Clinical practice in the new era

A fusion of molecular biology and classical medicine is transforming the way we look at and treat diseases • *by Athanasios G. Papavassiliou*

'... As genetics develops in the new millennium it will be important to remember that computer modelling or other sophisticated approaches to unravelling biological complexity can never replace the study of these remarkable "experiments of nature". It is vital, therefore, that the field evolves as a closely integrated partnership between the clinical and basic biological sciences; they will continue to have much to offer each other.' Sir David J. Weatherall, 1999.

The explosive growth in biomedical research during the last two decades has radically altered the manner in which the medical sciences approach disease pathogenesis and cure. The advances in and the thematic overlap among disciplines, such as molecular genetics, cellular biochemistry, molecular pharmacology and immunobiology, have made possible new perspectives and tools that are permeating experimental medical research, with recombinant DNA technology providing the catalytic factor. The provisions of 'old' medicine impregnated with the new understanding of human function are creating a new field: molecular medicine. This new concept tries to explain human illness as a 'malady of molecules' with the precision of the physical sciences and seeks to understand the structural and functional anomalies of genes and their protein products in the diseased state. Molecular medicine reflects the 'hybridisation' of classical medicine with basic research. It is not limited, as implied by its name, to the applications of molecular biology to clinical problem solving, but rather seeks to identify and confront clinical entities at the molecular level.

Frank Moore *Hospital*, 1992. Oil on wood with frame. Courtesy Sperone Westwater, New York

The provisions of conventional 'old' medicine impregnated with the new understanding of human function are creating a new field: molecular medicine. This new concept tries to explain human illness as a 'malady of molecules' with the accuracy of the physical sciences

The key terms in molecular medicine are 'cell signalling' and 'regulatory pathways'. The cell functionally resembles an integrated circuit, a piece of electronic machinery, which is called upon to make critical decisions for its homeostasis within a minimal time frame. Cascades of molecular interactions with rigid cohesion—but also with a margin for 'dialectic' coupling—analyse and integrate the broad variety of signals that bombard the cell at any given moment. Protein circuits are linked together in direct and pre-wired networks defined by specific peptide motifs. These fixed interactions rapidly transduce signals from the external environment to elicit specific biological responses (Hunter, 2000). Such inputs are transmitted down the cellular circuits through post-translational modifications of the proteins involved, such as tyrosine-, serine- or threonine phosphorylation. These 'nodes' of interaction can be thought of as the gating mechanism of the cellular circuit.

Ultimately, the cell's response to the incoming signal is defined by the combination of circuits and gates used, which converge into a limited number of key events. These can be the expression or suppression of one or several genes, activation of a set of enzymes, or even a complete arrest of the cell cycle. Bone morphogenetic stimuli, for instance, trigger the sequential expression of a set of genes to orchestrate bone matrix mineralisation. An increase in insulin concentration results in the activation of enzymes engaged in the glucose–lipid metabolism. UV-generated DNA lesions lead to the arrest of DNA synthesis and thus to a halt in tissue growth.

Molecular medicine is attempting to understand, and ultimately manipulate,

these information processing circuits to redirect the cell from the diseased to the normal state. Research in this field includes tumour development, autoimmune disorders, asthma, diabetes, atherosclerosis, obesity, stroke, viral infections, sterility, neurodegenerative diseases, etc. Concentrated efforts in the field of angiogenesis have already led to the development of various exciting and bold approaches for the treatment of cancer and various ischaemic and inflammatory diseases. Angiogenesis inhibitors, for instance, have been shown to have great potential in cancer treatment, and more than 20 pro- and anti-angiogenic agents alone or in combination with conventional therapies are now being tested in clinical trials (Carmeliet and Jain, 2000). These promising developments would not have been possible without precise biochemical knowledge about the regulation of angiogenesis at the molecular level. Another success story is the development of a compound by the Irish company, Elan, which could prevent and inhibit the formation of amyloid plaque in Alzheimer's disease. Again, this discovery is based on the exact understanding of why and how proteins in the brain of Alzheimer's patients are cleaved.

