the blood of ducks that had been fed a poisonous weed to protect himself against poisoning by his enemies. Today, a potion made from poison oak is available at homeopathic pharmacies to protect against the risk of poison oak.

Encouraged by some early results in animals, Weiner decided to pursue the cure of not only MS but also rheumatoid arthritis, giving by mouth the brain substance myelin to MS patients and collagen-rich cartilage from calf noses to the arthritis patients. As optimism and excitement increased, the search became one capable of attracting venture capital and biotech firms. Quinn's book captures this anticipating atmosphere in a highly readable form, taking in not only Wall Street but the media and academe as well.

The early positive screening results were, sad to say, not substantiated in the chronic clinical trials. Improvement was seen in some patients, but the results did not show a significant advantage of active treatment over placebo. The conclusion was heart breaking and the reader gets caught up in the anticipation as the bad news is reported for each trial.

The process of drug development is slow, expensive, and risky. This book was published before the latest report from the Tufts Center for the Study of Drug Development, a report whose expensive figures were $800,000,000 to bring a new chemical entity to market if we count the "dry holes" as well as the "gushers" and both the out-of-pocket expenses and the "cost of money," i.e., what you could have earned with the money spent if it were invested so as to generate a 11% return. Quinn's book accurately describes the many years spent from discovery to new drug approval, and the fact that even when a developer reaches phase I with a drug, i.e., the first human exposure, only 1 in 4 or 1 in 5 such drugs ever make it to market. Only 30% or so of approved drugs ever earn back the money invested in their development.

An especially fascinating part of the Weiner story is the high rate of improvement after placebo. (Fifty six percent was reported in one trial). Placebo benefit is partially explicable on the basis of optimistic anticipation and partially by spontaneous improvement. One can only guess at the explanation in the trials summarized in this book, but MS patients clearly have good reason for hoping that a new medication that showed promise would help them. (Ditto for the research physicians.)

Louis Lasagna
Sackler School of Graduate Biomedical Sciences
Tufts University
Boston, Massachusetts 02111

Cryptobiosis, Extremophily, and the Nature of Life

Life at the Limits: Organisms in Extreme Environments
By D.A. Wharton
Cambridge: Cambridge University Press (2002).
328 pp. $25.00

Traditionally, living things were distinguished from inanimate objects like rocks by their motility and growth, more than by an ability to reproduce. Emphasis on reproductive continuity arose only in the 17th century when microscopists discovered cells and Leeuwenhoek first saw protozoa and bacteria and considered that even the tiniest animalcules multiply only from like kinds. Henry Power noted that vinegar nematode worms could survive freezing and in the next century Reaumur found that some caterpillars could also. At first this suspended animation, or cryptobiosis, was confused with death and resurrection. But we now know that many nematodes, rotifers, tardigrades, arthropods, and microorganisms can survive freezing and/or drying, as can many seeds and fungal or other spores.

I used to tell my students that the ability of brine shrimp (*Artemia*) cysts to survive freezing close to absolute zero means that all the information for a living organism is structural—physically embodied in the structure and three-dimensional arrangement of our constituent molecules. Molecular motion is needed only during growth and function and is therefore less fundamental than structure. Wharton is an expert in animal cryptobiosis, which he accurately expounds here for the general public. But his canvas is much broader, encompassing microorganisms and plants also, which obey the same general principles.

Cyptobiosis tells us that life has two potential states. The animated state allows metabolism, growth, and reproduction and depends on diffusion and molecular collisions in liquid water and liquid lipid membranes; energy must continually be expended to maintain ion gradients and small molecule concentrations within the range compatible with life. During cryptobiosis, dryness and/or freezing prevent diffusion, so that the potential for animate life can be preserved as structure without energy expenditure.

