fine historical perspective on the study of human variation, the exposition of *cis* regulatory mutations, and the interesting analysis of mutations indicating that their nature and location are nonrandom. Examples of classical mutations in and around genes are well described and thoroughly referenced. The new and unusual mutations that are currently so fashionable are also discussed, though, to my disappointment, without emphasis and not in the context of their often unusual inheritance patterns. The absence of a section on mutations in *trans*-acting factors, which are ever increasing in importance, seemed an oversight.

Although the book is for the most part a synthesis, a major section on the analysis of nucleotide substitutions is presented in the form of a research article. The material is interesting, but its details interrupt the book's flow and it really belongs in a research journal. It required me to assume the different role of research article reviewer, and it seemed to me that some of the authors' conclusions concerning the nonrandom nature of these mutations could be questioned. Essentially all the mutations examined were discovered because they alter protein function and produce human disease. Yet they are analyzed at the DNA sequence level as though all nucleotides within the protein coding region of a gene were equally fair game for detrimental mutation. This criticism notwithstanding, the analysis of methylation-induced "hotspot" mutations in humans presents interesting and important data.

The book's shortcomings are minor considering the size of the undertaking and its general success. This is an informative, readable reference work, and I recommend it to anyone interested in the nature and source of variation in the human genome.

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