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Deciphering the biochemical pathways that underlie disease processes will result in the identification of a vast array of proteins that may become candidates for therapeutic intervention. Furthermore, with the avalanche of new data on genomic sequences and mRNA expression available, the biological community is anticipating the identification of many proteins with entirely new structures and functions (Eisenberg *et al.*, 2000). These novel proteins will offer new opportunities for pharmaceutical research to investigate disease pathways and to identify previously unknown molecular targets for diagnosis and treatment. The burgeoning field of bioinformatics—functional genomics/proteomics and structural computational biology—together with the promise of rational drug design constitutes the frontlines of these new horizons (Lockhart and Winzeler, 2000; Pandey and Mann, 2000). In particular, the identification and analysis of crucial elements in cell signalling, such as on–off switches, points of crosstalk or transcription integration centres, will open up completely new approaches to therapeutic intervention (Kloog and Cox, 2000; Herlaar and Brown, 1999; Kung *et al.*, 2000). For instance, fine mapping of the effectors of cell-cycle control could lead to ways of tricking cells into dividing in response to artificial signals. That may lead to the ability to regenerate nerves, liver, heart muscle and maybe limbs. The poor notion of 'expecting some future therapy' is gradually beginning to concede its place to the feasibility of intervention through the modification of human cells with remarkable precision and selectivity (Papavassiliou, 1998; Peng, 1999). Moreover, doctors may be able to tailor treatments to the individual pharmacogenetic profile of the patient (Roses, 2000).

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The biomedical sciences are in a transitional stage between the bloom of fundamental knowledge and the fruition of specialised clinical application. The elucidation of the intricate operational and control mechanisms that regulate biochemical pathways will have a profound impact on the diagnosis, treatment and prevention of a wide spectrum of diseases. But as exciting as the prospects of new technologies are, therapies for most diseases are still some way off. Intense research has not yet succeeded in 'grabbing by the horns' the Minotaur of malignancies and AIDS, which, to a large extent, remain unmanageable (Hanahan and Weinberg, 2000; Furtado *et al.*, 1999). The HIV protease inhibitor is a showcase example of rational drug design based on the exact understanding of the molecule. But the drug is prohibitively expensive for the majority of AIDS patients in the developing world, and a cheap and effective vaccine is not yet in sight.

Indeed, at the beginning of the 3rd millennium, after more than 100 years of intense medical research, mankind is still plagued by numerous diseases. We are still searching for efficient therapies for the treatment of chronic illnesses that dominate the medical scene of the developed world, such as diabetes, arthritis or cardiovascular diseases (World Health Organization, 1999). The Third World, in contrast, still suffers from age-old infectious diseases, such as malaria, diarrhoeal diseases or leishmaniasis. Moreover, old enemies that we thought we had defeated are back with a vengeance. We are no closer to eliminating or even controlling tuberculosis today than we were when Robert Koch first identified the causative agent, *Mycobacterium tuberculosis*. Sadly, every minute, more than ten individuals develop tuberculosis, amounting to eight million new cases annually. Two to 2.5 million of these tuberculosis sufferers will die. The situation is worsened by the increasing incidence of multidrug resistant strains, and the deadly combination of tuberculosis with AIDS (Kaufmann, 2000).

Nevertheless, glancing back through the history of medicine, there is a good omen. 20th Century medicine has accomplished an impressive number of goals, and has improved the quality of life in the developed world more than any other advance. The immediate challenge is to maintain the new direction of medical research, with simultaneous adjustments

to clinical practice. However, adjustment and change are inherent features of biological science.

In addition to the changes in medical practice that the new era of molecular medicine is bringing, a common language is emerging between clinical groups as diverse as haematologists, neurologists, endocrinologists and molecular biologists. Together with an immediate access to biological and clinical information through information technology, such improved communication of clinicians and scientists of all disciplines is bound to enhance the clinical perspective of biomedical research and to accelerate the invention of new diagnostic tools and therapeutic strategies (Horton, 2000).

Numerous gaps still exist in our understanding of life processes and their deviations—in terms of both biological mechanisms and of effector molecules. These 'blank spaces' will eventually be filled by rapidly accumulating knowledge in the same way that new elements gradually filled the chemical periodic table at the turn of the last century. What remains to be seen is to what degree the harmony among, and disruption of, these processes can be described using the languages of mathematics, physics and chemistry. It appears, however, that the ultimate achievement of biomedical science will be to attest that cellular function and dysfunction arise from a series of intermediary control events with an ever-increasing complexity, starting with the laws that govern the formation, regulation and mutual effects of cellular macromolecules. Molecular medicine seeks to unravel the precise formulation of these precise laws in order to diminish, and eventually erase, the dividing line between the physiological and the pathological, the healthy and the ill.

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