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EDITORIAL

Genes, Disease and Translational Research

'Translational research' is a term that is used in an almost entirely biomedical context; it describes the process by which the fruits of biological research enter the realm of clinical practice. An editorial in *Science* (2009, **324**, 855), authored by as many as thirteen scientists, administrators and editors entitled 'Translational careers', emphasizes the need to strengthen the support systems for promoting 'multidirectional translation'. In the United States a major investment has been made through the creation of a consortium of 39 translational centres 'with an annual funding component of $500 million by 2012'. This unprecedented effort, in recessionary times, is testimony to the belief that 'powered by the computational muscle of bioinformatics and the broad perspective of systems biology, advances in biomedical science now have the capacity to transform medicine'. The editorial notes that for effective realization of this hope it is necessary to have both 'systems and people', who will 'ensure a vibrant flow of information between the basic sciences and clinical medicine'. The steady advance of medicine through the 20th century has been fuelled by pathbreaking research in biochemistry, microbiology, physiology, chemistry and physics. Many discoveries have been serendipitous, reminding us of Pasteur's famous dictum that 'chance favours the prepared mind'. Drugs, diagnostics and vaccines have all been the end products of research that has been pursued with considerable patience and perseverance. In the last two decades the progress of biology has hastened dramatically; the genome sequencing revolution has raised public expectation of new cures for old diseases to a level that is, at times, alarming. When biology's advancing front meets with the ever expanding power of computers, the resultant mix evolves into the heady world of systems biology. Can all of modern biology's potential be 'translated' into successes in the clinic?

Sixty years ago Linus Pauling and his colleagues published a short paper in *Science* establishing that the haemoglobins from normal individuals and sickle cell anemia patients were different molecular species. A few years later, in the mid 1950s, Vernon Ingram established the difference as arising from a mutation of a single amino acid residue in a protein consisting of several hundred residues. Pauling was to comment that 'on such atomies man's fate depends'. Since sickle cell disease was inherited, Pauling correctly concluded that 'genes precisely determine the structures of proteins'. For students of biochemistry and genetics the sickle cell story is encountered early in their careers; a simple illustration of Mendelian inheritance and a dramatic example of the fragile thread that links biomolecular structure to physiological function. The thalassaemias, another well studied example of disorders of blood, present a related situation where gene defects translate into faulty protein production, with consequent clinical manifestations. Once again, the relationship between genes and disease is clear. The haemoglobin diseases are classic cases where the basic scientific issues are clearly understood. Have the insights gleaned over decades of painstaking research led to cures? The answer is sobering. While much has been learned about these diseases and clinical management, there are no simple, widely accessible 'cures' that have been discovered as yet. In the 1990s it seemed that 'gene therapy' would indeed emerge as the approach of choice for the treatment of single gene disorders. The apparent conceptual simplicity of this approach masked the complexities inherent in gene transfer from vectors to hosts and the interactions between hosts and vectors. The number of clinical trials in the United States grew dramatically by 2000, but the unfortunate development of 'treatment associated cancers' and the tragic death of a patient in a trial in 1999 marked the fall of gene therapy from favour, in the arena of translational research.

The current favourite in biomedical research is the field of stem cells. In the United States, legal restrictions on funding of human embryonic stem cell research have hampered basic progress. The Obama administration lifted these restrictions a couple of months ago, but the American President was quick to add a cautionary note: 'At this moment, the full promise of stem cell research remains unknown and it should not be overstated'. He added that, 'I cannot guarantee that we will find the treatments and cures we seek'. Indeed, stem cell enthusiasts promise cures for almost every neurodegenerative disease, diabetes, cancer and cardiac ailments and speak optimistically of regenerative therapies. Will stem cells

