The challenge of molecular medicine

The potential impact of molecular biology on medical problems is clear. But as participants at *Nature*'s conference on molecular medicine in San Francisco (22–23 September) found, producing practical therapies will not be simple.

San Francisco. Thirty years ago, as Bernard Fields (Harvard) recounted at *Nature*'s meeting last week, his interest in infectious diseases was greeted with disdain. Bacterial infections were a thing of the past, thanks to antibiotics, and vaccines had ensured the same was true of viral diseases such as polio; surely he could make better use of his time?

Other talks made it very clear (if anyone had any doubts) how wrong these pundits were. But as well as the resurgence of infections that man, in his hubris, had long thought conquered, the intervening years have seen a deepening in our understanding of disease brought about by the advent of molecular biology. And perhaps, as David Baltimore (MIT) remarked, it is not unreasonable that techniques developed in the search for knowledge should take 20 years to produce a workable medical technology.

Nature has of course already had at least one related conference (see *Nature* **366**, 505; 1993). But on that occasion it was the search for molecular models and tools that dominated, rather than (as here) the search for insights that might one day yield effective therapies. This transition can only become more important as time goes on, and is reflected in the impending launch of *Nature*'s latest sister journal, *Nature Medicine*. It has also prompted at least one graduate school to introduce a new curriculum, aimed at producing tomorrow's biomedical researchers (Donald Ganem, University of California, San Francisco (UCSF)).

In many cases, though, the transition is still at a surprisingly early stage. Tuberculosis is undergoing a worldwide resurgence, and is again a leading cause of death. Only the advent of the knockout mouse, however, has established that interferon γ, β_2-microglobulin and tumour necrosis factor α are all necessary for successful defence against the infection (Barry Bloom, Albert Einstein College of Medicine, New York). While this puzzling constellation may reflect the role of nitric oxide in killing bacilli ingested by macrophages, it underlines our poor understanding of the disease's pathogenesis. But the finding that Hispanics living in the Bronx in New York are as much at risk of tuberculosis as AIDS patients suggests that improved housing, sanitation and occupational health could be of major benefit even in developed countries.

Similar problems arise in the study of leishmaniasis, another major scourge in developing countries. Here, the puzzle is to understand why some infected individuals, like certain strains of mice, mount an ineffective immune response and succumb to systemic infection (Richard Locksley, UCSF). At least in mice, the answer appears to be that the immune response is dominated by the T_H2 lymphokine profile appropriate for extracellular parasites, rather than the T_H1 profile needed to eliminate intracellular parasites such as leishmania.

In other cases, it is the infectious agent itself that is new. One example is the recent outbreak of hantavirus in the United States (see *Nature* **370**, 409; 1994). Another is the necrotizing fasciitis recently dramatized by the media, which may be caused by streptococci that elaborate exotoxins previously thought to be confined to staphylococci (Richard Krause, Fogarty International Center, National Institutes of Health).

But the need for a better understanding of pathogenesis is by no means confined to infectious diseases. The finding that ICAM-1 and VCAM-1 are the only molecules responsible for monocyte adhesion to the arterial endothelium in the initial stages of atherosclerosis, for instance, surely suggests new therapeutic approaches (Russell Ross, University of Washington, Seattle). The key role of platelet-derived growth factor in the subsequent cellular proliferation may point to another target.

Our understanding of cancer, of course, has been more affected by molecular biology than that of any other condition, and recent developments — the possibility of screening shed cells for early detection of malignancy, for example (David Sidransky, Johns Hopkins University, Baltimore), or the isolation of the first gene responsible for hereditary predisposition to breast and ovarian cancer (Mary-Claire King, UC, Berkeley) — have already been covered in *Nature* (**369**, 13 & **371**, 279; 1994 respectively).

Even here, though, there were surprises. Primary tumours have long been known to suppress the growth of metastases, but the discovery that they do so by secreting an inhibitor of angiogenesis suggests new approaches to both diagnosis and therapy (Judah Folkman, Harvard). The possibility that not all tumours with unstable di- and trinucleotide repeats may have defects in mismatch repair, too, may have diagnostic implications (Paul Modrich, Duke University, Durham, North Carolina). But in other cases, such as cancer cell apoptosis, the phenomenon in question is so complex that it will be some time before research affects medical practice (Stanley Korsmeyer, Washington University, St Louis).

Sometimes the flow is reversed. Our understanding of signalling by the T-cell receptor, for instance, has been greatly enhanced by the study of immunodeficient patients (Arthur Weiss, UCSF). And the account by David Nathan (Harvard) of his work on thalassaemia over 25 years was a beautiful example of the fruitful interplay between molecular understanding and clinical care.

But in general, it is the tools with which to apply molecular insights that are in short supply. The most obvious, perhaps, is gene therapy, but as Inder Verma (Salk Institute, San Diego) remarked, this is beginning to resemble an onion — the more you explore it, the more tears you get. In particular, although adenovirus vectors have many advantages that retroviruses lack (notably growth to high titers and an ability to infect non-dividing cells), host immune responses seem likely to make them virtually unusable *in vivo*. Modifying cells in culture before returning them to the host (the so-called *ex vivo* approach) avoids these difficulties, and has so far had more promising results; suitably modified fibroblasts (and perhaps neurons) can even trigger regeneration of cholinergic neurons in the brains of mice and monkeys (Fred Gage, UC, San Diego).

Where genes cannot form the basis of therapy, drugs must suffice, and there has been no lack of attempts to develop them. Sometimes, research suggests a new target, like the farnesylation reaction used to attach the Ras oncoproteins to the cell membrane (Guy James, University of Texas Southwestern Medical Center, Dallas). On other occasions, known structures can serve as models for therapeutically important targets, allowing computerized selection of possible inhibitors (Fred Cohen, UCSF). Modelling of the malarial cysteine protease on the basis of related enzymes from kiwifruit and papaya has already uncovered at least one compound with promising antimalarial activity in mice.

More radical departures from traditional pharmacology may eventually have an even greater impact. Procedures for screening random oligomer libraries on the basis of their biological activity (so-called combinatorial chemistry), for instance, should eventually allow rapid isolation of (ant)agonists directed at almost any biological target (Paul Bartlett, UC, Berkeley). But whatever the exact route by which they are produced, it is clear that the long wait for medical applications of molecular biology will soon be over. The result can only be a steady stream of advances in patient care. **Nicholas Short**