Many organisms cannot enter the cryptobiotic state, for freezing or drying irreversibly disrupts their membranes, allowing small molecules to leak out or in, or lethally denatures their proteins. Only those with evolved adaptations can do so. These involve altering intrinsic protein or membrane lipid structure plus special adaptations, such as proteins that bind to ice crystals to prevent their growth or proteins that actively nucleate ice growth outside cells, where it is less damaging than inside. Some organisms that inhabit low temperatures avoid freezing by making glycoproteins that reduce their freezing temperature (e.g. arctic and antarctic fish) or concentrated polyol or sugar antifreezes (many temperate plants and insects).

A radically different way of coping with extreme conditions is extremophily, the ability to grow and multiply in extremes of temperature or pH or in concentrated salt or ionizing radiation. In contrast to cryptobiotes, which suspend animation in extremis but typically grow best in normal environments, extremophiles grow best under their favored extreme conditions and typically cannot under normal ones. This is because the fluidity of their membranes and the stability of their proteins are specifically adapted to their preferred extremes. Well-known examples are thermophilic, psychrophilic, acidophilic, and halophilic bacteria.

Wharton refers to extremophiles as showing capacity

adaptation and to cryptobiotes as showing resistance adaptation. His book centers on the contrasts and similarities between them. It is generally clear and accurate and opens a fascinating area to the general reader or student, but a well-rounded biologist should be familiar with much of it. His treatment of cryptobiosis—his specialty—and life in dry and cold places is livelier, more detailed, and more interesting than that on microbial extremophily, which is more pedestrian and cursory.

After discussing life in the deep sea adapted to high pressures, Wharton argues (rightly I think) that this is not really an extreme habitat for life, but only seems so to us. However, I should apply the same argument to anaerobic habitats, which he also, rather anthropomorphically, treats as extreme. His concluding discussion almost appears to equate novelty with extremism, arguing that aerobic habits were extreme when they first arose, but now that they are ubiquitous, anaerobiosis is "extreme." However, organic molecules are inherently more stable, and life probably began, under anaerobic conditions; oxidizing ones are inherently less friendly to most basic biochemical processes. Is it not better to regard aerobic and anaerobic life as simple alternatives, rather than one as extreme and the other normal? By contrast, extreme pH, high temperatures, salt concentrations, and dryness are inherently inimical to the stability of biological molecules and macromolecular assemblies, and we may reasonably treat organisms that cope with them as extremophiles.

Most space is given to how organisms now survive in frigid places or deserts and he only briefly touches on the question of where life started. In one place, he favorably mentions Hinton's plausible idea that life began on land in numerous small pools, but in another he categorically asserts the usual dogma that life began in the sea and had to solve problems in moving to land. What does he himself think? Elsewhere, he asserts that life evolved under conditions more extreme than now, but if this refers to early anaerobiosis, it is debatable. Possibly he means temperature extremes, as later he repeats the common recent dogma that the most ancient prokaryotes were hyperthermophilic. He seems not to realize that this view is unsound, because it assumes that the root of the universal tree lies between archaebacteria and eubacteria. However, this is almost certainly false, as palaeontology indicates that eubacteria are several times older than eukaryotes or their archaebacterial sisters, and numerous arguments indicate pretty conclusively that archaebacteria were evolutionarily derived from eubacteria (Cavalier-Smith, Ann. N.Y. Acad. Sci. *503*, 55–71, 1987; Cavalier-Smith, Int. J. Syst. Evol. Microbiol. *52*, 7–76, 2002). It is odd how often the origin of life and the nature of early cells is discussed without considering the direct fossil evidence for the actual course of history. When discussing evolution, we must take note of phylogeny, paleontology, and adaptive arguments. Such a synthesis strongly suggests that the last common ancestor of all life was a photosynthetic Gram-negative eubacterium with a double envelope, whereas Gram-positives with a single bounding membrane evolved later and were ancestral to both archaebacteria and eukaryotes, yet more recently (Cavalier-Smith, Int. J. Syst. Evol. Microbiol. *52*, 7–76, 2002).