be medicine's new frontier? Are public expectations based on a solid foundation of scientific research or is the field being driven by marketing strategies and hyperbole? James Wilson, who led the gene therapy trial that led to the death of a patient in 1999, presents a sobering assessment in an essay entitled 'A history lesson for stem cells' (*Science*, 2009, **324**, 727). He applauds the new American initiatives that have given 'scientists longer leashes as they explore this exciting field'. However he adds, somewhat sombrely, that 'in today's clamor of stem cell enthusiasm it is possible to detect haunting echoes of the early and ultimately troubled days of gene therapy'. Wilson describes the growth of the field in the early 1990s as 'hyper-accelerated translation to the clinic' driven among other factors by 'unbridled enthusiasm of some scientists in the field, fuelled by uncritical media coverage; and by commercial development by the biotechnology industry during an era in which liquidity could be achieved almost entirely on promise, irrespective of actual results'. Wilson notes that an NIH panel addressed growing concerns in a report in 1995, recommending a greater emphasis on a basic understanding of gene transfer mechanisms. The proponents disregarded the cautionary notes, leading to the debacle of the late 1990s. The tragic turn in clinical trials coincided with the 'bursting of the overall biotech bubble' leading to a general loss of confidence in gene therapies. The field in Wilson's words has now 'adopted a more sober approach to clinical trials and bolstered its commitment to basic vector biology and disease pathogenesis'. In considering the new frontier in translational research, stem cell therapies, Wilson notes that 'despite advances, our understanding of the biology of human embryonic stem cells and induced pluripotent stem cells remains thin with regard to clinical safety and utility'. Wilson's thoughtful perspective, based on harsh and tempering experience, must be required reading for policy makers and regulators in India, where stem cell research and translation may move faster than the gene therapy area. There is a role for scientific leadership which Wilson argues, 'must steadfastly discourage overselling the clinical reality of stem cell therapeutics and must effectively communicate how long it takes to go from laboratory bench to bedside'.

The promise of modern biology has been overwhelming. 'Biotechnology', a term that encompasses all the current areas of molecular and cell biology, has immense potential for 'translation' in fields as diverse as agriculture and medicine. Nowhere has the unity of biology been more manifest than in the genome; a unity that is most evident in the reductionist view of molecules and cells. How patient must one be in waiting for laboratory successes to transform the clinic? The case of cystic fibrosis is worth recalling. It is estimated that 'approximately one in twenty Caucasians carries a defective cystic fibrosis gene and about one child in 2000 inherits such a gene from both parents and consequently dies of the disease, usually by the age of 30' (Newmark, P., *Nature*, 1985, **318**, 309). The hunt for the gene began in the mid 1980s, resulting in the cloning and sequencing of the gene coding for a protein named the cystic fibrosis transmembrane regulator (CFTR). Disease causing mutations lead to chemical differences and defective function of the CFTR protein. In marking 20 years of the discovery of the cystic fibrosis gene, a *News Focus* article in *Science* (Couzin-Frankel, J., 2009, **324**, 1504) revisits the field. Two decades after the successful conclusion of the gene hunt, there is still no cure for cystic fibrosis. The early promise of gene therapy has not been realized. The author notes: '. . . as new gene discoveries pile up weekly and hype over the power of genes to transform medicine flows fast, cystic fibrosis offers an object lesson in how difficult it is, and how long it takes, to convert genetic knowledge into treatments'. Several researchers quoted in the *Science* article seem to agree that 'being humble in science' is a lesson that has been taught by the cystic fibrosis saga. The technologies of cloning and sequencing have propelled gene hunting to the frontline of biomedical research. Extravagant claims for the discovery of genes responsible for depression, schizophrenia and compulsive criminality appear regularly in the press. Despite the experiences of the past there is still a fond hope, widely held, that identification of disease genes will quickly translate into cures. The linkage between a variant of a serotonin transporter gene and depression has been laid to rest, prompting an article in *Science* entitled 'Back to the drawing board for psychiatric genetics' (2009, **324**, 1628).

Translational research is a term that is now commonly heard in India. Several new centres are on the anvil, which will face the formidable challenge of bridging the gulf between basic research in biology and the real life problems of clinical medicine. The absence of a large number of clinical centres which emphasize medical research and the separation between research laboratories and hospitals will prove to be a major impediment. Traditionally, research and education in medicine have been supported by the Indian Council of Medical Research and the Ministry of Health, while a multiplicity of agencies, the Department of Biotechnology foremost amongst them, fund biological research and efforts in related disciplines. Any purposeful attempt at achieving translation will require an unprecedented level of inter-departmental and ministerial cooperation, together with efforts to widen the base of collaboration between basic scientists and clinicians. This may happen only when basic researchers perceive the potential insights that will undoubtedly result from studies of clinical problems, and clinicians in turn, recognize the enormous power of modern biological techniques, that may sometimes prove invaluable in the clinic.

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