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EDITORIAL

Biology at millennium's end

Biology is a vast continent, with a great deal of virgin territory that remains to be explored. Biology's borders with the neighbouring areas of chemistry, physics, medicine, technology and even mathematics, are extended and diffuse. Specific sub-disciplines of biology comfortably straddle the 'no-man's' land between the 'hard' and 'soft' sciences. Indeed, biology provides a somewhat tenuous link between the traditional sciences and the 'social sciences'. Extrapolation from studies of animal populations and their behaviour to the human condition can often be seductive. The promise of 'applicable' biological research, to enhance the quality of life, has been dramatically realized over the course of this century. The explosive growth of molecular biology and biotechnology and their myriad applications in agriculture and medicine have propelled biology to the forefront of the sciences. It is now a cliche to say that we live in an age of biology. Unlike its sister sciences, biology is an all-encompassing field, a forgiving religion, which welcomes all comers. It is almost impossible to enter physics, chemistry, mathematics or engineering after the first flush of youth has passed. Formal degrees and a well-defined pedigree are a necessary passport to work in these fields. In contrast, defections to biology are easy to effect (and often profitable); remarkably, in many areas formal training in other disciplines is a great advantage. Mathematical and analytical skills, familiarity with chemical language and appreciation for quantitative thinking are best acquired when young. Biology's nuances can be appreciated at a more mature age.

Many of modern biology's major triumphs have been heralded by the 'converts'. Max Delbruck deserted physics at the height of the quantum revolution to found the area of bacteriophage genetics, an historic move in the context of the development of molecular biology. Linus Pauling, the quintessential chemist, displayed remarkable prescience, when he recognized the molecular basis of disease. The story of sickle cell haemoglobin is now commonplace; the connection between point mutations in genes and pathology has been repeatedly established. The molecular analysis of genes has been profoundly helped by physicists in search of greener pastures; most notably Francis Crick, whose discovery of the double helical structure of DNA, with James Watson, is now assured immortality and Walter Gilbert, a convert from particle physics, who ironically pioneered the chemical method for sequencing DNA. In India too, the major advances in biology have come from outside the traditional departments of botany and zoology. G. N. Ramachandran's path-breaking analysis of the structure of collagen and his profoundly important insights into polypeptide chain folding were born in Madras University's physics department, eventually legitimising a new subdiscipline of 'molecular biophysics'. Structural biology, now an area devoted to analysing the enormously complex molecular structures, that are a hallmark of cellular chemistry, is a creation of crystallographers and spectroscopists, who have traditionally been physicists or chemists. Biological research has indeed been enriched greatly by the immigrants; the New World drawing its strength from the pilgrims.