Eukaryotes are sisters of archaebacteria—together known as neomurans because their shared ability to make N-linked glycoproteins cotranslationally probably evolved when their common ancestor evolved glycoprotein walls to replace the murein peptidoglycan walls that characterize most eubacteria. As eukaryotes are sisters of archaebacteria and did not evolve from them (Cavalier-Smith, Ann. N.Y. Acad. Sci. *503*, 55–71, 1987; Cavalier-Smith, Int. J. Syst. Evol. Microbiol. *52*, 7–76, 2002; Cavalier-Smith, Int. J. Syst. Evol. Microbiol. *52*, 297–354, 2002), archaebacteria cannot be significantly older than eukaryotes. Most novelties that archaebacteria share with eukaryotes (e.g., histones and changes in signal recognition particle, protein secretion, and DNA handling enzymes) can be attributed directly or indirectly to secondary thermophilic adaptation. Numerous lines of evidence indicate that the ancestral neomuran evolved from a Gram-positive actinobacterium that had already evolved sterols. Recent claims that the actinobacterium *Mycobacterium* got cholesterol-making machinery by lateral transfer from eukaryotes (Gamieldien et al. Trends Genet. *18*, 5–8, 2002) are implausible as they ignore the other extensive evidence that eukaryotes evolved vertically from an actinobacterial ancestor (Cavalier-Smith, Ann. N.Y. Acad. Sci. *503*, 55–71, 1987; Cavalier-Smith, Int. J. Syst. Evol. Microbiol. *52*, 297–354, 2002), so the shared enzymes may simply reflect this direct vertical descent.

The argument that the ancestral archaebacterium was a hyperthermophile, and that mesophilic and halophilic archaebacteria are relatively derived, in part by acquiring eubacterial genes, is convincing. But the idea that archaebacteria are ancient is fallacious. Paleontology, phylogenetic, and adaptive arguments all polarize the direction of change from eubacteria to archaebacteria. The two most significant unique features of archaebacteria are both secondary adaptations to extremophily: their glycoprotein flagellar shafts and isoprenoid ether lipids. Eubacterial flagellin is acid-soluble, explaining why the neomuran ancestor of archaebacteria would have replaced it by acid-insoluble glycoprotein on colonizing acid habitats, but the reverse change would be pointless. Likewise, replacing acyl ester bilayers by isoprenoid ether lipid monolayers would have adapted the ancestral archaebacterium to hot acid, but the reverse would be selectively pointless—it did not occur in secondarily mesophilic archaebacteria.

The origin of biomolecules is much easier to understand if it occurred in a heterogeneous environment with geothermal activity to condense polymers and numerous small cool pools subject to freezing and drying to stabilize and concentrate them. The breakthrough to the first organisms in which membranes, genes, and catalysts cooperated is also much easier to understand in a cool heterogeneous environment such as polar tide pools (Cavalier-Smith, J. Mol. Evol. *53*, 555–595, 2001). It seems much more likely that early proto-organisms were cryptobiotes, able to survive temporary freezing or drying, than thermophiles having to evolve the genetic code and membranes beside oceanic vents in the enormous volumes of the deep ocean, as seems currently popular in some circles.

Given Wharton's expertise in cryptobiosis, it is odd that he does not consider the possibility that cryptobiosis might have been a feature of organisms from the

beginning, later lost by higher organisms that evolved better homeostasis, whereas extremophily is relatively derived. But it is not Wharton's style to speculate or question established dogma too strongly. If you want a straightforward non-technical account of how organisms cope with deserts, polar, abyssal, extra salty, or extreme pH habitats, this book provides it. Discussion of hyperthermophily is rather sketchy.

I end on a pet peeve—his acceptance of the thoroughly confusing and reprehensible changing of the name eubacteria to bacteria, the tendentious and misleading change of the name archaebacteria to archaea, and the gratuitous change of Eukaryota to Eukarya. Ugh! Archaebacteria are bacteria by any sensible criteria; to pretend otherwise is scientifically unsound and nomenclaturally destabilizing. People who study them are bacteriologists not archaeologists!

