malpractice suits, penalties for undertreatment will decline further.

With due modesty Rodwin urges changes on three fronts. First, physicians both individually and collectively must contemplate the nature of fiduciary relationships as thoroughly as lawyers, pension officers, and corporate directors have done. Medicine does have important lessons to learn from them. Second, federal and state authorities must be more consistent in prohibiting conflict of interest and more aggressive in policing it. Finally, Rodwin favors making medicine still more of a regulated industry. He wants auditing czars reviewing hospital financial records and conflict-of-interest review boards setting institutional policies.

It takes a strong heart to call for yet more bureaucracy and regulation in medicine, and it is entirely possible that such remedies may be worse than the disease. A noble profession would lose not only its appeal to present and future practitioners but its very sense of honor. On the other hand, one must respond to the dismay that a well-respected patient provoked at a recent medical meeting when she told her audience that she trusted her lawyer more than her doctor.

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Vignettes: Hard Words

You are always *busy*. You have a finger in every pie. . . . It gets you nowhere. It gets nothing done. You are the Mad Hatter of the Scientific World.

—*H. G. Wells* to Julian Huxley, as quoted by Krishna R. Dronamraju in *If I Am To Be Remembered: The Life and Work of Julian Huxley* (World Scientific)

I do not mean to be harsh, but your very versatility and you[r] polemical cleverness make it necessary for some older people to tell you bluntly where they think the trouble lies. Otherwise you might go on through life doing half-baked work which wins applause from the uncritical and the unsophisticated, working hard and sincerely, and thus never realizing that your work was superficial. . . . You have very unusual experimental ability; you have exceptional drive; you write well; your enthusiastic personality will make you a stimulus to others; you think clearly when your drive does not carry you away. The only flaw in this gem is that [you are] too clever always to be thorough . . . [and you] believe . . . that tricky sophistical argument is justified if the end is justified.

—*Edwin G. Boring* to B. F. Skinner, as quoted by Daniel W. Bjork in *B. F. Skinner: A Life* (Basic Books)

Practical Proteins

Protein Structure. New Approaches to Disease and Therapy. MAX PERUTZ. Freeman, New York, 1992. xiv, 326 pp., illus. $44.95 or £33.95; paper, $34.95 or £22.95.

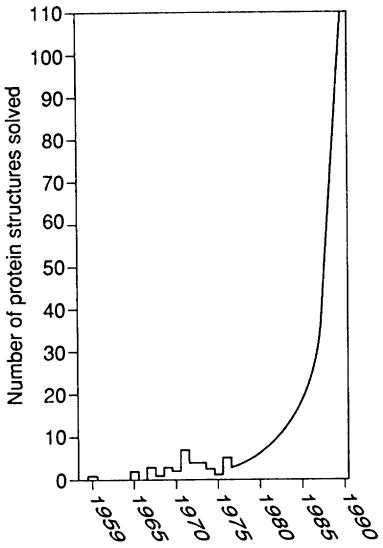
The dramatic impact that knowledge of the three-dimensional structure of protein molecules is now having on efforts to develop new therapies for disease is the occasion for this enticing book by Max Perutz. Rich in autobiographical recollection, the book captures the excitement that accompanied selected discoveries with which Perutz has been familiar. The book is not a textbook or an attempt to review the entire field; rather, Perutz has selected favored examples of protein structures to focus on some larger issues in biology and the prospect of using the structural knowledge to therapeutic advantage.

There is something in the book for everyone. In addition to Perutz's own recollections there are accounts of important discoveries that herald the 21st century in molecular medicine—Bernal and Crowfoot's discovery in 1934 that protein crystals, if maintained in a hydrated state, could reveal protein structures; Lwoff's discovery that bacteriophage transformed cells; Levi-Montalcini's discovery of a factor that could accelerate differentiation in nerve fibers. These add to the excitement and convey a sense of the process of discovery. For a graduate student the book can be an enchanting eye-opener to the prospects of using macromolecular structure determination for therapeutic purposes. For the medical student and undergraduate it should be an important supplement to biochemistry texts. A strong point is the demonstration of the connections between structure and function at the appropriate level, whether stereochemical or cellular.

Beginning with Waldmann, Winter, and colleagues' discovery that a rat anti-T cell antibody, modified in two cycles of protein engineering based on crystal structures, could induce prolonged remission in human leukemia patients, Perutz discusses work on molecules important to immunobiology. Focusing on the structure of chymotrypsin determined at the Medical Research Council laboratory of which he was the head, Perutz points out how the structures of serine proteinases validated the classic 1948 prediction of Linus Pauling that enzymes enhance reaction rates by their complementarity to transition states. Structures of proteins that regulate transcription and of DNA-binding anti-cancer drugs show how they function. Perutz's own major research focus, the structures of hemoglobin, provided the first insight into the exact molecular basis of a disease, sickle cell anemia. Perutz uses hemoglobin structure as the exemplar for showing how small-molecule "drugs" interact with protein molecules—affecting in this case oxygen affinity and cell sickling—and later for analyzing effects of genetic variants.

The book introduces iterative structure-based design of drugs to "fit" target sites on specific proteins by describing studies from the University of California at San Francisco of compounds that inhibit action of HIV protease and so shut down the HIV infective cycle. Initial insights were generated by computational "docking" of all the known three-dimensional structures of small compounds into the enzyme functional site. Structures of the resulting complexes as determined by crystallography showed how the compounds could be improved and were then used to iteratively improve efficacy. The principles of structural complementarity are underscored in the book by structural analyses of other antiviral agents, discovered by serendipity rather than by computational screening, that show how they too evoke their effects by complementarity to their target sites.