At the turn of the century, biology had its inheritance; Linnaeus, Mendel, Darwin and Pasteur ranked among the immortals. In the dying years of the 19th century, Eduard Buchner (somewhat surprisingly more famous for his funnel) demonstrated cell-free fermentation by the 'juices of yeast', establishing that life processes undoubtedly follow the laws of chemistry (and physics). Biochemistry was born and quickly divorced from traditional chemistry; a clear separation of the animate from the inanimate. But, in the caste system of the sciences, biology ranked low. Almost half a century was to pass before the ugly duckling began to turn into a swan. The transformation was complete by the 1970s as biological research moved from triumph to triumph on an extremely broad front. The results of research appeared to quickly relate to practical advances in diverse fields, medicine and agriculture among them; areas of direct societal impact. These developments have been largely fuelled by the ability to isolate, clone, amplify, sequence and manipulate DNA; a package of techniques that form the heart of recombinant DNA technology. Even as the 20th century neared its end, biology's first mega project began to take shape. The 1980s saw the beginning of the discussion on the scientific utility of sequencing whole genomes of organisms. Deciphering the order in which the letters (bases) are strung together in a genome, provides a comprehensive view of the genetic instructions encoded by nature; somewhat picturesquely called the 'Book of Life'. Few would have anticipated, even in the early 1990s, that these 'mega projects' in biology would be completed so quickly. In the last few years, several genomes of microorganisms have fallen to the onslaught of large-scale sequencing. These include, pathogens like *Helicobacter pylori*, the bacterium associated with gastric ulcers and most importantly, *Mycobacterium tuberculosis*, the causative organism in TB (S. T. Cole *et al.*, *Nature*, 1998, **393**, 537). Knowledge of their genomes provides a high resolution map of the enemies' territory, presumably providing insights that may be used for eventual conquest. The results of major international efforts in genome analysis are pouring in at present. The fall of chromosome 2, of *Plasmodium falciparum*, the most dangerous of the malarial parasites is a signal advance (M. J. Gardner *et al., Science*, 1998, **282**, 1126). A *tour de force* in the sequencing arena is nearing completion, the genome of the fruitfly, *Drosophila melanogaster*, which constitutes a staggering length of ~180 million bases. In principle, the keys to the vaults containing the secrets of differentiation and development of a complex organism are now available. The human genome project appears to be moving so fast, that this may be one instance, where a major collaborative international project is completed ahead of schedule. A conservative completion date, 2005, projected at the start has now been advanced to as early as 2002. The first battle has been won, with the sequencing of chromosome 22 (I. Dunham *et al., Nature*, 1999, **402**, 498) although the thought is sobering that in reaching this objective only 33.4 million bases have been sequenced, as compared to the approximately 3.5 billion, present in the human genome. The paper reporting the chromosome 22 sequence had 217 authors spread over nine institutions on three continents, a clear signal that biology is now a clear rival to particle physics in the area of 'big science'. On another front, the determination of the detailed structures of the molecular assemblies that constitute the cellular machinery, the advances in the last year have been sensational. Even as 1999 draws to a close, the structure of the 30 S and 50 S subunits of the ribosome have succumbed to X-ray diffraction (W. M. Clemons Jr. *et al., Nature*, 1999, **400**, 833; N. Ban *et al., Nature*, 1999, **400**, 841). There is now a near atomic resolution picture of these massive multimolecular complexes. Close on the heels of these successes, a 7.8 Å structure of the intact ribosome, the factory for cellular protein synthesis, which has a molecular size of ~2.5 million Da, has been reported, albeit at lower resolution (J. H. Cate *et al., Science*, 1999, **285**, 2095). The transition in the space of a little less than a century from the crystal structure of common salt to the detailed architecture of assemblies of hundreds of thousands of atoms, signifies a pace of scientific advance that is truly breathtaking. While these achievements may be hard to appreciate by the casual observer, some of biology's successes are more widely visible. Animal cloning is no longer the realm of science fiction. Even a project to resurrect the woolly mammoths from the frozen wastes of Siberia does not seem completely far fetched (*Science*, 1999, **285**, 1007).

Biotechnology, the practical arm of biology, primarily fuelled by recombinant DNA methodology, is now a widely appreciated field. Vaccines, drugs, gene therapy, gene-based diagnostics and genetically modified crops are frequent subjects of discussion. Vaccines and drugs are now sought against diseases which pose major public health problems, most notably tuberculosis, malaria and AIDS. The task is not made easy by the complexities of immunology and the infinite capacity of pathogens for eluding and countering attack. A balanced and rational approach, to evaluating the potential of biotechnology to contribute to human progress, requires a wider understanding of biology and its inherent complexity. The raging debates on genetically engineered crops and the ongoing discussion on the efficacy of even long-used vaccines for TB and polio, are a pointer that public discussion of the fruits of biology is likely to intensify in the future. There is a great imperative to enhance the breadth, scope and quality of biology education. Future administrators, politicians and even lay people may benefit from some exposure to the nuances of a field that is likely to dominate the future.

At the millennium's end, there is a temptation to speculate on the years to come. A thousand years is however, a timescale beyond the comprehension of ordinary humans. A century, which seems closer to the biblical lifespan of three score and ten, seems more manageable. But science is the graveyard of futurologists. Biology's century began with the underpinning of Darwin's grand evolutionary synthesis. But the last one hundred years have been relentlessly dominated by triumphant reductionism. However, there are already signs that the pendulum has begun to swing the other way. The preservation of our biological heritage is already a major concern. Taxonomy and systematics appear to be staging a comeback. There can be few certainties in science; but you do not need a crystal ball to hazard the guess that at least the first few decades of the coming century will be dominated by biology.

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