

CURRENT SCIENCE

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CORRESPONDENCE

Gene therapy

The introductory puff piece on page 339 and the article itself (P. N. Rangarajan and G. Padmanaban, *Curr. Sci.*, 1996, 71, 360–368) on Gene Therapy seemed strangely anachronistic in 1996. The authors seem to be totally unaware that gene therapy like King Balshazzar has been weighed in the balance of actual practice and found wanting. The US National Institutes of Health, having funded this narrow field for a decade at about \$200 million per year conducted its own in-house evaluation. This 'Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy (December 7, 1995)' finds that in spite of the huge expenditures *not one human has been cured* by gene therapy (see page 658).

Quite a record. The cost to society per life saved so far is infinite. Even after your authors' 'light at the end of tunnel' appears, those costs will not come down much. Indeed such high-tech medicine aimed at a few patients, however heart-rending the stories, is a major cost driver in medicine today. It is also a major attention-diverter for the scientific community away from the enormous problems in preventive medicine which affect tens of thousands.

Today research funds are driven more by the number of researchers and their need to be kept busy in their subspecialties. That is a major part of the cause of the impending crash of the US health care system. As a science policy analyst I have been emphasizing to governments that the *only* way to contain runaway research costs is to allocate research funds by the potential benefits, in this case the number of persons affected, and the seriousness of the disability. Those of us paid from the public purse for our research

must very seriously ask whether the public has a reasonable chance of obtaining any return on its investment. Or have scientists become 'welfare queens in white coats' expecting to be supported for doing our research irrespective of the outcome.

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Rangarajan and Padmanaban reply:

It is easy to be critical and cynical with information interpreted to one's own way of thinking. Every emerging area including molecular biology as a field and recombinant DNA as a technology have faced strident criticisms in terms of utility, before they were accepted as powerful tools not only in basic research but also in terms of applications. When the introduction of a single new drug into the market is estimated to take 15 years and in excess of \$300 million, we are surprised that gene therapy is expected to deliver on its promises within a decade of investment. The euphoria created on gene therapy due to public pressure, commercial interests and media hype is well known. We are quite aware of the NIH panel report, which has characterized NIH spending of \$200 million as 'appropriate', but has recommended instituting short-term grants to fund innovative research and to test new ideas (*Nature Medicine*,

1996, 2, 7–8). Another commentary states 'Human gene therapy has not yet come of age, but there can be no justification for doubting its eventual success, as an adjunct to traditional therapies or as a definitive therapy on its own. The most revolutionary aspect of human gene therapy has been the conceptual one and that phase is over. We have now reached the difficult evolutionary stage of making it work.' 'Human gene therapy is not yet ready for prime time at least at the clinical level. But it is ready for and needs prime time nurturing and development' (*Nature Medicine*, 1996, 2, 144–147). Hopefully, these will not be considered as anachronistic in 1996! The consensus is to 'go back to the basics' and fill in the missing links as discussed in our article. The fact remains that gene therapy offers hope of cure not only to genetic disorders, but also to cancers and infectious diseases. Infact, serendipity has led to the birth of DNA (genetic) vaccinations, a facet of gene therapy research that holds tremendous promise. One is not just thinking of unaffordable treatment to a few patients, but approaches based on direct DNA injection, genetic immunization, etc., that will be cost effective and benefit millions, especially in the developing world. Once again, there are hurdles to cross and these are worth crossing.

Professional science analysts and those who are in a position to advice governments should necessarily have a balanced view. It is easy to give populist advice such as to allocate research funds on the basis of potential benefits, number of persons affected, seriousness of disease, etc. Such advice will be lapped up by politicians but history is replete with instances of blue sky research, serendipity

as well as goal-oriented research contributing to human welfare. While, governments in general should be helped to decide on priorities, gene therapy as such has tremendous possible applications for mankind and sweeping gener-

alities will only harm a great cause. Let us not straight jacket issues and make scientists appear as in 'white coats for self-preservation'. The community is as much interested in human welfare as any one else professing the same.

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NEWS

Report and recommendations of the panel to assess the NIH investment in research on gene therapy

Executive summary of findings and recommendations

Dr Harold Varmus, Director, National Institutes of Health (NIH), appointed an *ad hoc* committee* to assess the current status and promise of gene therapy and provide recommendations regarding future NIH-sponsored research in this area. The Panel was asked specifically to comment on how funds and efforts should be distributed among various research areas and what funding mechanisms would be most effective in meeting research goals.

The Panel finds that:

1. Somatic gene therapy is a logical and natural progression in the application of fundamental biomedical science to medicine and offers extraordinary potential, in the long-term, for the management and correction of human disease, including inherited and acquired disorders, cancer, and AIDS. The concept that gene transfer might be used to treat disease is founded on the remarkable advances of the past two decades in recombinant DNA technology. The types of diseases under consideration for gene therapy are diverse; hence, many different treatment strategies are being investigated, each with its own set of scientific and clinical challenges.
2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene

therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host.
4. In the enthusiasm to proceed to clinical trials, basic studies of disease pathophysiology, which are likely to be critical to the eventual success of gene therapy, have not been given adequate attention. Such studies can lead to better definition of the important target cell(s) and to more effective design of the therapeutic approach. They often can be carried out in appropriate animal models. Pathophysiologic studies may also suggest alternative treatment strategies.
5. There is a clear and legitimate need for clinical studies to evaluate various aspects of gene therapy approaches. Although animal investigations are often valuable, it is not always possible to extrapolate directly from animal experiments to human studies. Indeed, in some cases, such as cystic fibrosis, cancer, and AIDS, animal models do not satisfactorily mimic the major manifestations of the corresponding human disease. Clinical studies represent not only practical implementation of basic discoveries, but also critical experiments which refine and define new questions to be addressed by non-clinical investigation.

6. Interpretation of the results of many gene therapy protocols has been hindered by a very low frequency of gene transfer, reliance on qualitative rather than quantitative assessments of gene transfer and expression, lack of suitable controls, and lack of rigorously defined biochemical or disease endpoints. The impression of the Panel is that only a minority of clinical studies, illustrated by some gene marking experiments, have been designed to yield useful basic information.
7. Overselling of the results of laboratory and clinical studies by investigators and their sponsors – be they academic, federal, or industrial – has led to the mistaken and widespread perception that gene therapy is further developed and more successful than it actually is. Such inaccurate portrayals threaten confidence in the integrity of the field and may ultimately hinder progress toward successful application of gene therapy to human disease.

Based on these findings, the Panel recommends the following:

1. In order to confront the major outstanding obstacles to successful somatic gene therapy, greater focus on basic aspects of gene transfer, and gene expression within the context of gene transfer approaches, is required. Such efforts need to be applied to improving vectors for gene delivery, enhancing and maintaining high level expression of genes transferred to somatic cells, achieving tissue-specific and regulated expression of transferred genes, and directing gene transfer to

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