The structural analysis of human growth hormone attached to the soluble form of its cell surface receptor, as developed by Wells, deVos, and Kossiakoff, has opened tremendous new possibilities for understanding and manipulating the human response to growth hormones and cytokines more generally. Surprisingly, the structures show that a single growth-hormone molecule functions by drawing two recep-



"Annual number of protein structures solved 1959–1990." [From *Protein Structure;* courtesy of Dr. Arthur Lesk]

tor molecules together in the membrane plane, thus signaling to the inside of the cell and stimulating growth patterns. Too recent for inclusion in this book, these findings have had an enormous impact in an already very significant market in therapeutics.

Acknowledging the rapid rate of advance, the book ends with a descriptive list of 25 proteins not discussed in the text whose structures are of clear importance for therapeutic design. The level of excitement in this field is high. Perutz, who had so much to do with the origins of protein-structure determination—indeed, his book begins with a gem, a beautiful 37-page intuitive introduction to protein crystallography and nuclear magnetic resonance—still points the way with adroit perception to the rapidly unfolding future.

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Neutron Stars

Isolated Pulsars. K. A. VAN RIPER, R. EPSTEIN, and C. HO, Eds. Cambridge University Press, New York, 1993. xiv, 438 pp., illus. $59.95 or £40. From a workshop, Taos, NM, Feb. 1992.

Although the existence of neutron stars was predicted in 1934, the first successful observation was not until 1967, when Jocelyn Bell noticed "a bit of scruff" in the output of the radio telescope at Cambridge University. Radio pulsars were thus discovered; they were soon shown to be isolated, spinning, magnetic neutron stars. There are now more than 500 known neutron stars. *Isolated Pulsars* brings together work on the theory and observation of these stars from radio waves to gamma rays.

A neutron star has a radius of about 10 km and a mass approximately that of the sun and can spin as rapidly as several hundred revolutions per second. Physical conditions in a neutron star and in nearby space are extreme. The density of material at the center of the star is 10^{14} to 10^{15} g cm^{-3}. The magnetic field at the surface can be 10^{12} gauss, 3×10^6 times stronger than the strongest laboratory field on Earth, and the gravitational field at the surface is 10^{11} times stronger than that on Earth. Tidal forces are strong enough to rip solid objects apart thousands of kilometers above the surface.

The observed signal from most isolated pulsars results from nonthermal radiation generated by a wind of relativistic particles (somehow produced by the rotating star) moving out through the strong embedded magnetic field. As the name "pulsar" implies, radio emission from the spinning object consists of periodic sequences of brief pulses. Masses of a few neutron stars in binary systems have been measured; all are approximately 1.4 times the mass of the sun. Although investigators have not been able to measure other characteristics of pulsars directly, some of the things we would like to know are the radius, the nature of internal material, the interior structure, the nature of the "surface," and the magnetic field strength and morphology.

The brightest pulsars are the youngest, and the brightest by far is the pulsar within the Crab Nebula, which spins at a rate of 30 revolutions per second. Biggs *et al.* show a beautiful light curve (the time history of one cycle of pulsed emission) from the Hubble Space Telescope and use a polar diagram to illustrate small differences between visible observations and ultraviolet data.

Observations of the Crab pulsar in the range 0.5 to 10,000 MeV with the four instruments of the Compton Gamma-Ray Observatory are presented by Thompson *et al.*, Busetta *et al.*, Ulmer *et al.*, and Wilson *et al.* Measured light curves from the Crab pulsar, which do not vary much as energy changes, are shown, and some data from the Vela pulsar and from PSR1509-58 are presented. Data for the Crab pulsar are probably definitive, but high-energy observations of other young pulsars are currently under way and available information about these stars will soon be out of date.

Descriptions of the mechanism that produces high-energy radiation in the pulsar magnetosphere are provided by Ho, by Harding and Daugherty, and by Chiang and Romani. Chiang and Romani's contribution contains particularly helpful illustrations. Even after 25 years of study, the pulse generation mechanism of pulsars is not well understood. These papers, together with a group concerning the theory of radio pulses, illustrate that the mechanism for radio emission is believed to be different from that for high-energy emission. Cordes compares radio emission and gamma emission from the Crab pulsar.

The surface of an isolated neutron star is generally believed to have a temperature of about 10^5 K—hot enough to radiate soft x-rays as a black body. Ögelman, Becker, and Finley describe ROSAT detection of such radiation from several young or nearby pulsars. Since neutron stars are probably born hot, cooling with time, the rate of cooling gives information about the conductivity of the interior. Several papers present calculations of cooling curves, which depend on the nature of interior reactions such as the direct Urca process, and compare them with observations. Lai *et al.* discuss the properties of atoms on the surface and the effects produced by extremely strong magnetic fields. Because the magnetic force on the electron is stronger than Coulomb forces, atoms are expected to have a cigar-like structure.

All pulsars, as spinning, magnetized bodies, will slow down with time because of the torque applied by the emitted radiation. Through continuous monitoring of the arrival times of radio pulses and measurement of the pulse period, investigators can readily determine the rate of loss of rotational energy. The steady slowdown of some pulsars, however, is interrupted by glitches—sudden increases in the rotation rate, followed by decay back to a steady slowdown. Observation of the rotation rate just after a glitch can provide valuable information about the interior of the neutron star. Baym, Epstein, Alpar, Link, and Van Riper discuss how behavior during a glitch may be determined by the coupling of superfluid neutrons in the core to the solid crust by the magnetic field.

Other contributions to the volume discuss possibilities for the formation of planets in circular orbits around pulsars, the evolution of spin rates and magnetic fields, and the maximum rotation rate of a neutron star. In "How fast can neutron stars rotate?" Herold *et al.* conclude that a rate of 1800 revolutions per second is possible. They include an interesting illustration showing an observer's view of the surface of a rotating neutron star distorted by general relativistic effects. Overall, this