Thomas Cavalier-Smith
Department of Zoology
University of Oxford
Oxford OX1 3PS
United Kingdom

The Illustrious Life of a Tobacco Pathogen

The Life of a Virus: Tobacco Mosaic Virus as an Experimental Model, 1930–1965
Edited by Angela N.H. Creager
Chicago: The University of Chicago Press (2002).
398 pp. $27.50

Today, we are aware of viruses and the diseases they cause and we have a concept of the nature of life. We know that heredity is mediated through nucleic acid. But, many of us may not be aware that the development of scientific and technological knowledge in these fields as well as in virology and molecular biology in general is based on ground-breaking research on a tobacco pathogen, *Tobacco mosaic virus* (TMV).

The story of TMV and its impact as a model system for research from the early 1930s to the 1960s is told by Angela N.H. Creager, associate professor in the Department of History and Program in the History of Science at Princeton University. Professor Creager was inspired to write this book by the name of the building (Stanley Hall) at the University of California in Berkeley in which she did her laboratory work as a graduate student. Angela N.H. Creager provides a perceptive and insightful overview of the historical background and progress in virus research and the major incentives arising from the research of the Nobel laureate (1946), Wendell Stanley, who, in 1935, obtained TMV in pure form as needle-shaped crystals. This was a major achievement since for the first time a tangible, visible substance was obtained that caused mosaic disease in plants. Until then, symptoms could only be produced by extracts from plants afflicted with the disease. The disease-causing agent itself was a mystery, characterized only as a filterable "contagium vivum fluidum," a "ghost" substance, or "virus." However, in the year 1939, following Stanley's isolation, TMV became the first virus to be visualized with an electron microscope and, suddenly, viruses could be defined in terms of proteins rather than just disease symptoms.

From this point, the story told by Creager unfolds with TMV emerging as a major and preferred model object, not only for research on other viruses and their diseases, but also for debates about the nature and origin of life: TMV was a molecule capable of self-reproduction and, therefore, appeared to represent life in its simplest form. TMV was intensively studied as a representative virus, with the expectation that knowledge gathered could be applied to other viruses. In fact, its use demonstrated how other viruses and biological objects could be isolated and studied. The characterization of TMV as a macromolecular particle thus inspired efforts to obtain and understand the agents of papilloma and influenza, using the same physical-chemical instruments (i.e., ultracentrifuges). The purification in 1956 of infectious ribonucleic acid (RNA) from TMV led to the isolation of infectious acid from Coxsackie virus and poliomyelitis virus and, thus, to the new concept of virus infectivity mediated by nucleic acids.

The core of the book thus provides a strong impression of how TMV served as a reference virus in studies that led to the development of new experimental techniques and important conceptual changes. The book illustrates how TMV became a crucial tool and experimental standard not only in research on biological macromolecules but also in the development of commercial instrumentation in science. During the war, Stanley further adapted his centrifuge-based method of isolating virus to develop a new kind of influenza vaccine that was mass produced for the army and subsequently for civilian use. The Rockefeller Foundation funded further development of this instrumentation for laboratory research, encouraging life scientists to collaborate with physicists, chemists, and mathematicians. This development led to the successful commercialization of ultracentrifuges that, in turn, stimulated the development and commercialization of other instruments such as the electron microscope, electrophoresis equipment, scintillation counters, and spectrophotometers. In addition, when virus research benefited from this expanded technological infrastructure, new sources of financial support for virus research became available. In fact, it was the state of knowledge on TMV that helped to justify large-scale funding of virus research and provided a pragmatic guide for the investigation of human pathogens. The public was confident that laboratory research would help to defeat diseases like polio because of a widespread perception that such research had a positive impact during World War II (e.g., the influenza vaccine provided by Stanley). The National Foundation for Infantile Paralysis (NFIP) thus granted millions of dollars to virus research in the 1940s and 1950s. By 1950, the United States federal government also began funding research on a large scale with the promise of improving public health.

Stanley's purification of TMV crystals also stimulated the use of mutant TMV strains to analyze the chemical