J. Pharm. Pharmacol. 1994, 46: 321


# Guest Editorial—Modern Medicines: the Converging Sciences

The three first met when young. "My hope", said Francis Crick, "is to discover the blueprint of life". "Mine is to develop the electronic superhighway", said Bill Gates. "And mine", said Galen, "is to bring health through medicines". Unable to converse with these giants, I espied on their tumbling interrogation of each other's simultaneously divergent and convergent dreams and ambitions; I knew they would influence what I would do. "What first?", they asked. "Why, to unravel the structure and functioning of DNA", said the enigmatic F.C. "To compress information into a language that can be easily read by machines and effectively used by people", said B.G., driving his technical juggernaut; "Mine", said the other G., extemporaneously, "is to create potions that are effective and safe".

And like most who are driven, they, and those who followed, succeeded. Based on our current ability to understand and to control gene expression, some estimate that by the next millenium we shall be in possession of 100 times the amount of biological information than was known from the beginning of time to 1990! Computers enable us to create, manage, and exchange information at such astonishing speeds that they have helped to change the destiny of the world (why else did the USSR tire of the superpower struggle?). Medicines improve the quality of life for tens of millions of people each day. From beta-blockers to betaseron, the advances in human health care due to synthetic and biotechnology products are dramatic and worthy of the highest praise. Now, as the three visionaries predicted it would, and as I have begun to realize, these respective worlds are converging as disease becomes understood, diagnosed and treated at an increasingly higher order of genetic hierachy and function. Until ten years ago, Galen's legacy was obvious. From concoctions of newt and toad, to (re)fine(d) chemicals, then to designer drugs, the march was continuous, though linear. Then, the major advances in the natural sciences, the analogue provided both by information software and by computer hardware technologies, the advent of AIDS, and the intractable nature of many severe diseases has led to drugs that can modulate or even mimic gene function. These included low molecular weight agonists or antagonists of protein function; transcription activation factors; therapeutic proteins; antisense or triple-helix forming oligonucleotides that modulate the production of aberrant proteins; therapeutic ribozymes; and even genes as drugs.

Modern drugs function in a specific though complex manner. Their common need is effective delivery to their (often intracellular) sites of action, at the right moment and frequency relative to the needs of the patient. For example, examine the use of gene therapy methods for transferring genes into a patient's cells in order to produce a therapeutic gene product, such as a protein. Our own work is designed to transfer genes into patients using DNA expression vectors of approximately a million daltons molecular weight in size. These vectors can be regarded as pieces of genetic software, for engineered into them are both genes and other DNA sequences that harness the body's chemistry to control (as the three friends had discussed) the in-vivo production of the therapeutic gene product. A key event for any gene therapy method is the efficient nuclear location and persistence of these macromolecular assemblies of genetic material within the cell.

Perhaps at too great a cost to the development of medicines, drug delivery has often been of secondary importance in commercial drug discovery. Alza's scientists reached to alter this 25 years ago when they started their adventure of wrapping drugs in polymeric controlled delivery systems. Genentech recognizes the importance of delivery when its Annual Report calls for controlled release delivery systems for growth hormone to improve upon patient compliance. That apparent drug activity is the product of intrinsic drug activity and its availability at its site of action has been poorly woven into the drug discovery process. Anticodon scientists now realize this as they attempt to deliver oligonucleotides into target cells. Gene therapists are beginning to comprehend the importance of delivery for the successful use of genes as therapeutics and are starting to retrace the paths taken by drug-targeting scientists.

Those trained in pharmaceutical sciences that were based largely on mechanistic chemistry and phenomenological pharmacology learnt how to synthesize, formulate and apply low molecular weight drugs. The advent of protein drugs has shown that drug delivery approaches developed for low molecular weight drugs could not easily be applied to macromolecular polyvalent proteins. Similarly for therapeutic genes, their unique spatial and temporal requirements demand different delivery methods. Delivery technology has generally been applied to create new products from old drugs. While this will continue, the product development team must turn its attention much earlier to the issue of effective delivery. A drug is only part of a medicine, and drug delivery should not be a supplementary event to the discovery of a drug. As Arnold Beckett and Takeru Higuchi repeatedly taught, the delivery of the drug (i.e. the route, rate and frequency of its input into the body and its movement to sites of action) requires as much scholastic attention and importance being given to it as does the chemistry and pharmacology of the active ingredient.

Modern thinking in medicine highlights the need for a new approach to drug delivery science and technology. A shared understanding of biological and disease issues, and development in modern materials sciences is essential. An approach that truly combines the skills and insights of molecular and cell biologists, material scientists, and physical, chemical and pharmaceutical scientists would be a good first step. The body is the blueprint for the development of new enabling drug delivery technology that should exploit rather than circumvent biological processes, for as we move towards treating disease through gene modulation using both small drugs as well as the larger constellations of genetic information, we must learn to deliver drugs as the body delivers its own. The three friends spoke of this too, except then, even fewer were listening.

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