1.4. Perspectives for the future

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1.4.1. *Gazing into the crystal ball* (E. ARNOLD)

We live in an era when there are many wonderful opportunities for reaching new vistas of human experience. Some of the dreams that we hold may be achieved through scientific progress. Among the things we have learned in scientific research is to expect the unexpected – the crystal ball holds many surprises for us in the future. Alchemists of ancient times laboured to turn ordinary materials into precious metals. These days, scientists can create substances far more precious than gold by discovering new medicines and materials for high-technology industries. Crystallography has played an important role in helping to advance science and the human endeavour in the twentieth century. I expect to see great contributions from crystallography also in the twenty-first century.

Science of the twentieth century has yielded a great deal of insight into the workings of the natural world. Systematic advances are permitting dissection of the molecular anatomy of living systems. This has propelled us into a world where these insights can be brought to bear on problems of design. The impact in such fields as health and medicine, materials science, and microelectronics will be continually greater.

1.4.1.1. *What can we expect to see in the future of science and technology in general?*

Just as few were successful in predicting the ubiquitous impact of the internet, it is difficult to predict which specific technologies will accomplish the transition into the culture of the future. It is possible to envision instantaneous telecommunication and videoconferencing with colleagues and friends throughout the world – anytime, anywhere – using small, portable devices. Access to computer-based information *via* media such as the internet will become continually more facile and powerful. This will permit access to the storehouse of human knowledge in unprecedented ways, catalysing more rapid development of new ideas.

Experimental tests of new ideas will continue to play a crucial role in the guidance of scientific knowledge and reasoning. However, more powerful computing resources may change paradigms in which ever more powerful simulation techniques can bootstrap from primitive ideas to full-blown theories. I still expect that experiment will be necessary for the foreseeable future, since nearly every well designed experiment yields unexpected results, often at a number of levels.

In the realm of biology, greater understanding of the structure and mechanism of living processes will permit unprecedented advances in health and medicine. Even those scientists most sceptical of molecular-design possibilities would be likely to admit that revolutionary advances have been achieved. In the area of drug design, for example, structure-based approaches have yielded some of the most important new molecules currently being introduced worldwide for the treatment of human diseases ranging from AIDS and influenza to cancer and heart disease. This is a relatively young and very rapidly changing area, and it is reasonable to expect that we have witnessed only the tip of the iceberg. Dream drugs to control growth and form, aging, intelligence, and other physiologically linked aspects of health and well-being may be developed in our lifetime. As greater understanding of the structural basis of immunogenicity emerges, we should also expect to benefit from structure-based approaches to vaccine design.

Other areas where molecular design will play revolutionary roles include the broad field of material sciences. Traditionally, 'materials science' referred to the development of materials with desired physical properties – strength, flexibility, and resistance to damage by physical and chemical agents. Now, materials science includes key foci in development of new biomaterials and in the burgeoning field of nanotechnology. The acrobatics of new smart materials could include computation at speeds that may be much faster than can be accomplished with silicon-based materials.

1.4.1.2. *How will crystallography change in the future?*

Potential future advances in the fields of crystallography, structural chemistry and biology are tantalizing. Successful imaging of single specimens and single molecules at high resolution may eventually be achievable. Owing to the limitations of current physical theories and experimental possibilities, large numbers of molecules have generally been required for detailed investigations of molecular phenomena. Given the complexity of large biological molecules, only techniques such as X-ray crystallography and NMR have been suitable for describing the detailed atomic structures of these systems. It may eventually be possible to use X-ray microscopy to obtain detailed images of even single specimens. Merging of information from multiple specimens as is currently done in electron microscopy may be very powerful in X-ray microscopy as well.

X-ray sources will continue to evolve. High-intensity synchrotron sources have allowed the development of dramatically faster and higher-quality diffraction data measurements. Complete multiwavelength X-ray diffraction data sets have been measured from frozen protein crystals containing selenomethionine (SeMet) in less than one hour, leading to nearly automatic structure solution by the multiwavelength anomalous diffraction (MAD) technique. At present, such synchrotron facilities are enormous national or multinational facilities that sap the electric power of an entire region. Perhaps portable X-ray sources will be developed that can be used to create synchrotron-like intensity in the laboratory. If such sources could have a tunable energy or wavelength, then experiments such as MAD would be routinely accessible within the laboratory. Better time resolution of molecular motion and of chemical reactions will be achieved with higher-intensity sources.

Sample preparation for macromolecular structural studies has undergone a complete revolution thanks to the advent of recombinant DNA methods. Early macromolecular studies were limited to materials present in large abundance. By the late 1970s and early 1980s, molecular biology made it possible to obtain desired gene products in large amounts, and new methods of chemical synthesis permitted production of large quantities of defined oligonucleotides. Initial drafts of the entire human genome have been mapped and sequenced, allowing even broader access to genes for study. The combination of structural genomics and already ongoing studies will lead to knowing the structure of the entire human proteome in a finite amount of time. Many materials are still challenging to produce in quantities sufficient for structural studies. Engineering methods (site-directed mutagenesis, combinatorial mutagenesis and directed evolution techniques) have permitted additional sampling of molecular diversity, and we can expect that even more powerful methods will be developed. Engineering of solubility and crystallizability will help make more problems tractable for study. Perhaps, as suggested before, techniques for visualization of single molecules may become adequate for *in situ* visualization of molecular interactions in living cells and organisms. However, traditional considerations of amount, purity, specific activity *etc.* will remain important, as will hard work and good luck.

The phase problem has continued to be a stumbling block for structure determination. Experimental methods, including isomor-

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